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ΠΕΡΙΟΔΙΚΟ ΤΗΣ ΙΑΤΡΙΚΗΣ ΕΤΑΙΡΕΙΑΣ ΑΘΗΝΩΝ

2020, Τόμος 37, Συμπληρωματικό Τεύχος 2

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12–15 Σεπτεμβρίου 2019 | Λάρισα

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11th Congress of the International Association for the HISTORY OF NEPHROLOGY

12–15 September 2019 | Larissa, Greece

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11ο Συνέδριο της Διεθνούς Ένωσης για την ΙΣΤΟΡΙΑ ΤΗΣ ΝΕΦΡΟΛΟΓΙΑΣ

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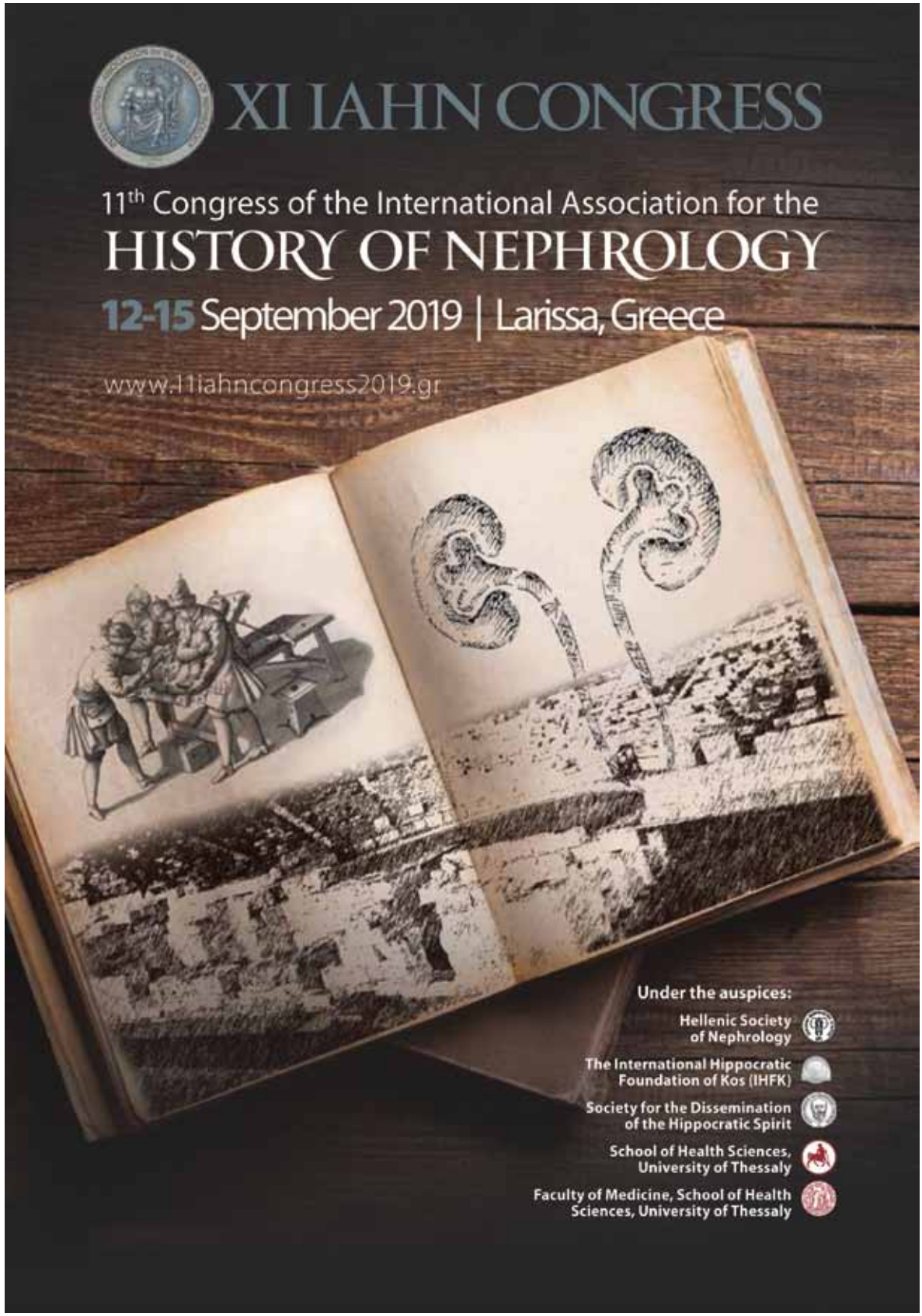

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INTRODUCTORY REMARKS
ΕΙΣΑΓΩΓΙΚΑ ΣΧΟΛΙΑ

Prologue

The current Supplement of the Hellenic Medical Archives contains the Proceedings of the XIth IAHN Congress in Larissa - Greece, on 12–15 September 2019. We are grateful to the 185 year-old Athens Medical Society for deciding to publish them in its Journal. The Congress abstracts have already been published, independently of the Book of Abstracts, in vol. 31, issue 2, 2019 of the Hellenic Nephrology (https://www.ene.gr/eneojs_new/index.php/en/issue/view/80), the Quarterly Journal of the Hellenic Society of Nephrology, which we deeply thank. The Congress and the publication followed on the same very successful previous ones, albeit with some innovations. It always desirable to follow tradition in every aspects of life but with some new practices in order to prolong the survival of its main principles. And, as *survival is not enough*, further development is needed.

The result is much more due to the authors' enthusiastic participation and the spirit of good will during the editorial procedures and far less to the organisers and editors. The novelties introduced were the inclusion in the Congress of speakers from close and far away, ranging from Latvia to Morocco and from the USA to Australia. There were five plenary lectures, 29 oral and 23 poster presentations on familiar or exotic issues. A second novelty was that the posters were not displayed as physical papers on the walls but as short oral communications and thirdly, there were several video presentations. The whole was topped by cultural events. The visit to the unique monastic city of Meteora, to the modern Archaeological Museum of Larissa, to the tomb of the Father of Medicine and finally the attendance of a special dance performance based on Hippocrates' life allowed participants a better understanding of the place and its history. Hence, a link was built between archaeology and nephrology, and on this we will elaborate further on.

The publication was decided for the first time to include all submitted papers, as the allocation of an abstract to the oral or poster session does not always do justice to good works and is constrained by the time available and the politics of any organisation. We introduced a very strict editing in four levels including proofreading, standard editing, extensive editing, and occasionally rewriting. We are grateful for the collegiality shown by the authors in all steps of the editing procedure. Thanks are due to several groups and persons. The IAHN's Council, the Organising, Publishing and Local Committees, the University of Thessaly and the Larissa municipal authority, Manolis Stephanakis of Technogramma Printing House, Emily Diamandopoulou, Founder, Rhyme and Reason Language Services, Sklia Kiki, text modulator, **and lastly but not last the Sponsors.** Above all, to the participants and authors who did not spare time, effort and costs to come and contribute to the success of the Congress and the following Publication. To all of them we are deeply grateful. Our goal was to publish a volume containing an array of interesting contributions to the History of Nephrology. If we succeeded in this, the readers will judge.

Ioannis Stefanidis
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INTRODUCTORY REMARKS
ΕΙΣΑΓΩΓΙΚΑ ΣΧΟΛΙΑ

Introduction
(Archaeology's and Nephrology's errata)

ARCHIVES OF HELLENIC MEDICINE 2020, 37(Suppl 2):12–19
ΑΡΧΕΙΑ ΕΛΛΗΝΙΚΗΣ ΙΑΤΡΙΚΗΣ 2020, 37(Συμπλ 2):12–19

A. Diamandopoulos

Chairman of the Publishing Committee, ex IAHN President, ex ISHM President, Louros Foundation for the History of Medicine, Athens, Greece

Εισαγωγή:
Τα λάθη της Αρχαιολογίας
και της Νεφρολογίας

Περίληψη στο τέλος του άρθρου

In this Introduction to the Proceedings of the Larissa XIth International Congress of the International Association for the History of Nephrology, we present some general thoughts on the errors made by Archaeology and Nephrology and efforts to rectify them. Starting from the claim made by the Organising Committee about Larissa as the place where Hippocrates died, we elaborate on the validity of this claim and the discovery of his tomb there. We then proceed to presenting two other Medieval legendary discoveries of his tomb, the one connected with the Capsula Eburnea and the other with the Holy Grail. Similarities are traced between these tombs and those –equally legendary– of Plato and Hermes Trismegistus. Examples of Nephrology's historical errors presented are those connected with the treatments by bloodletting, cupping, mercury and arsenic administration, treating dialysis water with aluminium and the widespread use of plastic. All these methods and materials had been highly applauded when first introduced and it took many years –even millennia– for their detrimental effects on the kidneys and the environment to be accepted and steps to be taken to eliminate their use. In an apologetic manner, we tried to present some explanation of their proponents' faith in their beneficial effects and to suggest a cautious way when dealing with "miraculous" treatments of the past but also with some modern ones. Intelligence and science are not always infallible. Common sense, art, and in-depth knowledge should be the cornerstone on any Congress on the study of the History of its field.

Key words

Archaeology's errors
Capsula Eburnea
Hippocrates' tomb
Lunar library
Nephrology's errors
Plato's tomb
Smaragdina

Following the example of the previous editors of the IAHN Proceedings, chiefly Professors Natale de Santo and Garabet Eknoyan, it is compelling to add some more general thoughts in the Congress Proceedings, this time on Archaeology and Nephrology, as stated in the preceding Prologue. As the subject is vast, we will mention only errors, fake discoveries and the attempts to rectify them.

1. ARCHAEOLOGY'S ERRORS

The term "Archaeology" is used here in its broader sense, including archeology *per se*, history and legend. The starting point this time will be tombs, burials and their contents. This choice is natural for archaeology, which mainly focuses on the dead, their activities and environment. Their last environment is the tomb, which, surprisingly, sometimes moves around. It is fitting for these Proceedings to start the discussion on false discoveries with Hippocrates' tomb(s).

1.1. Larissa

The grant claim of the city of Larissa, which hosted the Congress, is that it is *"The place where Asclepios was born and Hippocrates died"*. It is worth elaborating on this. The first mention that Hippocrates died in Larissa (where he definitely lived for long and worked) was made 500 years after his death by Soranos of Ephesus.

The information was oft repeated by Byzantine authors and was more or less correct, although several reservations have been expressed. For example, in the 1st century AD, Pausanias when visiting the area and Hippocrates' admirer, Galen, did not mention it while the Thessalians never made any relevant claim in Antiquity.[1]

The notion reappeared 200 years ago, first by the Greek intellectual cleric Anthimos Gazes (1758–1828), who claimed to have seen the tomb amongst some Muslim graves outside Larissa. Then, in 1857, local medical doctor S. Samartzides claimed that he had even seen a cover plate, inscribed

with the letters ΙΠΠΟΚ ΚΩ and some others. The plate was supposedly later hung on a wall of the women's bath at the local Turkish Pasha's mansion. A Greek Government investigation at the time did not trace the plate there or anywhere else.[2] The story about Hippocrates' tomb in Larissa features two interesting details. The first comes from antiquity, in the form of a legend that bees built a beehive on it whose honey treated children mouth's soars.[3] The second is a 19th century reference to a golden snake found in the tomb. These details rather than adding they subtract something from the credibility of the tomb's suggested inhabitant. But let us not be pedantic. Hippocrates definitely died and was buried somewhere. Larissa is the most probable place as he stayed there for a long time, when very old. Although written 500 years later, Soranos' reference to the tomb's location cannot be altogether dismissed. No other place had been suggested by then and rarely were famous doctors' tombs the focus of travellers. Indicatively there is no reference to Galen's tomb. Let us not destroy a common belief just because of minor –albeit correct– details. Thus, yes, Hippocrates died in Larissa and the location of his tomb has not been documented yet, but a cenotaph was built instead. This is the most credible hypothesis. However, there have been two other absolutely incredible "tombs" that were considered genuine by many more people and for many more years from the Early Middle Ages onward. The first concerns the Capsula Eburnea [Ivory Casket].

1.2. Capsula Eburnea

The legend, of Byzantine or Islamic origin, started to circulate around the 6th cent AD. According to this, Julius Caesar/the King/Sultan was informed that Hippocrates' tomb existed somewhere, in a derelict state. Galen received permission from the Sultan (sic) and opened the grave. He found only an Ivory Casket and inside it 25 maxims supposedly written by Hippocrates, concerning cutaneous eruptions. Galen offered the manuscript to an Arab savant (sic). It was then extensively copied and consequently translated into Latin. For centuries, it was held at University and Monastic Libraries, helping monks and doctors to predict a patient's forthcoming death based on the signs of eruptions, the *signa mortis*. Hence, the manuscript was also titled "Hippocrates' Prognosticon".[4] It was held that the Father of Medicine had instructed the manuscript to be buried with him and kept as a secret.[5] Its impact on medical education has long ceased to exist.

1.3. Queen Saracinth

The third and most exotic of Hippocrates' tombs is described in the story of the Holy Grail. Skipping even the briefest presentation of this famous medieval romance, we will focus only on aspects relevant to the "discovery" of his tomb. The names of the people and places involved are an amalgamation of everything and anything from ancient history, oriental legends and Christian religion. It starts with Hippocrates and his retinue leaving Rome to visit Antony, King of Persia. On arrival, they find the King lamenting the death of his son Dardanes. Hippocrates diagnosed that he was not yet dead and managed to revive him. Rich rewards followed but Hippocrates is killed by his wife (!!) who used a poisonous wild boar. Hippocrates begged the King to deliver his body back home to his relatives, presumably somewhere near Persia. The king obliged. After many imaginative adventures, Queen Saracinth, a pagan baptised by a follower of Joseph of Arimathea starts searching for his tomb. Eventually her servants trace it after a long sea voyage. There is an excellent miniature of the scene in the Bibliothèque nationale de France [MS fr. 95 Estoire del saint Graal, f. 69v (S I 182.34)] depicting the servants in lamentation, reminiscent of similar scenes around Christ's dead body. Interestingly, the tomb is painted with crosses on it, as Hippocrates was *a posteriori* presumed to be Christian. Justness dictates that we should not finish the trinity of tombs lauding Hippocrates without referring to the tomb of his more ardent enemy, the Methodist medical writer Thessalus of Tralleis (1st cent. AD, Rome). Together with Julian, another founder of the Methodist group, he had written many treatises against Hippocrates, even renouncing his Aphorisms. On his tomb in Appian Way, he asked for an epigram to be written claiming "Thessalus the Conqueror of the Physicians".[6]

After Hippocrates, we continue with two more tombs, Plato's and Hermes Trismegistus'.

1.4. Plato's tomb

The rationale for including Plato's alleged tomb in this paper is that the philosopher is almost the only ancient source contemporary to Hippocrates who mentions him by name. Similarly to Hippocrates he was also considered a Christian before Christ[7] and lastly, the legend about an epigram found in his tomb resembles the familiar medieval story of Capsula Eburnea. In spite of the textually well-documented location of his tomb near the namesake Athens Academy, a legend appeared, first in Aquinas's writings in the 13th century.[8] It was suggested that a tomb was discovered and opened in Constantinople during the reign of Constantinos and Helen (in another version Irene). In it, they found an inscription on a golden plate, writing that *"Christ will be born of a Virgin, and I will believe in Him. Plato"*. The story, though incredible, persisted for centuries

and was the focus of a polemic against Papacy even three centuries later.

1.5. Hermes' Tomb

The last tomb, that of Hermes (!!) was uncovered by Alexander the Great in Hebron. It contained an emerald plaque, *Tabula Smaragdina*, a compact and cryptic piece of the *Hermetica,* claimed to be written by Hermes Trismegistus, a hybrid god between the Greek god Hermes and the Egyptian Toth. In reality, it is believed to be an Arabic work written between the sixth and eighth centuries. In an alternative version, it was found in the hands of a corpse sitting on a golden throne in a crypt under the statue of Hermes in Tyana.[9] It became the base of Alchemy and cosmology and persisted well into the 16th century.

1.6. Conclusions A / Modern survivals

Concluding the first part of the Introduction, Larissa is the only legitimate candidate as Hippocrates' place of burial although, strictly speaking, there is yet no sound archaeological documentation for this. The rest of the tomb locations presented are obviously fake inventions of the Medieval imagination. But without trying to introduce a neologism, what is wrong with a fake story and or object? There are many pseudo-Hippocratic treatises, apart from the dubious ones in the Corpus Hippocraticus, which give us a good idea about ancient medicine. Even if these were not written by Hippocrates, they could have been written by him and as many people believe that he was the author, we accept them as pseudo-Hippocratic and the matter is settled. Galen himself had the excuse ready. In the preface of the Regimen, discussing the chapter on diet and baths, he admits that its authenticity was reasonably questioned given its literary and theoretical weakness. However, those accepting Hippocrates as the author were not irrational, as it followed the spirit of his writings.[10] The same can be said of other imaginative stories and objects. The fake ones I presented share several characteristics. All of these tombs "belonged" to famous ancient doctors and philosophers. All of them were discovered accidently by illustrious persons (Julius Caesar, the Sultan, Alexander the Great, Emperor Constantine). All of them conveyed their message with a precious material (gold, ivory, emerald). And the messages *per se* were basically correct (the therapeutic properties of honey, the prognostic value of skin lesions, the principles of alchemy, the combination of ancient wisdom and Christianity). What was really missing from all these texts were the sound facts to support them. Imagination, in a manner of medieval philanthropy trying to "correct the injustice", supplied in abundance the evidence that "happened" to be missing by creating the *"realfake"*.[11]

Surprisingly, after the final conquest of reason over imagination these old fairy tales continue to inspire, given humanity's underlying thirst for readymade solutions to its problems with a "magic" parcel delivered like a pizza to us and preserving human knowledge for our descendants. Thus, as late as in the 20th century, C.G. Jung identified *The Emerald Tablet* with a table made of green stone, which he encountered in the first of a set of dreams and visions beginning in late 1912, and culminating in his writing of a collection of seven mystical or "Gnostic" texts, which he published privately in 1916, under the title *Seven Sermons to the Dead* (Latin: *Septem Sermones ad Mortuos*), *written by Basilides of Alexandria, the city where East and West meet*. Jung did not identify himself as the author of the publication, ascribing it to the early Christian Gnostic religious teacher, Basilides (117 to 138 AD). The latter claimed to have inherited his teachings from the Apostle Saint Mathias. A more obscure story indeed than the original Smaragdina!![12] The Smaragdina is still discussed in popular art and in the 2020 US Black Metal Album "Snare of All Salvation" by Häxanu features the Emerald Tablet as lyrics. The secret treatises of Hippocrates were the subject of the *Perils of Nyoka*, a 1942 Republic serial directed by William Witney. It starred Kay Aldridge as Nyoka the Jungle Girl, who, with help from Larry Grayson, attempts to discover the Golden Tablets of Hippocrates. The tablets contain the medical knowledge of the Ancients – not to mention being buried along with gold and other treasure. Also hunting for the tablets are Queen Vultura ("Ruler of the Arabs") and Cassib. *Perils of Nyoka* was one of 26 Republic serials re-released as a film on television in 1966. The title of the film was changed to *Nyoka and the Lost Secrets of Hippocrates*. Similarly, Capsula Eburnea lent its name to an Italian Medical Journal published recently.[13] More importantly, a year ago, Israel's Beresheet spacecraft was launched toward the moon carrying a 30-million-page archive of human knowledge etched in a DVD-size metal nickel disc. The Lunar Library, as the archive is known, constitutes a "civilization backup" to help ensure that our distant descendants never lose humanity's collective wisdom. A modern Capsula Nickeliana. The Arch Mission Foundation is building a space-based archive designed to survive for 6 billion years or more – a million times longer than the oldest written records in existence today. The Foundation Chairman Nova Spivack's goal is to flood the solar system with other versions of the Lunar Library in caves and mountains on Earth, on other locations on the moon, on Mars and in deep space.[14] Future archaeologists are in for a treat.

2. NEPHROLOGY'S ERRORS

The second part of the introduction discusses some errors in Nephrology. In contrast to Archaeology, which opens tombs and brings to life their genuine or imaginary inhabitants, Nephrology, exceptionally, with its errors delivers alive people to death.

2.1. Blood letting

We had traced two of Hippocrates' Aphorisms recommending bloodletting for a urinary disorder: [Aphorism 6.36] *Venesection cures dysuria; open the internal veins of the arm*. [7.48] *Strangury and dysuria are cured by drinking pure wine [drunkenness], and venesection; open the vein on the inside*.

These aphorisms are based on the ancient belief that certain veins correspond to certain organs. By cutting a certain vein, the corresponding organ would be relieved by the excretion of extra or toxic fluids that had accumulated in it. The correct principle behind this erroneous practice was the elimination of inflammatory toxins from the blood. In Hippocrates' time, this was sought through bloodletting, whereas nowadays it is attempted through dialysis.[15] This theory was erroneous and had led to horrific cases of bloodletting, especially during the Middle Ages. However, up to the mid-20th century, bloodletting was a common therapeutic intervention despite the fact that as early as the 17th century it was ridiculed by the French playwright, actor and poet Moliere. He accused the widespread doctors' order for any disease "Clysterium donare, Postea seignare, Ensuitta purgare" in his theatrical work *"Le malade imaginaire"*.

Venesection was one of two modes for bloodletting, the other being cupping: small conical or roundish vessels made from glass, horn, bamboo, plastic attached on the patient's skin to cause local hyperemia (dry cupping) or blood removal (wet cupping). Cups were an attributa on doctor's graves in Greek Antiquity before being replaced by the matula. [Wet] cupping therapy was popular as *"Al-Hijama"* in Egypt and Arabic countries. It was inserted in Asian medical systems such as Unani, Ayurveda, Chinese, Tibetan, and Oriental Medicine in Asia, the Middle East, and later found its way to European countries up to the 19th century. Then it received harsh criticism from the medical community and declined. In recent decades, it had made a comeback for many ailments. It is used mainly in South East Asia on people with renal failure and/or dialysis, under a strict hospital protocol. Results are claimed to be excellent.[16–19]

2.2. Mercury

"Mercury in the treatment of syphilis may have been the most colossal hoax ever perpetrated in a profession which have never been free of hoaxes".

Leonard Goldwater in his book:
A History of Quicksilver,
Baltimore, York Press, 1972

Mercury (Hg), a fluid metal, has a long history. Large deposits of Hg are found in the earth as cinnabar, which is a compound of mercury and sulfur, and has been mined by people for thousands of years. It was reputably found in Egyptian tombs from 1500 BC. In 2nd century China, the study of mercury centred on a search for an elixir of life to confer longevity or immortality.[19] The Mayas, about 500 AD also used it. Aristotle (384–322 BC) remarked on it and coined the name "quicksilver" or liquid silver. Next, Theophrastus of Eresus (371–286 BC), stated that quicksilver "*[...] is made by pounding cinnabar with vinegar in a copper mortar with a copper pestle".* Pedanius Dioscorides (40–90 AD) writes about making quicksilver by heating cinnabar and condensing the vapour. Plinius The elder (23/24–79 AD) did not call it "quicksilver" but Hydrargyrum, "water silver" [in Greek].[20] It is one of the oldest antibacterials. Razes (9th/10th century) recommended it for leprosy and Paracelsus (15th/16th century) for syphilis. It retained its role as the main treatment of venereal diseases, hence the saying *"One night at the arms of Venus leads to a whole life on Mercury".* In 18th, 19th and first part of the 20th century, mercury was used extensively for an array of diseases but prominently for syphilis.[21] Despite some grave warnings[22] the element was still recommended till the mid-20th century for severe oedema in combination with digitalis.[23,24] They cause diuresis by reducing the reabsorption of sodium in the ascending loop of Henle, thus causing more water to be delivered to the distal convoluted tubule. The main form of administration was the compound Calomel (from the Greek words *"calo"* meaning beautiful and *"melas"* meaning black) because the substance had been used initially as a cosmetic and its colour is black. It was an all-curing drug with purgative and diuretic effects frequently leading to dehydration. When combined with bloodletting, as was the norm, many died of hypovolemic shock brought on by this "heroic" treatment. One of the most ardent believers in such a treatment was Benjamin Rush in Philadelphia. Utilizing excessive purges with calomel and generous bloodletting, he is believed to have killed thousands during the yellow fever epidemic there in 1793. William Cobbett, a harsh critic of Rush, claimed that Rush's depletion therapy was *"one of those great discoveries which are made from time to time for the depopulation of the earth"*. Rush was so enraged; he sued

Cobbett in civil court for defamation of character and won.[25]

In 1799, when former President George Washington fell ill with an acute respiratory illness, Rush's use of calomel and bloodletting killed him before the disease could.[26] Unfortunately, earlier physicians misconstrued hallmark symptoms of mercury poisoning, such as excessive salivation, as signs of mercury's efficacy.[27] In severe cases of inorganic mercury intoxication, the function of the kidneys can be limited and death might occur due to acute kidney failure.[28] After understanding the pathogenic mechanism of the "mercurial nephrotic syndrome" the mercurial diuretics were withdrawn from the market by the 1960s. At present, drastic measures are taken to remove all forms of mercury from the EU.[29]

Nevertheless, the battle against nephrotoxic anti-syphilis medications was not over.

2.3 Arsenic

Simultaneously with the decline of mercury another heavy metal treatment arose: arsenic. Paul Ehrlich's major triumph was the discovery in 1910 of Salvarsan (Compound 606). He screened just over 600 synthetic compounds to discover it. By the end of 1910 –the year the drug was given its trade name *Salvarsan*– some 65,000 doses had been administered to over 20,000 patients, a previously unheard of series before marketing, as was noted at the first presentation of the clinical results in Wiesbaden in 1910. It had such a remarkable effect in treating symptoms and, with time, killing the *Treponema pallidum* that it was acclaimed as the "magic bullet".[31] These panegyric comments were coming mainly from Germany, the motherland of the Dye Industry that produced Salvarsan. In Britain, the comments were more reserved. Just two years after the triumphant results in Wiesbaden, Dr McDonagh was wondering: *"As all of us require an unbiased opinion upon Salvarsan, it would have been better to have given a summary of the whole of the Fifth German Congress of Neurologists held last October in Frankfurt, as then we could have heard both sides. Hearing only one side leaves this side widely open to criticism. In this country more than any other we have heard so much as to what the "great" or "well-known" syphilologists think of Salvarsan. Notice that their greatness has increased since the advent of the drug, although as often as not, they have never given an injection. Why an able clinician or a reader of many books should be able to judge a subject of which his experience is nil must be an enigma for many."*[32] Over time, more and more side effects were noted, mainly neurological, dermatological, liver and renal symptoms. Eventually, in the mid-20th century the harmless antibiotic penicillin replaced both mercury and arsenic in the treatment of syphilis, saving many kidneys.

2.4. Aluminium

The discussion on aluminium is justified as it was blamed as the main culprit for Dialysis Encephalopathy.

Aluminium is the most plentiful metal in the earth's crust. It is present in the environment combined with other elements such as oxygen, silicon, and fluorine. Its name was coined in 1812 by the English chemist Sir Humphry Davy (1778–1829) from the mineral alum, descending from the Latin word "alumen" meaning "bitter salt". Aluminium sulphate is used in water treatment for the coagulation of organic and mineral colloids prior to sedimentation and or filtration. It was exactly the substitution of aluminium salts by aluminium and ferrous sulphate in the water-treatment plants in West Scotland that led to the encephalopathy epidemic in home dialysis centres in the late seventies. In the same period, in 1977, a master's thesis was submitted to Durham University containing many historical and social data on the industrial production of aluminium in North England and Scotland.[33] It is an interesting work worth reading by historians of industry. It discusses the question posed by Solla Price "Is technology historically independent of science?"[34] Nephrology was established as a separate specialty on the advances of technology and science was added later on the accumulated experience. Kevin Quinn reports in his thesis about the initial conflict between technology and science in 18th century North England and Scotland that George Dodds, the manager of Boulby alum works wrote to one of the partners on 3 March 1786: *"I can now tell you that Sir Thomas Dundas is for putting his Scheme in execution […] and a person at present is learning to make alum with Dr Bark of Edinburgh – what will come of this romantic scheme, I do not know, but it will probably now tried if Chemical Skill will make an improvement in that very nice and essential point of our business".*[35] The last extract of this book refers to a strange relationship between kidneys and aluminium in 18th century England. While processing shale-containing pyrite and after many manipulations, warming, diluting, brewing with sewage etc., at the final phase: *"The liquor is transferred to a wooden cooler leaving the sediment behind and 20 gallons of urine added […] It is observed that the best urine is that which comes from poor labouring people who drink little strong drink (sic) […] but sometimes they mingle it with sea water which cannot be discovered by weight".*[36]

By coincidence, I was in that very area, Scotland, completing my PhD Thesis at Glasgow University, when the first

reports on the deleterious impact of aluminium added into water for dialysis were presented.[37] Thus, I had the questionable advantage due to my age to witness the initial scorn of the medical establishment when afterwards, in my green age as a young consultant in St. Andrew Hospital, Patras, Greece, I undertook to establish the first dialysis unit there in 1977. Everything was ready at last and I was attending the 15th EDTA Congress in Istanbul in 1978, where I was presenting my first paper at an International Meeting. Unexpectedly, I received a call in my hotel room early in the morning by the then General Secretary of the Ministry of Health, a famous Nephrologist and a very good friend of mine. He angrily demanded to know why I had not started dialysis yet in my hospital. I explained that I could not start it without a water deionizer, being impressed by Dr Alasdair Iain MacDougall's lectures back in Glasgow on the implication of the water's aluminium in Dialysis Encephalopathy. The General Secretary resorted to four-letter words, ordering me to start dialysis *without fancy useless apparatuses*. I refused. Eventually, he had second thoughts and passed a law making the installation of such equipment in every dialysis centre necessary. This was the behind the scenes story of how water purification for dialysis started in Greece.

2.5. Plastic

Plastic has been the cornerstone of modern Nephrology, which started to flourish on the semi-empirical spread of dialysis. William Kolf experimented on haemodialysis in Nazi-occupied Holland using plastic sausage containers as membranes. With the spread of the method everything became plastic. Packages, haemofilters, tubes, bags, syringes everything was and is plastic. This was unavoidable in era when it was believed that *"plastic would create a world brighter and clearer than any previously known. […] a world free from moth and rust and full of colour […] a world in which man, like a magician makes what he wants for almost every need, out of what is beneath him and around him: coal, water, and air".*[38] Now we know better. Even 20 years after plastic's laudation the multitalented Norman Mailer (1923–2007), who died from renal failure, went to the extremes, crying: *"I sometimes think there is a malign force loose in the universe that is the social equivalent of cancer, and its plastic. It infiltrates everything. It's a metastasis".* Plastic production increased exponentially, from 2.3 million tons in 1950 to 448 million tons by 2015 and is expected to double by 2050. More than eight billion tons of plastic have been produced to date, and every year, about 8 million tons of plastic waste escapes into the oceans from coastal nations taking up to 400 years to degrade. The manufacture, use and disposal of various plastics can pose numerous health risks, including the risk of cancer. Plastics are the culprits for the increase of estrogens in the planet with the consequent effects on males. Apart of their environmental impact, the plastics in dialysis produce polymerizers that circulate in the patient's blood and are to blame for several symptoms. Even when the dialysis waste is burnt, free dioxins are emitted. Industry has responded and more friendly plastics are produced mainly based on plant and non-petroleum by-products. Their real advantage has yet to been proven.[39]

2.6. Conclusions B

From this discussion, it is evident that both sciences, Archaeology and Nephrology are prone to errors, some of them glaring, against the dictum that *"Intelectus est infalibilis"*. But, so what? The astrophysicist Carl Sagan once said: *"That's perfectly all right: it's the aperture to finding out what's right. Science is a self-correcting process".* Unfortunately, it does it very slowly sometimes requiring centuries. Science runs forward better than it does backward; thus, it becomes troublesome to detect other scientists' errors.[40] For lack of time, for emotional persistence in a wrong theory, for lack of knowledge or technical resources or sadly for selfish reasons like building a career, as, Norman Mailer put it nicely: *"The desire for success lubricates secret prostitution in the soul".* Consequently, it is necessary to be hesitant to accept all the old fancy or scientifically clad theories and treatments and this stands true for many new ones not tested by time. However, it is not scientific to reject a priori on scientific grounds something that we have not tested scientifically. "*It pays to keep an open mind, but not so open your brains fall out.*" Carl Sagan again. A middle line of action in scientific research is a wise guideline. However, this may not be feasible in the hot bench of pioneering research where someone has to pursue the goal even in an almost monomaniac way. But Congresses on the History of Science can and should do so. They should resemble post-modern museums. These are not museums which visitors enter like a Temple, to receive a single Truth, Reality, Uniqueness, and accumulation of information for the better identification with an ideal, but museums seen as agoras-places of meeting, discussion and confrontation with different variants of what is perceived as being the truth.[41] In that sense, our XIth IAHN Larissa Congress avoided being purely "scientific". Because, as it has absurdly stated *"Science is the enemy of Truth"* The slogan had been introduced by Paul Feyerabend who attacked science not because he actually believed it was no more valid than astrology or religion; quite the contrary. He attacked science because he recognised science's vast superiority over other modes of knowledge, and he worried that science could become

a totalitarian force. Many people today [increasingly in this COVID-19 era] on hearing that some method is "scientific" do not feel instructed; they feel warned. The term "Scientific" applied to some recommended habit is beginning to have something grotesque about it, as likely to be in opposition to the general conclusions of humankind and our human common sense. In the philosophical field we reason – in the scientific one we understand.[42] In an aphoristic way this was interpreted as *"Art lost its forum, science lost its limits".* In Larissa, we attempted to give a little forum to Art and put a small limit to Science. If we succeeded, the readers of this volume will judge.

ΠΕΡΙΛΗΨΗ

Εισαγωγή: Τα λάθη της Αρχαιολογίας και της Νεφρολογίας

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Σε αυτή την Εισαγωγή των Πρακτικών του 11ου Διεθνούς Συνεδρίου της Διεθνούς Ενώσεως της Ιστορίας της Νεφρολογίας εκτίθενται μερικές γενικότερες σκέψεις που αφορούν στα λάθη της Αρχαιολογίας και της Νεφρολογίας, όπως και των προσπαθειών που έγιναν για να διορθωθούν. Αρχίζοντας από τον ισχυρισμό της Οργανωτικής Επιτροπής ότι η Λάρισα είναι ο τόπος που απέθανε ο Ιπποκράτης και πως εκεί εντοπίσθηκε ο τάφος του, επεκτεινόμεθα στον έλεγχο και των δύο αυτών διεκδικήσεων. Παρουσιάζονται στη συνέχεια δύο μεσαιωνικοί μυθικοί τάφοι του Πατέρα της Ιατρικής, ο ένας σχετιζόμενος με την Capsula Eburnea και ο άλλος με τον θρύλο του Ιερού Δισκοπότηρου. Εντοπίζονται ομοιότητες με τους εξ ίσου μυθικούς τάφους του Πλάτωνος και του Ερμή Τρισμέγιστου. Παρουσιάζονται κατόπιν παραδείγματα από τα ιστορικά λάθη της Νεφρολογίας που αφορούν στην αφαίμαξη, την χρήση του υδραργύρου, του αρσενικού και του αλουμινίου, όπως και την εκτεταμένη χρήση πλαστικών. Όλα αυτά τα υλικά και οι μέθοδοι είχαν ζωηρά επευφημηθεί όταν πρωτοπαρουσιάσθηκαν και χρειάστηκαν πολλά έτη – μερικές φορές χιλιετίες – ώστε να αναγνωρισθούν οι βλαπτικές επιπτώσεις που είχαν στους νεφρούς και να σημειωθούν βήματα για τον περιορισμό τους. Με μια απολογητική διάθεση προσπαθήσαμε να δικαιολογήσουμε την πίστη των υποστηρικτών τους και να προτείνουμε μια πολύ προσεκτική προσέγγιση των ισχυρισμών για «θαυματουργικές» θεραπείες του παρελθόντος αλλά και του παρόντος. Η ευφυΐα και η επιστήμη δεν είναι πάντα αλάθητες. Η κοινή λογική, η τέχνη και η εν τω βάθει μελέτη θα πρέπει να είναι η λυδία λίθος κάθε Συνεδρίου που ασχολείται με την Ιστορία της Επιστήμης.

Λέξεις ευρετηρίου: Capsula Eburnea, Λάθη Αρχαιολογίας, Λάθη Νεφρολογίας, Σεληνιακή βιβλιοθήκη, Σμαραγδένοι πίνακες Τρισμέγιστου, Τάφος Ιπποκράτη, Τάφος Πλάτωνος

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BIOGRAPHY
ΒΙΟΓΡΑΦΙΑ

In memoriam
Charles Raymond Pax George (1940–2019)

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ΑΡΧΕΙΑ ΕΛΛΗΝΙΚΗΣ ΙΑΤΡΙΚΗΣ 2020, 37(Συμπλ 2):20–21

J.S. Cameron

Kings College, London, UK

Εις μνήμην:
Charles Raymond Pax George
(1940–2019)

Περίληψη στο τέλος του άρθρου

Key words

Aboriginals renal failure
Charles Raymond Pax George
Concord Hospital in Sydney
John Jacob Abel
Killora Australia

The International Association for the History of Nephrology (IAHN) has lost one of its leading members in the field of the history of nephrology: Charles George. He died in London shortly after attending the IAHN meeting in Larissa last September, during emergency surgery to treat active bacterial endocarditis. Just a few days previously, he had been awarded the fellowship of the Royal College of Physicians of London, and a few of us had the pleasure of dining with him and Elizabeth in the College. He is –and long will be–much missed.

Charles was born in Killora, NSW, Australia and attended school and university in Sydney, graduating in 1966 and being awarded FRACP in 1975. He began work in nephrology almost by accident, and never stopped. He worked in Seattle with haemodialysis pioneer Belding Scribner, then at Guys with myself and Chisholm Ogg in London, doing research on platelet physiology in renal disease. He went back to a post in the Concord Hospital in Sydney in 1973, where he spent his working life there as a renal physician.

Charles set up a haemodialysis unit and a transplant programme. He realised the special needs of Aboriginal Australians, in whom renal failure is so common, pioneering the use of the disposable dialysis REDY unit for use in often primitive outback dwellings, where water was in short supply.

Early on, he developed an interest in medical history which naturally focussed on nephrology. He was a meticulous researcher, chasing down obscure references and delighting in original notebooks and documents. He also favoured original and sometimes controversial conclusions to his work. He obtained a degree in history in the 1995 for a critical look at the work of John Jacob Abel, and later achieved a PhD. He was the only member of the IAHN with a degree also in History. He delighted in words and language, and assembled an impressive bibliography. He became a President of the IAHN having been a founder member in 1994. He assembled an impressive collection of old books dealing with nephrology, which visitors could trawl through.

He was excellent company, and always up for an argument or a discussion, the two blending effortlessly, but thoughtful and balanced. A brief essay into politics was not however successful. In his later years, he spent half of his time in Oxford in England, a country of which he was now also a citizen.

He was accompanied at many IAHN meetings by his wife Elizabeth, née Gordon, whose company we all enjoyed. He is survived by her, two sons and two daughters.

ΠΕΡΙΛΗΨΗ

Εις μνήμην: Charles Raymond Pax George (1940–2019)

J.S. CAMERON

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Αρχεία Ελληνικής Ιατρικής 2020, 37(Συμπλ 2):20–21

Η Διεθνής Ένωσις της Ιστορίας της Νεφρολογίας (IAHN) απώλεσε ένα από τα ηγετικά στελέχη της. Ο Charles George απεβίωσε στο Λονδίνο τον Σεπτέμβριο του 2019 μετά από εγχείρηση για σταφυλοκοκκική ενδοκαρδίτιδα έχοντας μόλις μεταβεί εκεί από τη Λάρισα όπου συμμετείχε ενεργώς, όπως πάντα, στο XI International Congress of ISHN. Ο Charles γεννήθηκε στο Killora της βορειοδυτικής Αυστραλίας και αποφοίτησε από την Ιατρική Σχολή του Πανεπιστημίου του Σύδνεϋ. Μετά από μακροχρόνια μετεκπαίδευση στο Σιάτλ και το Λονδίνο επιστρέφει το 1973 στο Νοσοκομείο Concord του Σύδνεϋ όπου εργάσθηκε για το υπόλοιπο της ενεργούς ιατρικής σταδιοδρομίας του. Οργάνωσε ένα μεγάλο πρόγραμμα αιμοκάθαρσης και μεταμόσχευσης με ιδιαίτερη έμφαση στις μεγάλες ανάγκες των Αβοριγανών λόγω των κακών συνθηκών υγιεινής στις κοινότητές τους. Από νωρίς ενδιαφέρθηκε για την Ιστορία και ήταν το μόνο μέλος της IAHN με διδακτορικό στο αντίστοιχο αντικείμενο. Το πάθος του ήταν η γλωσσολογία και η συλλογή σπάνιων βιβλίων. Συμμετείχε ενεργά στις δραστηριότητες της IAHN, της οποίας διετέλεσε και Πρόεδρος. Ήταν εξαίρετος ομιλητής και πάντα με χαρά τον συναντούσαμε μαζί με τη σύζυγό του Elizabeth. Θα μας λείψει και τώρα και στο μέλλον.

Λέξεις ευρετηρίου: Αβοριγανοί, νεφρική νόσος, Charles Raymond Pax George, John Jacob Abel, Killora Αυστραλίας, Νοσοκομείο Concord, Σύδνεϋ

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BIOGRAPHY
ΒΙΟΓΡΑΦΙΑ

Professor Miroslav Mydlík, MD, DSc. (1932–2018†) A scientist

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ΑΡΧΕΙΑ ΕΛΛΗΝΙΚΗΣ ΙΑΤΡΙΚΗΣ 2020, 37(Συμπλ 2):22–28

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Καθηγητής Miroslav Mydlík, MD, DSc. (*1932 – †2018) – Ένας επιστήμονας

Περίληψη στο τέλος του άρθρου

Professor Miroslav Mydlík MD, DSc. was one of the most important pioneers in the field of nephrology in Central Europe during the second half of the 20th century. He was very active as a physician, scientist, internist and nephrologist, especially in the field of renal replacement therapy in patients suffering from acute or chronic renal failure and with acute poisonings. He was a founder of a Dialysis Centre at the First –now Fourth– Internal Clinic of the University Hospital of L. Pasteur in Košice. He carried out the first haemoperfusion through active charcoal in the former state of Czechoslovakia (1977). He was one of those clinical scientists who raised Slovak nephrology to international level.

Key words

Acute and chronic renal failure
Haemoperfusion
Miroslav Mydlík
Renal replacement therapy Slovakia

1. INTRODUCTION

Professor Miroslav Mydlík, MD, DSc. was one of the leading medical personalities of Central Europe during the second half of the 20th and early 21st century. As an internist and nephrologist, he devoted all his life to his work, influencing the development of medicine in the state of Czechoslovakia and the Republic of Slovakia.[1–9]

Professor Mydlík (fig. 1) was born on 21 July 1932 in Košice, then in Czechoslovakia, and died on 6 September 2018 in Košice, now in Slovakia. After finishing high school at the 1st State Gymnasium in Košice in 1951, he started his medical studies and successfully graduated from the Medical Faculty of Charles University (MF-CU) in Prague, in 1957.

After graduation, he began working as a house physician at the Department of Infectious Diseases of the Faculty Hospital of the Regional Institute of National Health (KÚNZ) in Košice. In December 1959, he was appointed house physician at the Internal Clinic of the Faculty Hospital KÚNZ in Košice.

Figure 1. Professor Miroslav Mydlík, MD, DSc. (1932–2018).

2. POSTGRADUATE EDUCATION

He successfully passed the 1st degree (1961) and 2nd degree attestation in internal medicine in 1964. From 1964 to 1979, he worked as an Assistant Professor at the First Internal Clinic [later renamed as Fourth Internal Clinic of the Medical Faculty of P.J. Šafárik University (UPJŠ)]. From 1972 to 1975, he was a leading teacher to undergraduate

students of the UPJŠ Medical Faculty. In 1971, he successfully defended his PhD thesis in clinical nephrology and, in 1973 he passed his specialisation in nephrology, the first person in Slovakia to do so. In 1984, he successfully defended his academic title of Doctor of Medical Sciences at the MF-CU in Prague. Due to the political situation at the UPJŠ Medical Faculty, he only became Associate Professor of Internal Medicine in 1990. In 1992, he was appointed Full Professor of Internal Medicine by the President of the Czechoslovak Republic Václav Havel. In 2004, he became Professor Emeritus at the UPJŠ.

3. POSITIONS COVERED

Professor Mydlík was an Assistant Professor at the First Internal Clinic of the UPJŠ Medical Faculty and Head of the Dialysis Centre from 1964 to 1979. From 1979 to April 1992, he worked as a nephrology registrar while serving as Head of the Dialysis Centre of the Fourth Internal Clinic at Faculty Hospital, subsequently renamed Faculty Hospital of Louis Pasteur (FHLP) in 1993, and currently University Hospital of Louis Pasteur (UHLP). He was Head of the Fourth Internal Clinic (1992–1997); founder and Head of the Nephrology Clinic (1997–2003). He served as UPJŠ vice-rector for international relations (1994–1997); Head of the Subchair of Nephrology and Dialysis of the Postgraduate School of Medicine in Bratislava (1991–2003)**;** President of the Medical Association in Košice (1990–2002); and principal expert for nephrology of the Ministry of Health of the Slovak Republic (1994–2007).

4. CLINICAL ACTIVITIES

In 1963, Mydlík performed the first percutaneous renal biopsy and in January 1966 he founded a Dialysis Centre at the First Internal Clinic. He was also one of the founders of the Nephrology Section of the Slovak Internal Society (1969). He carried out the first haemoperfusion through active charcoal in the former Czechoslovakia (1977) in a patient suffering from paraquat poisoning.[10] He enhanced and advanced the quality of the Dialysis Centre (1970–1990) and gradually introduced additional extracorporeal elimination methods and CAPD, which are still used in various dialysis centres.[11]

He was interested in improving the Nephrological Laboratory of the First later the Fourth Internal Clinic and Nephrology Clinic. From 1969 to 2008, many special biochemical laboratory methods were introduced under the leadership of Eng. Katarína Derzsiová. On 24 October 1997, thanks to Professor Mydlík's initiative, the Nephrology Clinic of FHLP and of the UPJŠ Medical Faculty was established, the first of its kind in Slovakia. Due to conditions prevailing at that time, most dialysis centres were privatised, including the Nephrology Clinic in 2006.

Professor Mydlík, as the former Head of the Dialysis Unit and Head of the Fourth Internal Clinic and Nephrology Clinic of the Medical Faculty of UPJŠ and FHLP, conducted important clinical studies on over 1,300 patients who underwent renal biopsy,[12] 1,500 patients who underwent renal replacement therapy, 380 patients with acute poisonings[13] and 229 patients with acute renal failure.[14]

5. RESULT OF HIS ACTIVITIES

As President of the Medical Association in Košice, Professor Mydlík organised 12 East-Slovakian Medical Days in Nový Smokovec, the High Tatras. From 1994 to 2018, he organised 25 memorials named after his teacher Professor František Pór, MD, who was a founder of the 1st Internal Clinic of the UPJŠ Medical Faculty and of the Faculty Hospital in Košice (1948). Professor Pór was Head of the First Internal Clinic from 1948 to 1971. Professor Mydlík prepared the program of the 25th memorial, but he did not participate as he was ill. From 1995 to 2017, he also organised 23 scientific meetings in cooperation with the Medical Association of Košice for general practitioners. Most of the meetings were held in Ruskov, near Košice. As a Board member of the Slovak Nephrological Society, he organised many National Nephrological Congresses and International Nephrological Symposiums.

As the leading Nephrology expert of the Slovak Republic's Ministry of Health, he developed a network of new dialysis centres to provide evenly covered services throughout Slovakia.

As the Head of the Subchair of Nephrology and Dialysis of the Postgraduate School of Medicine, he continuously performed undergraduate and postgraduate educational activities. He trained numerous physicians, nephrologists and enabled them to perform attestation examinations in nephrology. For many years, he was chairman of the Attestation Committee.

6. SCIENTIFIC ACTIVITIES

Professor Mydlík's studies were focused on internal medicine and nephrology and also on clinical biochemistry, to which he devoted his entire active life.

The main topics of his research were: "Metabolic changes in chronic renal failure (CRF)", "Metabolic disorders of some vitamins in CRF", "Vitamin B_6 and oxalate as uremic toxin", "Haemoperfusion in acute poisoning *in vivo* and *in vitro* and acute intermittent porphyria". In addition to these and in cooperation with Eng. Katarína Derzsiová, he studied renal function after long-term runs, the results of which were important for sports physicians and were presented at several national and international congresses and published in regional and international journals.[15–21]

He published over 450 scientific papers in regional and foreign journals and over 790 presentations at domestic and international congresses in Europe, the USA and Asia. Professor Mydlík's first publication was in 1961, in the journal *"Vnitřní lékařství"*, which remained one of his favourite journals. February 2012 marked 50 years since his first publication in this journal. Up to 2012, he had contributed 105 articles to this journal.[22] Most of the original papers had a clinical-biochemical focus and were researched at the Nephrological Laboratory.

He was also a co-author of the first Slovak monograph in nephrology: *Dzúrik R, Šašinka M, Mydlík, Kovács L et al.:* ***Nephrology****. Bratislava, Herba, Ltd. 2004, 877 p,* (fig. 2). Together with Professor Julius Vajó, MD, DSc., they were editors of a very important book: *Mydlík M, Vajó (Eds.).* ***History of the University Hospital of Louis Pasteur in Košice,*** Edit. UPJŠ in Košice, 470 p (2013), (fig. 3).

Since 1993, Professor Mydlík, in cooperation with the Medical School, initiated the awarding the honorary title of "Doctor Honoris Causa" (DHC) of UPJŠ in Košice to seven outstanding professors of nephrology from Europe and the USA: Shaul G. Massry (1993, USA), Joel D. Kopple (1995, USA), Horst Klinkmann (1997, Germany), Franciszek Kokot (1997, Poland), Natale G. De Santo (1999, Italy), Guido Bellinghieri (2000, Italy) and Vittorio Bonomini (2006, Italy), (fig. 4). All these awardees were also visiting professors at the UPJŠ Medical School in Košice. The day after the award of the degree, an International Symposium on Nephrology was held on "Metabolic changes in chronic renal failure" (six after DHC, three on the occasion of the anniversary of Professor Mydlík, and one in memory of Professor Válek).[23]

7. TEACHERS WHO DIRECTED HIM TO NEPHROLOGY

7.1. Professor František Pór, MD

Professor František Pór, MD, his teacher and superior

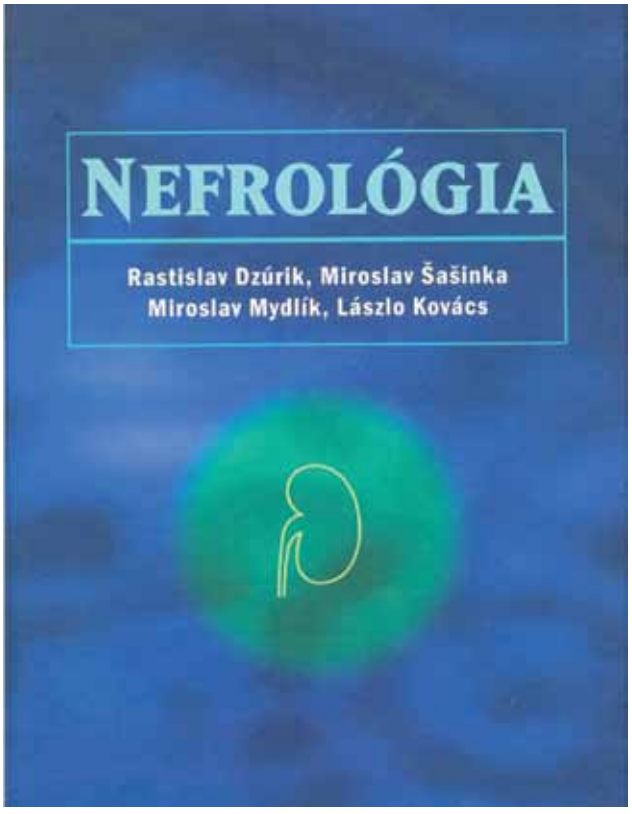

Figure 2. Dzúrik R, Šašinka M, Mydlík M, Kovács L et al. Nephrology 2004.

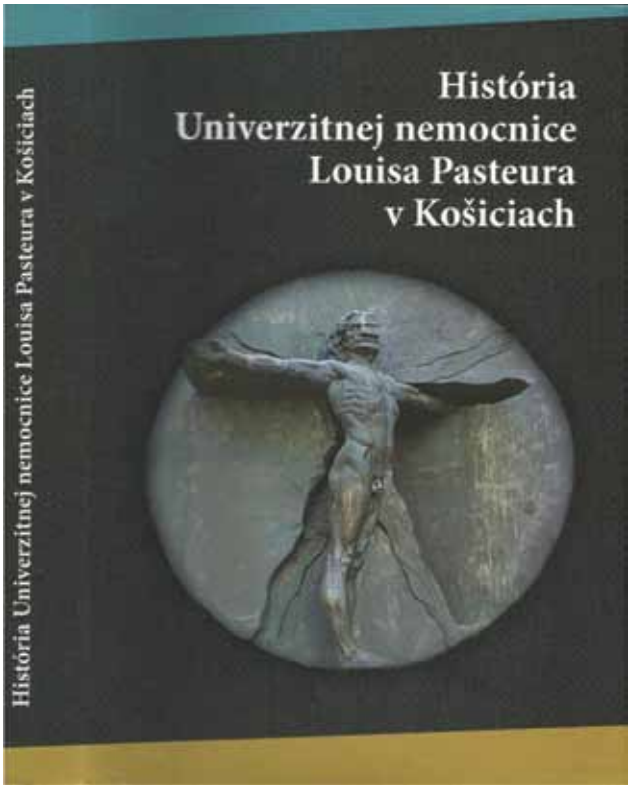

Figure 3. Mydlík M, Vajó J (eds) History of the University Hospital of Louis Pasteur in Košice, 2013.

Figure 4. Doctors Honoris Causa of UPJŠ, Košice.

was one of the most remarkable physicians in Czechoslovakia. Professor Mydlík gave a lecture on his work: "Professor František Pór – an Outstanding Internist from Former Czechoslovakia" at the 43rd Congress of the International Society for the History of Medicine, in Abbano-Terme, Italy, 2012.[24]

7.2. Professor Jan Brod, MD, DSc.

Professor Jan Brod, MD, DSc. was one of the greatest nephrologists and cardiologists who worked in Prague and other places worldwide. Professor Mydlík gave lectures on his work: *"Jan Brod and his contribution to hypertension and nephrology"* at the 7th Congress of the International Association for the History of Nephrology (IAHN) in Torun, Poland, 2010 and *"The kidneys" by Jan Brod: the impact of the textbook on nephrology"* at the 8th IAHN Congress in Ancient Olympia-Patras, Greece, 2013.[25,26] In Prague, Mydlík learned the kidney biopsy procedures under the supervision of Professor Brod, which he immediately adopted in Košice upon his return.[12] He also actively participated in a research project on "The measurement of blood pressure by direct and indirect methods", published in 1966.[27]

8. POSITIONS IN SCIENTIFIC SOCIETIES

Professor Mydlík was a Board Member of the Slovak Nephrological Society (1969–2007); a member of the European Renal Association-European Dialysis and Transplantation Association, a member of the European Society for Artificial Organs, and a member of the International Society for Artificial Organs. He was an Honorary Member of the Polish Society of Nephrology (1995), the Slovak Medical Society (1997), the Czech Society of Nephrology (2002), the Slovak Society of Nephrology (2007), the Slovak Society of Internal Medicine (2012) and an Honorary Member of the Czech Medical Society (2009). He was a Council member of the International Association for the History of Nephrology (2010–2015). In September 2016, Professor Mydlík contributed to the foundation of the European Association

of Professors Emeriti (EAPE) in Athens, where he gave a talk and was elected to the Council at Large of the newly founded association.

9. LAST YEARS

After his retirement on 31 August 2003, he did not stop working. He started working in a non-state dialysis centre and in the outpatient nephrological department of Nephron Ltd. until December 2007. He continued to work one day a week up to December 2017 at an internal-nephrological outpatient department at the 4th Internal Clinic, UHLP and as a scientific contributor to the Institute of Experimental Medicine, UPJŠ Medical School. He also continued to give lectures to Slovak and foreign university medical students. From 2010 to 2017, Professor Mydlík was a promoter of "Survival is not enough", an event organised by the Italian Institute for Philosophical Sciences for the World Kidney Day (WKD). He continued to organise a yearly event on WKD in Kežmarok where he was a consultant of the Dialysis Centre Dialcorp Ltd.[28–30]

10. HONOURS

Professor Miroslav Mydlík was a Visiting Professor at the Faculty of Medicine of Bruxelles (Belgium), at the Nephrological Clinic of the Medical University in Katowice (Poland) following an invitation by Professor Franciszek Kokot and at the Moscow Institute of Medicine of the URSS Academy at the invitation of Professor Irina J. Tareieva.

He was awarded many honours, the most important of which were: the Purkyně Medal of the Czechoslovak Medical Society (1979); the International Distinguished Medal of the National Kidney Foundation (USA), (1994), (fig. 5); the University of Messina Medal, Italy (2000); the "Sigillo Magno" Medal of Bologna University (2002); the "Golden Kidney" Medal of the Slovak Nephrological Society (2002); the Campania Sicily Branch Medal of the Italian Society Branch of Nephrology; the Teofil Rudolph Niederland Prize – the highest honour awarded by the Presidium of the Slovak Medical Society, as the highest prize to a top specialist (only one scientist per year) for his long-term significant scientific and professional activities in medicine (Bratislava, 2009); the UPJŠ Gold Medal, Košice (2009); "The Lifelong Contribution Award for Medical and Biological Sciences" awarded by the Board of the Literary Fund of the Slovak Republic (2014); **On 8 December 2015, he was admitted to the "Hall of Glory of Slovak Medicine"** in Bratislava, for outstanding results in his lifelong professional scientific and pedagogical work, for the successful representation of Slovak medicine at home and abroad and for his significant contribution to the development of continuing education healthcare workers and the Slovak Medical Society.

Figure 5. Professor Mydlík was awarded the International Distinguished Medal of the National Kidney Foundation (USA), (1994).

On 27 September 2018, at the Meeting of the Scientific Council of the Medical Faculty of UPJŠ, on the occasion of the 70th anniversary of its foundation, Professor Miroslav Mydlík was awarded a medal in memoriam. The medal was received by Eng. Katarína Derzsiová.

11. OTHER INTERESTS AND ACTIVITIES

He was interested in world literature, fine arts, theatre, classical music, the history of Egypt, Greece and Italy and the history of medicine, mainly the history of nephrology. Since 2003 to 2017 he regularly attended the IAHN congresses mostly as an active participant. His lifelong literary interests were the works of Franz Kafka. Since 1963, when he became acquainted with Kafka's work in an article in "World literature", he started considering the idea of creating a monument to the Prague-born German writer Franz Kafka in the High Tatras. Kafka had been treated for lung tuberculosis in Tatranské Matliare from 18 December 1920 to 27 August 1921. Professor Mydlík achieved this dream on 16 May 2001, when a monument of Franz Kafka was unveiled in Tatranské Matliare and the 1st International Medical and Literary Symposium, dedicated to the writer, took place there. Professor Mydlík organised eight International Medical-Literary Symposiums dedicated to Kafka (2001–2014), in the High Tatras. The last Franz Kafka Medical and Literary Memorial was held in Kežmarok (2017), on

the occasion of the release of a book by Miroslav Mydlík and Katarína Derzsiová entitled *Lung tuberculosis of Franz Kafka. The influence of disease on his literary work*. Events were scheduled for the release of the book at the UPJŠ Historical Hall in Kosice and at the Franz Kafka Centre in Prague but were not held in the end.

12. CONCLUSIONS

Professor Miroslav Mydlík, MD, DSc. will be remembered forever, not only as an extraordinary internist and nephrologist, a propagator of Czechoslovak and Slovak nephrology but also as a good and close friend of many Slovak and Czech nephrologists and also of many outstanding foreign nephrologists. He left a historical impact on the international medical and scientific community. His impact in the field of nephrology in Slovakia was significant. He was a scientist, a teacher, a clinician – "a great professor", and a man.

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ΠΕΡΙΛΗΨΗ

Καθηγητής Miroslav Mydlík, MD, DSc. (*1932 – †2018) – Ένας επιστήμονας

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Αρχεία Ελληνικής Ιατρικής 2020, 37(Συμπλ 2):22–28

Ο καθηγητής Miroslav Mydlík, MD, DSc. ήταν ένας από τους σημαντικότερους πρωτοπόρους στον τομέα της Νεφρολογίας στην Κεντρική Ευρώπη κατά το δεύτερο μισό του 20ού αιώνα. Ήταν πολύ δραστήριος ως γιατρός, επιστήμονας, παθολόγος και νεφρολόγος, ειδικά στον τομέα της θεραπείας υποκατάστασης της νεφρικής λειτουργίας σε ασθενείς που πάσχουν από οξεία ή χρόνια νεφρική ανεπάρκεια και με οξείες δηλητηριάσεις. Ήταν ιδρυτής του Κέντρου Αιμοκάθαρσης στην 1η –τώρα 4η– Παθολογική Κλινική του Πανεπιστημιακού Νοσοκομείου L. Pasteur στο Košice. Διεξήγαγε την πρώτη αιμοπροσρόφηση μέσω ενεργού άνθρακα στην πρώην Τσεχοσλοβακία (1977). Ήταν ένας από τους κλινικούς επιστήμονες που ανύψωσε τη σλοβακική Νεφρολογία σε διεθνές επίπεδο.

Λέξεις ευρετηρίου: Αιμοπροσρόφηση, Θεραπεία υποκατάστασης νεφρικής λειτουργίας Σλοβακία, Miroslav Mydlík, Οξεία και χρόνια νεφρική ανεπάρκεια

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BIOGRAPHY
ΒΙΟΓΡΑΦΙΑ

Dimitris Oreopoulos, my father

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ΑΡΧΕΙΑ ΕΛΛΗΝΙΚΗΣ ΙΑΤΡΙΚΗΣ 2020, 37(Συμπλ 2):29

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Δημήτρης Ωραιόπουλος,
ο πατέρας μου

Περίληψη στο τέλος του άρθρου

Dimitrios Oreopoulos is best known for his innovations and contributions to the field of peritoneal dialysis. As his daughter, however, I have a different perspective on my father's greatest legacy, which I believe is love, faith, fearlessness and passion.

I have created a video that shares my experience of our father-daughter relationship, his role as a teacher and colleague to many around the world in the nephrology community, his belief in the necessity of compassion and connection during the delivery of medical care and his views on Christianity.[1]

My father was my friend, mentor, and the greatest humanitarian I have ever known. My childhood is filled with good memories of foreign trainees at our home for Christmas and Thanksgiving dinners so they would not be alone for the holidays. I often witnessed my father give money to individuals in need, charities, and the Church. He maintained a corporate account that was used to help patients pay for medication or rent when they could not afford it.

My father taught me that words and ideas can change the world; he wrote letters to the Prime Minister, Steve Jobs of Apple, and Members of Canadian Parliament when he had a concern or a commendation, and was unafraid of failure or large problems that needed to be solved. He was able to create the first Greek School for children and the first Greek nursing home in Toronto, Canada, wrote a children's book and founded a medical journal that promoted the restoration of humane medicine. Always modest about his impressive accomplishments, he never strived to impress others.

One of the qualities I admired most about my father was that he could have a meaningful conversation with anyone no matter the race, age, religion or cultural background. He always found something to connect with people on. He made others feel loved and respected through being genuinely interested in their story, without passing judgment. My father's efforts in his own spiritual journey and his faith in the belief that there is always good to be found in any situation were also a part of his legacy that had a lasting impact on me.

ΠΕΡΙΛΗΨΗ

Δημήτρης Ωραιόπουλος, ο πατέρας μου

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BIOGRAPHY
ΒΙΟΓΡΑΦΙΑ

Dr Richard Bright
A reminder from a family link

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ΑΡΧΕΙΑ ΕΛΛΗΝΙΚΗΣ ΙΑΤΡΙΚΗΣ 2020, 37(Συμπλ 2):30–32

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Dr Richard Bright
Μια υπενθύμιση από έναν οικογενειακό δεσμό

Περίληψη στο τέλος του άρθρου

Key words

Bright's Descendant
Richard Bright
The Inner Circle WW2
Winston Churchill

Bright, born in 1789, studied Medicine at Edinburgh and Guy's Hospital. He became interested in pathology and used his artistic skills to draw organs post mortem, including a "granular kidney". He believed that "dropsy" was related to kidney malfunction-the patient with granular kidneys had died from dropsy. He published 23 cases with dropsy, most with renal failure; 17 died. Autopsies showed nephritis and the term Bright's Disease was adopted. In 1851, Bright developed aortic stenosis and later died, unexpectedly, in 1858. *What prompted this reminder of Bright?* A 94-year-old lady attended my renal clinic. She introduced herself as a descendant of Bright. She had renal impairment. Subsequently she showed me a book she had authored – "The Inner Circle. A view of war at the top" – an account of her work, among much else, in the underground Cabinet War Rooms in London. Churchill spent much time there. There, she reorganised records of war events for battle leaders to update themselves when in London. She also administered domestic and technical arrangements when Churchill travelled to war conferences attended by Roosevelt and Stalin. She died aged 98, her renal function stable.

Dr Richard Bright is one of the outstanding figures in the history of nephrology. Born in 1789, he grew up in a small village, Ham Green, south-west of the city of Bristol. As a schoolboy, his father once wrote of him, to his teacher, "although he may never show great brilliance or genius, yet he will make a respectable figure in any profession"! How wrong can fathers be? In his teens, Bright decided that medicine was the career for him, though his father had a low opinion of the profession. He studied in Edinburgh and then at Guy's Hospital. As a student, he was said to have "taught himself to smell, to listen and to feel with his hands". He always wanted to be a physician and was apprenticed to a long-standing and much revered Guy's physician, Dr Babington. Bright developed a strong interest in pathology, thanks mainly to another teacher at Guy's, Dr Astley Cooper. He studied every organ in detail *in vitro* and frequently used his not-inconsiderable artistic skills to record the post-mortem appearances. In 1811, he first drew *"a granular kidney"*. He qualified in September 1813. In 1816/1817, he worked in an isolation hospital but contracted typhus complicated by pneumonia. The illness and convalescence occupied most of 1817. His father came to London and Bright visited him regularly at his hotel. Here he met friends of his father including Isambard Kingdom Brunel, the renowned engineer, later to become his patient.

Bright always felt it mandatory to illicit physical signs at the bedside and later, if appropriate, relate his findings to changes found at autopsy. He applied this approach to the condition known as "dropsy"–excess fluid retention– and believed it to be linked to kidney malfunction. The patient whose granular kidneys he had drawn as a student had died of dropsy. On a visit to Paris he met Dr Pierre Rayer, who was first to write of "la maladie de Bright"– *Bright's disease*.

In 1820, Bright became assistant physician at Guy's and in 1824 full physician and lecturer.

His teaching methods were often criticised by colleagues. He actually undressed his patients to examine them! He used the "suspect method of percussion" and outlandishly used a stethoscope, referred to by some as "a foolish toy"! He taught the importance of analysing all types of patients' specimens. Urine samples had to be tested for the presence of albumin by heating a spoonful of urine over a candle and observing whether it became opaque before it boiled.

In 1827, he published 23 cases, most having "renal insufficiency dropsy". Seventeen died. Each case was illustrated by his own, hand-coloured, meticulous drawings of the pathological material. Three of the original kidney specimens remain in Guy's museum. His work was met

with a mixed response. One group believed, since the cases were from Southwark –a poverty-stricken area of south London– that the disease affected only the poorer classes. But by 1829 Bright's disease was recognised to affect all strata of society.

In 1832, he was elected Fellow of the Royal College of Physicians and the next year chosen to give the three Goulstonian Lectures. The final lecture was on the renal origins of dropsy. It included reports of 296 urine analyses. He described 4 varieties of nephritis found at post-mortem; blood urea levels were high and often associated with a history of convulsions and left ventricular hypertrophy. He later showed that following scarlet fever, proteinuria and kidney damage could occur, i.e. acute, post-streptococcal nephritis as we know it today. Treatment included diet and bed rest. How little things have changed!

In 1851, Bright self-diagnosed aortic valve disease. He developed oedema and some thought him to be suffering from his own disease because he concealed the cardiac condition. But he continued seeing patients, among them royalty, Alfred Lord Tennyson, the renowned poet and Isambard Brunel whom he had met through his father. Brunel had ankle oedema and loin pain; Bright diagnosed renal failure. Brunel died of a stroke and renal failure in 1859 aged 53 but Bright had died some months earlier. His death was unexpected. The Times obituary stated "The lamented gentleman had received patients and was out in his carriage on Saturday 11th December, after which he complained of indisposition and retired to his chamber, which he was destined never to leave again." *The Lancet* editor, Dr Thomas Wakely, who had often been scathing, sometimes personally so, about Bright and his work, surprisingly wrote a glowing testimony: "…the medical profession has lost one of the most original, observant and philosophical minds…he contributed more than, perhaps, any other to form the medical opinion of his day". Bright had had a gastro-intestinal haemorrhage and died on 16th December 1858 aged 69.

What then reminded me of Richard Bright"?

During a renal clinic, before I retired, I called for a new patient. An elderly lady, tall and upright, came into the room and shook my hand firmly. "Before we begin, Dr Phillips, you may be interested to know that I am one of the living descendants of Dr Richard Bright". The patient, who turned out to be a great-great niece of Bright, had moderate renal impairment, but she was 94 years old! Her creatinine was 140 umoL/L. She was normotensive and an ultrasound scan was normal. I reassured her that there was nothing of great concern. She replied "I don't mind what you do as long as you don't stop my two brandies and soda that I have each evening after supper"! Three years later the patient invited me to lunch and afterwards showed me a book she had written entitled *"The Inner Circle. A view of war at the top".* Amongst many other stories, it told of her appointment to develop an information system in the Cabinet War Rooms housed under Whitehall in Central London-Winston Churchill's main work base during the Second World War. Her boss was General Ismay, Chief of Staff to Churchill. The rooms were visited frequently by allied military leaders from around the world. The information system enabled them quickly to get up-to-date with news from different theatres of war. Her second role was to organise the domestic and technical requirements of the British contingents attending major conferences such as in Teheran, Yalta, Moscow and Potsdam. She had contact with allied political leaders including Churchill, Roosevelt and Stalin. In her book, she recalls an event in Teheran at a dinner celebrating Churchill's 69th birthday. A Persian waiter carried in a large, elaborate ice cream dessert. He could not take his eyes off Stalin. The ice cream started to slide off its tray. Still not noticing, he headed towards the leaders. The dessert slid onto the head of the Russian interpreter next to Stalin, who continued without pause! So, my reminder of Richard Bright stemmed from meeting his great, great niece-a wonderful character from an amazing family. Her renal function remained stable. She died aged 98.

The following is a poem about Richard Bright for the St Bartholomew's Hospital Journal:

Dr Richard Bright of Guy's had several patients large in size.
Their legs were swollen as could be, their eyes so puffed they could not see.
To this oedema Bright objected and so, he had them venesected.
He took a teaspoon by the handle, held it above a tallow candle
And boiled some urine o'er the flame (as you or I might do the same).
To his surprise, we find it stated, the urine was coagulated.
Alas, his dropsied patients died. The thoughtful doctor looked inside.
He found their kidneys large and white, the capsules were adherent quite.
So that is why the name of Bright is associated with nephritis.

Anon

ΠΕΡΙΛΗΨΗ

Δρ Richard Bright – Μια υπενθύμιση από έναν οικογενειακό δεσμό

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Αρχεία Ελληνικής Ιατρικής 2020, 37(Συμπλ 2):30–32

Ο Bright γεννήθηκε το 1789 και σπούδασε Ιατρική στο Εδιμβούργο και στο Guy's Hospital. Ανέπτυξε ενδιαφέρον για την παθολογική ανατομική και χρησιμοποίησε τις καλλιτεχνικές δεξιότητές του για να σχεδιάσει όργανα, κατά τη νεκροτομή, συμπεριλαμβανομένου ενός «κοκκώδους νεφρού». Πίστευε ότι η «υδρωπικία» σχετιζόταν με τη νεφρική δυσλειτουργία – ο ασθενής με κοκκώδεις νεφρούς είχε πεθάνει λόγω υδρωπικίας. Δημοσίευσε 23 περιπτώσεις υδρωπικίας, οι περισσότερες εκ των οποίων με νεφρική ανεπάρκεια. 17 εξ αυτών απεβίωσαν. Οι νεκροψίες ανέδειξαν νεφρίτιδα και υιοθετήθηκε ο όρος Νόσος του Bright. Το 1851, ο Bright ανέπτυξε στένωση αορτής και αργότερα, το 1858, πέθανε απροσδόκητα. *Πώς προέκυψε αυτό το άρθρο για τον Bright;* Μία 94χρονη κυρία επισκέφθηκε τη νεφρολογική κλινική μου. Μου συστήθηκε ως απόγονος του Bright. Παρουσίαζε νεφρική ανεπάρκεια. Μου έδειξε ένα βιβλίο που είχε συγγράψει –"The Inner Circle. A view of war at the top"– μία καταγραφή του έργου της, ανάμεσα σε πολλά ακόμη, στους Υπόγειους Πολεμικούς Θαλάμους στο Λονδίνο. Ο Τσώρτσιλ πέρασε πολύ χρόνο εκεί. Εκεί, η ίδια αναδιοργάνωνε τα αρχεία των πολεμικών γεγονότων προς ενημέρωση των αρχηγών του στρατού κατά τη διαμονή τους στο Λονδίνο. Επίσης, διοργάνωνε εγχώρια και τεχνικά θέματα όταν ο Τσόρτσιλ ταξίδευε σε πολεμικές διασκέψεις με τον Ρούσβελτ και τον Στάλιν. Πέθανε σε ηλικία 98 ετών, με σταθερή νεφρική λειτουργία.

Λέξεις ευρετηρίου: Απόγονος Richard Bright, Richard Bright, Υπόγειοι Πολεμικοί Θάλαμοι Λονδίνο ΠΠ2, Winston Churchill

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BIOGRAPHY
ΒΙΟΓΡΑΦΙΑ

Greek giants in Nephrology

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ΑΡΧΕΙΑ ΕΛΛΗΝΙΚΗΣ ΙΑΤΡΙΚΗΣ 2020, 37(Συμπλ 2):33–37

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Έλληνες γίγαντες στη Νεφρολογία

Περίληψη στο τέλος του άρθρου

Key words

Aretaeus
Billis
Hellenic Society of Nephrology
Metaxas
Oreopoulos
Papastamatis
Rufus
Valtis
Vosnides
Yatzidis

Rufus of Ephesus and Aretaeus of Cappadocia (1st–2nd century CE) can be considered as the first Greek "giants" of Nephrology since they are the first exponents of Hippocratic medicine who recognised the specific function of the kidney and described renal diseases. In the modern era, several Greek doctors contributed to the establishment and advancement of Nephrology in Greece. This paper refers only to those who worked in Greece and are no longer alive. Hippocrates Yatzides (1923–2013), one of the founders of EDTA in 1964, is deemed a pioneer of haemodialysis as, in 1965, he used activated uncoated carbon haemoperfusion to treat barbiturate poisoning. Yatzidis's early attempts to establish a national Society of Nephrology, in 1966, were fruitless. Three years later, Sotiris Papastamatis (1912–1979), associate professor of Medicine at the University of Athens and his close friend Dimitrios Valtis (1917–1973), professor of Medicine in the University of Thessaloniki, collaborated in the foundation of the Hellenic Society of Nephrology (HSN). Other departed colleagues noteworthy for their contribution to the advancement of the study of renal diseases and the introduction of chronic haemodialysis in our country are Panos Metaxas (1929–2007) (Valtis's disciple, president of the 8th International Congress of Nephrology held in Athens in 1981), Antonis Billis (1932–2013) (Papastamatis's disciple, president of the 2nd National Congress of Nephrology), and Gregory Vosnides (1943-1996) (Billis's disciple, secretary of the 32nd EDTA-ERA Congress held in Athens in 1995, co-organiser with Spyros Marketos of the 1st International Congress of the History of Nephrology held in Kos in 1996). Further to breaking new ground in the development of Nephrology in our country, these colleagues have served and continue to serve as role models for younger Greek nephrologists.

IN ANCIENT TIMES

In Greek mythology, giants were beings of human appearance but of great size and strength, known for their battle with the Olympian gods. The word is used metaphorically for persons of great ability and influence who act as leaders. In that sense, two Greek doctors who lived in the time of the Roman emperor Trajan (53–117), Rufus from Ephesus – a centre of the medical profession in that time, and Aretaeus from Kappadocia, who practiced in Rome and Alexandria, can be considered as the first Greek "giants" of Nephrology, since they are the first exponents of Hippocratic medicine who recognised the specific function of the kidney and described renal diseases. In particular, in one of his surviving works, entitled Περί των εν κύστει και νεφροίς παθών ("On diseases of the bladder and kidneys"), Rufus describes the location of the kidneys, the ureters and the urethra, and strives to provide a rational explanation of the altered function of the kidneys in disease. For example, he proposes that haematuria is due to a widening of the renal tissue, making blood pass together with urine. He also describes medical signs reminiscent of chronic renal failure (chronic, silent symptoms, resulting in cachexia, lethargus, and generalized oedema) and of diabetes mellitus (heavy polyuria, thirst, emancipation, and death caused by oedema). On the other hand, Aretaeus, in his treatise *De causis et signis acutorum morborum* ("On the causes and symptoms of acute diseases"), was the first to recognise the role of the kidneys in excreting urine while extracting it from the blood. Moreover, in his work *De causis et signis diuturnorum morborum* ("On the causes and symptoms of chronic diseases"), he connects gout with renal disease and diabetes with nephrotic syndrome (diabetes induced dropsy), he repeats earlier descriptions of renal colics and renal infections, and provides a detailed classification of renal stones according to their size, shape, opacity, etc.[1] (fig. 1).

Figure 1. The first two Greek "giants" of Nephrology: Rufus from Ephesus (left) and Aretaeus from Cappadocia.

IN THE MODERN ERA

In the modern era, several Greek doctors contributed to the establishment and advancement of Nephrology in Greece. I will refer only to a few of those who practiced as nephrologists in our country and are no longer alive. As underlined by Professor Garabed Eknoyan "[although] *the study of diseases of the kidney has a long history that can be traced to antiquity* […] *it was in 1960 when the inaugural International Congress of Nephrology convened with the subsequent establishment of the International Society of Nephrology that "nephrology" entered the parlance of medicine*."[2] The Congress, held at Geneva and Evian in September 1960, was organised by five scientific societies (Société de Néphrologie, Scandinavian Society for Kidney Research, American Society for Clinical Investigation, Societa Italiana di Nefrologia, and Renal Association). The International Society of Nephrology (ISN) was created following the Congress in the same year. It was founded thanks to the vision of Professor Jean Hamburger, who became its first president.[3] Three years later, in 1963, the late professor of Internal Medicine at the University of Athens Arkagathos Goutas (1895–1982) sent a letter to some of his colleagues informing them that "on the occasion of the 2nd International Congress of Nephrology to be held this year, ISN decided to publish a list of the members of the National Societies of Nephrology by country and of the researchers on specific Nephrology topics of countries that have not established a relevant scientific society yet", and inviting them to a meeting to jointly decide on the appropriate way to respond to this initiative. The meeting concluded without any decision being made.[4]

In the meantime, during a symposium on acute renal failure held on 2 September 1963 at the lecture theatre of the Royal Free Hospital in London, William Drukker, Stanley Shaldon and David Kerr planned the creation of the European Dialysis and Transplant Association (EDTA)[5] On Thursday, 24 September 1964, some 30 delegates from Belgium, Denmark, UK, France, Germany, Ireland, Italy, Netherlands, Sweden, USA and Greece were invited to a founding meeting at the Queen Wilhelmina Hospital of the University of Amsterdam.[6] Greece was represented by Hippocrates Yatzidis, adjunct professor at the Second Department of Internal Medicine of the Athens Medical School, headed by Professor Goutas. The next day, some 34 papers were presented at the first meeting of the new association. Yatzidis presented his work on the use of activated uncoated carbon haemoperfusion to treat barbiturate poisoning. His full paper was published in French in *Nephron* in the same year.[7] Due to this presentation, which William Drukker credits as "classical",[6] Yatzidis is deemed as a pioneer of haemodialysis. It is interesting to note that in a paper published the following year, Willem Kolff, who is considered the "father of artificial organs", wrote: *"A safe and inexpensive method to treat patients with terminal uremia is urgently needed. We have been stimulated by a report from Doctor H. Yatzidis in Athens, Greece, to look into the possibility of absorbing nitrogenous substances from the blood of uremic patients by hemoperfusion over activated charcoal*…"[7] Yatzidis, therefore, can be acknowledged as the first Greek "giant" of Nephrology in the modern era. It is worth mentioning that Hippocrates Yatzidis (1923–2013) was a principal mentor to Dimitrios Oreopoulos (1936–2012), one of the "giants" of nephrology at an international level, before the latter left Greece to Belfast, at first, and then to Toronto, where he crucially contributed to the evolution and worldwide spread of the method of continuous ambulatory peritoneal dialysis (fig. 2).[8]

Figure 2. Dimitrios Oreopoulos (left) and Hippocrates Yatzidis in October 1990, in Athens.

Yatzidis's early attempts to establish a national Society of Nephrology, in 1966, were fruitless.

Three years later, on 12 September 1969, two more Greek "giants" of Nephrology, Sotiris Papastamatis, adjunct Professor of Medicine at the University of Athens and his close friend Dimitrios Valtis, Professor of Medicine at the University of Thessaloniki, collaborated in the foundation of the Hellenic Society of Nephrology. The founding members were 22, from both Athens and Thessaloniki. Papastamatis was elected as the first president, and Valtis as the first vice-president of the new society.[4] Further to the Hellenic Society of Nephrology, Sotiris Papastamatis (1912–1979) contributed to the foundation of two other major Greek medical societies, which played a key role in the continuing education of Greek doctors: the Society for Medical Studies and the new chapter of the Athens Medical Society, the oldest scientific institution in modern Greece (est. 1835). He was also the first to establish dialysis units in two of the largest hospitals in Athens: the Athens State General Hospital and "Evangelismos" Hospital. Dimitrios Valtis (1917–1973) was professor and chairman of the 1st Department of Internal Medicine at the "AHEPA" University Hospital in Thessaloniki and served as dean of the Medical School of the Aristotelian University of Thessaloniki. Valtis introduced renal replacement treatment in Northern Greece in 1967, and contributed to the first cadaver renal transplantation in Greece, performed by the professor of Surgery Constantine Tountas, at the "AHEPA" hospital, in 1968[9] (fig. 3).

Two other departed colleagues, disciples of the two founders of the Hellenic Society of Nephrology, also merit the designation of "giants" of Nephrology. Panos Metaxas, Valtis's disciple, was a member of the 1st Council of the Hellenic Society of Nephrology and president of the 8th International Congress of Nephrology held in Athens on 7–12 June 1981, with 3,000 participants (fig. 4). He was one of the several Greek nephrologists, including Dimitrios Oreopoulos and Antonios Billis, who were trained at the Belfast City Hospital under Mollie McGeown (1923–2004).

Antonios Billis, Papastamatis's disciple, served as vice-president (1972–1974) of the 2nd Council of the Hellenic Society of Nephrology, presided by professor Valtis, and as president (1974–1976) of the 3rd Council of the Society, and of the 2nd National Congress of Nephrology, held in Athens on 3–5 November 1982. The Nephrology Department of "Evangelismos" hospital in Athens, where he worked as chief, was named after him. Gregory Vosnides, the youngest of the Greek "giants" of nephrology in the modern era, was a fellow of Antonios Billis (fig. 5). He served as presi-

Figure 4. George E. Schreiner, president of the International Society of Nephrology, addressing the opening ceremony of the 8th International Congress of Nephrology at the Herodus Atticus Theater. Panos Metaxas, Congress president, is looking at him.

Figure 3. The founders of the Hellenic Society of Nephrology: Sotiris Papastamatis (left) and Dimitrios Valtis.

Figure 5. Antonios Billis and Gregory Vosnidis (first and last from left to right) at the opening ceremony of the 8th International Congress of Nephrology (Athens, 1981).

dent of the Hellenic Society of Nephrology (1994–1996), and as secretary of the 32nd EDTA-ERA Congress held in Athens on 11–14 June 1995. Furthermore, as president of the Hellenic Society of Nephrology, he contributed, along Spyros Marketos, to the organisation of the 1st International Congress of the History of Nephrology held in Kos on 14–16 October 1996, almost a month before his tragic demise.[10] The Nephrology Department at "Laikon" hospital in Athens was named after him.

CONCLUSIONS

These are our late colleagues who symbolise Greek "giants" of nephrology. Further to breaking new ground in the development of nephrology in our country, these colleagues have served and continue to serve as role models to younger Greek nephrologists. And this attribute should be viewed as one of their most important accomplishments.

ΠΕΡΙΛΗΨΗ

Έλληνες γίγαντες στη Νεφρολογία

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Ως πρώτοι Έλληνες «γίγαντες» της Νεφρολογίας μπορούν να θεωρηθούν ο Ρούφος ο Εφέσιος και ο Αρεταίος ο Καππαδόκης (1ος–2ος αιώνας μ.Χ.), για τον λόγο ότι ήταν οι πρώτοι θιασώτες της Ιπποκρατικής Ιατρικής που αναγνώρισαν την ειδική λειτουργία του νεφρού και περιέγραψαν νεφρικές νόσους. Στη σύγχρονη εποχή, πολλοί Έλληνες γιατροί συνέβαλαν στην εδραίωση και εξέλιξη της Νεφρολογίας στη χώρα μας. Εδώ αναφέρονται μόνο ορισμένοι που εργάστηκαν στην Ελλάδα και δεν βρίσκονται πλέον στη ζωή. Ο Ιπποκράτης Γιατζίδης (1923–2013), ένας από τους ιδρυτές της EDTA το 1964, αναγνωρίζεται ως πρωτοπόρος της αιμοκάθαρσης δοθέντος ότι το 1964, χρησιμοποίησε στήλη ενεργού άνθρακα για την αντιμετώπιση μιας περίπτωσης δηλητηρίασης με βαρβιτουρικά. Οι πρώτες προσπάθειες του Γιατζίδη για την ίδρυση εθνικής Εταιρείας Νεφρολογίας απέβησαν άκαρπες. Τρία χρόνια αργότερα, ο Σωτήρης Παπασταμάτης (1912–1979), υφηγητής τότε του Πανεπιστημίου Αθηνών και ο στενός του φίλος Δημήτριος Βαλτής (1917–1973), καθηγητής Ιατρικής στο Πανεπιστήμιο της Θεσσαλονίκης, συνεργάστηκαν στην ίδρυση της Ελληνικής Νεφρολογικής Εταιρείας. Άλλοι εκλιπόντες συνάδελφοι των οποίων η συμβολή στην προώθηση της έρευνας επί των νεφρικών νόσων και την προαγωγή των μεθόδων αιμοκάθαρσης στη χώρα μας αξίζει να μνημονευθεί είναι ο Πάνος Μεταξάς (1929–2007) (μαθητής του Βαλτή, πρόεδρος του 8ου Διεθνούς Συνεδρίου Νεφρολογίας που διοργανώθηκε το 1981 στην Αθήνα), ο Αντώνης Μπίλλης (1932–2013) (μαθητής του Παπασταμάτη, πρόεδρος του 2ου Πανελλήνιου Συνεδρίου Νεφρολογίας) και ο Γρηγόρης Βοσνίδης (1943–1996) (μαθητής του Μπίλλη, γραμματέας του 32ου Συνεδρίου της EDTA-ERA που έλαβε χώρα στην Αθήνα το 1995 και συνδιοργανωτής με τον Σπύρο Μαρκέτο του 1ου Συνεδρίου της Ιστορίας της Νεφρολογίας, το 1996 στην Κω. Πέραν της συμβολής τους στην καθιέρωση και την εξέλιξη της Νεφρολογίας στη χώρα μας, οι συνάδελφοι αυτοί χρησίμευσαν και εξακολουθούν να χρησιμεύουν ως πρότυπα για μίμηση από τους νεότερους Έλληνες νεφρολόγους.

Λέξεις ευρετηρίου: Αρεταίος, Βαλτής, Βοσνίδης, Γιατζίδης, Ελληνική Νεφρολογική Εταιρεία, Μεταξάς, Μπίλλης, Παπασταμάτης, Ρούφος, Ωραιόπουλος

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BIOGRAPHY
ΒΙΟΓΡΑΦΙΑ

Hippocrates Yatzidis
A great yet humble Greek Professor to remember

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ΑΡΧΕΙΑ ΕΛΛΗΝΙΚΗΣ ΙΑΤΡΙΚΗΣ 2020, 37(Συμπλ 2):38–41

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Ιπποκράτης Γιατζίδης:
Ένας σπουδαίος αλλά παράλληλα ταπεινός Έλληνας καθηγητής που αξίζει να θυμόμαστε

Περίληψη στο τέλος του άρθρου

Professor Hippocrates Yatzidis was the "father of nephrology" in Greece and one of the most pioneering nephrologists worldwide. He was born on 22 September 1923 in Athens and died on 27 August 2013. Passionate about his science, he devoted himself to creating high-profile Nephrology Units and to nephrological research. He was the director of many research units in Greece and other countries and he even took over the management of the Geneva Medical Centre for a while. He always encouraged continuous training for himself and his colleagues so as to keep up with advances and provide the best possible and up-to-date treatment to patients. Yatzidis' charcoal artificial kidney is perhaps his crowning achievement and a major breakthrough in Nephrology worldwide. He published many scientific papers, most of them in international journals, and with many citations. In the early 70s, he co-founded the Nephrology Department of the "Areteion" Hospital of Athens to support patients in need of renal care. In the last period of his life, he continued his research at the experimental surgery laboratory of the Athens Medical School. He was known for his kindness and generosity to his associates. The present article aims to present his life and work achievements.

Key words

Carbon artificial kidney
Professor Yatzidis

Figure 1. Professor Hippocrates Yatzidis.

1. INTRODUCTION

Yatzidis' research work, conducted entirely in Greece, was recognised internationally for its originality and contribution to the establishment of Nephrology as a specialty. The high quality of his research is demonstrated by the publication of his work in international journals such as *"Nature"*, *"Clinical Nephrology"*, *"Experientia"*, *"JAMA"*, the *"British Medical Journal"*, *"Biomedicine"*, *"Nephron"*, *"Kidney International"*, *"Lancet"*, the *"New England Journal of Medicine"*, *"Peritoneal Dialysis International"*, *"Clinical Chemistry"* and others. These have oft been cited by foreign researchers and Yatzidis had received dozens of official invitations from universities and research centres abroad as an invited speaker. He was included in the publication "Two thousand men of achievement" and "Who's who in science from antiquity to the present" as the Founder of Nephrology in Greece and as an Inventor of the Activated Carbon Artificial Kidney, known as "Yatzidis Kidney".

2. EARLY LIFE

Professor Hippocrates Yatzidis was born in Athens on 22

September 1923. He completed his secondary education at the Lycee Leonin French Senior High School in Athens. He started his studies at the Medical School of Athens in 1943 but, due to the Civil War, stopped in 1947 to do his military service. After three years in the army, he continued his studies in 1950. He graduated in October 1950 and was immediately hired as an external assistant to specialise in the Second Internal Medicine Clinic of the University "Hippokrateio" Hospital of Athens. After two months, he was appointed internal assistant, a position he held until the end of 1954. At the end of his term, he was awarded a doctorate by the University of Athens, having been trained in Internal Medicine and Cardiology.[1]

Throughout his life, he dealt with many scientific and research issues. His first work, titled "Determination of total blood, plasma and cellular volume with polyvinyl-pyrrolidone", was presented as his own technique in May 1953[2] at the Athens Medical Society and its applications constituted the subject of his doctoral dissertation. During 1952–1954, Yatzidis collaborated with Arkagathos Goutas, Hippocrates Chevrenis, George Michaelides, Phaedonas Fessas, Antigoni Koidakis, Frixos Costaesa to co-author 11 works on cardiology issues, anti-coagulant treatment, systemic lupus erythematosus, radioisotopes and anaemia after gastrectomy.

Between 1955 and 1959, Yatzidis completed his post-graduate studies in France with a scholarship from the French Government. He worked as a paid Resident Médecin des Hopitaux de Paris at the Metabolic Disease Clinic, at the Bernard René Research Centre CN School of Medicine and the Department of Clinical Chemistry of the University of Paris, under Professor Jean Hamburger. During this time, he focused his efforts on acquiring clinical and laboratory experience and less on writing articles. In 1956, he wrote the first article on nephrology with Professor E. Richet, entitled "Coagulation disorders and changes in plasma and urine coagulation factors in nephrotic syndrome". This internationally original work interprets certain points of the mechanism of the various forms of proteinuria and was published in 1957 in the journal *Revue Francaise des Etudes Cliniques et Biologiques*.[3]

In 1959, Hippocrates Yatzidis returned to Greece and served as senior registrar and then as lecturer at the Second Internal Medicine Clinic of the University of Athens. Arkagathos Gouttas, professor and director of the clinic, nurtured unlimited appreciation and admiration for his new associate and thus provided him with as many opportunities as he could to develop the clinic's kidney activity. As a result, Yatzidis, urged by director Arkagathos Gouttas, succeeded in attracting a team of young and enthusiastic doctors dedicated to him and to the new specialty of Nephrology at a time when such units were rare even abroad.

The most important members of this team were Dimitrios Oreopoulos, Nikos Rizos, Christos Velentzas, Alexandros Simvoulidis, Dora Mayopoulou-Simvoulidou, Diogenis Triantaphyllidis, Charalambos Gavras, Pavlos Toutouzas, Nikos Tsaparas, Amalia Stavroulakis (later Tsapara), Sonia Voudiklari, Aristomenis Fertakis, Georgios Psimenos, Andreas Kravaritis, Manta Garidis, Antonis Tzamaloukas and others. The team of these doctors had great excitement and zest for hard work. He required his associates to work hard, but he was the most devoted and hard worker of all. Their dream was to study abroad for a specialty in nephrology and then return to apply their new knowledge in Greece in collaboration with Yatzidis. This is how the first foundations of modern nephrology were built in Greece.

3. FIRST PUBLICATIONS

In 1958, the first publication on the artificial kidney and its contribution to the treatment of acute anuria was based on Yatzidis' experience with 200 haemodialysis sessions in Paris. Soon he introduced the application of artificial kidney for acute kidney failure in Greece. The filters were handmade and the vascular access to connect the patient to the artificial kidney was initially made with glass tubes. Very soon, just a year after Scribner's introduction of Teflon shunts in the US, Yatzidis' partners had learned to make Teflon shunts on their own and to surgically implant them intra-venously and intra-arterially into the patient's wrist.[4] The Artificial Kidney Department at "Hippokrateio" Hospital began operating intensively in 1958 and patients with acute renal failure were referred to it from all over Greece.

Yatzidis paved the way for renal biopsies and, in 1960, he presented his observations on 30 open kidney biopsies via puncture to the Athens Medical Society. Two years later, he presented the causal classification of 70 cases of nephrotic syndrome based on physical examination and pathology findings. At the same time, he described the necrotising findings of a patient with hypertension from obstruction of the left renal artery. In 1963, Yatzidis and his colleagues described for the first time in Greece a case of a patient with unilateral fibrillation and a case of a patient with infarction and lupus erythematosus.[5]

One of the most important contributions of Yatzidis and his team in nephrology was the use of activated carbon columns as a method of dialysis in patients with renal

insufficiency and in cases of barbiturate poisoning (Yatzidis Artificial Kidney).[6] With these works, Yatzidis became well known and internationally recognised as a leading kidney specialist in Greece and an important member of the kidney community.

4. PARTNERSHIPS AND LATER CAREER

Yatzidis' plan for a dynamic future Nephrology Unit was to send his associates abroad, each one to deal with a field of nephrology and implement it upon returning to Greece. Thus, A. Counselidis and D. Mayopoulou went to Paris to study clinical and laboratory immunology, D. Oreopoulos to Belfast to study calcium and kidney diseases, D. Triantafyllidis to London to study hypertension, G. Roasted to Oklahoma to study the organisation and operation of the Artificial Kidney Unit for patients on dialysis, percutaneous kidney biopsy and its histopathology, N. Tsaparas and A. Stavroulakis to Texas to study experimental nephrology and electrolytes.

During 1967–1972, Yatzidis continued his research. Thus, in 1968, he collaborated with H. Gavras to publish their work on renal hypertension. This work was a great start to Gavras' subsequent brilliant career in the field of hypertension. In 1968, Yatzidis was one of the first to use arteriovenous communication for chronic dialysis, and in 1969 he published the first results in *"Medicine"* and the *"New England Journal of Medicine"*.[7]

Yatzidis stayed at the "Hippokrateio" Hospital for a while under Professor Danopoulos, but eventually went into private practice and worked in an artificial kidney unit at the Athens General Clinic. Fortunately, in 1972 he cooperated with Professor Tundas, Professor of Surgery at the "Aretaio" Hospital, who wanted him as an associate to develop a kidney transplant program. At the "Aretaio" Hospital, Yatzidis organised the Nephrology Centre of the University of Athens, with a Nephrology Clinic and an Exemplary Artificial Kidney Unit.

In 1972, he published his experience of the role of heparin in the treatment of uremic pruritus in *"JAMA"*.[8] In 1975, he announced at the First Panhellenic Congress of the Athens Medical Society the very important observation on endogenous hypervitamin A in chronic renal failure.[9] In 1972, he expanded his activity to the study of new locust bean gum and published the first relevant work in *"Kidney International"*.[10] In 1981, he first described the role of biotin[11] in the pathogenesis and treatment of uremic neuropathy and, at the same time, he began his study on cyanide and thiocyanates in renal failure.[12] This study led to the discovery of the role of sodium thiosulphate in the pathogenesis and treatment of arthritic and vascular calcifications in uremic patients and nephrolithiasis.[13] In 1984, he drew the attention of nephrologists to the role of peroxalemia in uremic dialysis patients. In 1991, he described the use of glycine dipeptide (glycylglycine) to produce new solutions for chronic peritoneal dialysis as well as dialysis solutions. The range of Yazidis' interests is clearly outlined in one of his latest papers on the plasma protein-free cholesterol bond and its role in atheromatosis.

Yatzidis had a particular love for biochemistry. When he was at "Hippokrateio" Hospital, he set up a separate biochemical laboratory in the nephrology clinic for precision biochemical tests before the time of automated analysts. For the needs of his research work, he improved many laboratory methods and introduced some new ones of his own inspiration, some of which are: Method for the immediate determination of true creatinine, [14] simple method of determination of inulin[15] without urine collection, simplified method for the determination of para-amino-hippuric acid in plasma, simple, rapid and accurate method for the determination of blood sulphates, estimation of renal glomerular filtration from serum creatinine, new colorimetric method for the quantification of urine proteins, [16] enhanced diuretic reagent for the determination of serum proteins,[17] combined Jaffe enzyme method for the determination of serum creatinine.[18]

He was elected professor at the Medical School of Athens in 1990 and the Academy of Athens awarded him with the Excellence in Science prize in March 1988 as a reward for his clinical and research work.

5. CONCLUSIONS

During his 40 years of service as an academic lecturer, Yatzidis taught generations of students and residents in Internal Medicine. Many Greek nephrologists cooperated and learned alongside with him. He guided and supervised dozens of doctoral theses and recitations. At least 15 of his students became professors and associate professors in Greece and abroad.

He was a regular member of 30 scientific societies and an honorary member of the Hellenic Nephrological Society. He was a member of the editorial committees of 6 foreign language medical journals. He was one of the founding members of the European Dialysis and Transplantation Association (EDTA) (Amsterdam, 1964). He served as chairman of the National Research Institute and the Biomedical Research Committee of the Ministry of Health.

ΠΕΡΙΛΗΨΗ

Ιπποκράτης Γιατζίδης: Ένας σπουδαίος αλλά παράλληλα ταπεινός Έλληνας καθηγητής που αξίζει να θυμόμαστε

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Ο καθηγητής Ιπποκράτης Γιατζίδης υπήρξε ο «πατέρας της Νεφρολογίας» στην Ελλάδα και ένας από τους πρωτοπόρους νεφρολόγους παγκοσμίως. Γεννήθηκε στις 22 Σεπτεμβρίου 1923 στην Αθήνα και πέθανε στις 27 Αυγούστου 2013. Έχοντας πάθος με την επιστήμη του, αφιερώθηκε στη δημιουργία νεφρολογικών μονάδων υψηλού επιπέδου, καθώς και στην έρευνα. Έχει διατελέσει διευθυντής πολλών ερευνητικών μονάδων τόσο στην Ελλάδα όσο και σε άλλες χώρες και ανέλαβε για λίγο τη διοίκηση του Ιατρικού Κέντρου της Γενεύης. Πάντα υπέρμαχος της συνεχούς κατάρτισης για τον ίδιο και τους συναδέλφους του, έτσι ώστε να συμβαδίζουν με τα νέα δεδομένα και να παρέχουν την καλύτερη δυνατή και επίκαιρη θεραπεία για τους ασθενείς. Ο «Τεχνητός Νεφρός Γιατζίδη» είναι ίσως το πλέον σημαντικό του επίτευγμα και μια αξιοσημείωτη ανακάλυψη στη Νεφρολογία παγκοσμίως. Η δραστηριότητά του στη συγγραφή επιστημονικών κειμένων εκδηλώθηκε σε πολλά δημοσιευμένα άρθρα, τα περισσότερα από τα οποία σε διεθνή περιοδικά και με πολλές αναφορές. Στις αρχές της δεκαετίας του 1970 ίδρυσε το Τμήμα Νεφρολογίας του Νοσοκομείου «Αρεταίειου» Αθηνών για να υποστηρίξει ασθενείς που χρειάζονται νεφρολογική παρακολούθηση. Την τελευταία περίοδο της ζωής του συνέχισε την έρευνά του στο Εργαστήριο Πειραματικής Χειρουργικής στην Ιατρική Σχολή Αθηνών. Ήταν γνωστός για την καλοσύνη και τη γενναιοδωρία του στους συνεργάτες του. Το παρόν κείμενο στοχεύει να ακολουθήσει τα επιτεύγματα της ζωής και της εργασίας του.

Λέξεις ευρετηρίου: Καθηγητής Γιατζίδης, Τεχνητός νεφρός με χρήση άνθρακα

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BIOGRAPHY
ΒΙΟΓΡΑΦΙΑ

Three hundred years of Nephrology in Scotland

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ΑΡΧΕΙΑ ΕΛΛΗΝΙΚΗΣ ΙΑΤΡΙΚΗΣ 2020, 37(Συμπλ 2):42–46

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Τριακόσια χρόνια Νεφρολογίας στη Σκωτία

Περίληψη στο τέλος του άρθρου

Key words

Dialysis hepatitis
Edinburgh medical education
Scottish enlightenment
Richard Bright
Robert Christison
Thomas Graham
Thomas Latta

A remarkable flowering of scientific and philosophical thinking, the Scottish Enlightenment, took place in the second half of the 1700s, centred on Edinburgh. The city's new medical school benefited, developed new integrated teaching methods, exploded in size, and sent its graduates around the world. One was Richard Bright, the creator of the specialty of nephrology. Robert Christison, professor of medicine in Edinburgh, was one of those who prominently extended Bright's observations, but his lasting influence was probably limited by his opposition to women doctors. Almost at the same time, Edinburgh graduate Thomas Latta described the first use of intravenous fluids to rescue patients with terminal shock from cholera. Meanwhile in Glasgow, Thomas Graham was describing the principles of dialysis. Scotland took up dialysis and transplantation as treatments for renal failure a hundred years later. Dialysis for AKI from 1959, and the first successful transplant in the UK was performed in Edinburgh in 1960. Establishment of early units for chronic dialysis and transplantation followed, still at a time when the viability of neither was assured. Research centred on complications of dialysis, and on immunosuppression. Edinburgh suffered a devastating dialysis-associated hepatitis outbreak in 1969–1970. This was a major but temporary setback to the development of services. It was followed by a remarkable research initiative that created a landmark, early commercially successful recombinant protein product – hepatitis B vaccine.

1. MEDICINE AND MEDICAL EDUCATION IN 18th CENTURY SCOTLAND

For 200 years from the early 1700s, medical education was a dominant activity of Scotland's universities. This was particularly true of Edinburgh, whose medical school was founded in 1726, in a university created by the City, not under the auspices of a religious body.[1]

The founders of Edinburgh Medical School had travelled to Leiden to experience the new approach developed by Herman Boerhaave. After a founding basis in science, this integrated clinical medicine and practice. Previous norms had been largely theoretical teaching, followed by apprenticeship.

With an astonishing array of great minds attracted to the city, Edinburgh's medical school expanded enormously to become the dominant element of the University. Many notable academics were appointed, a new teaching hospital was built, and Thomas Jefferson wrote in 1789 that so far as science was concerned, "no city in the World can pretend to a competition with Edinburgh".[1] From 1801–1850, Scotland produced 7689 medical graduates to the rest of the UK's 302. By 1895, many new schools had been founded but medical students still comprised half of the 3000 matriculating students at Edinburgh University.[1]

This was far more doctors than Scotland could employ, and Edinburgh's medical graduates, swelled by the growth of other Scottish schools, took the medical-scientific revolution not only to the rest of the UK, but to the limits of the British Empire, and beyond. Edinburgh graduates established medical schools in many nations in North America, South Asia, and China, exporting their mode of instruction too. The Scottish Doctor became a trope in literature and film.

2. WILLIAM CULLEN, TOP TEACHER 1755–1790, ON DROPSY

William Cullen was one of the key attractions to studying in Edinburgh. Like many students, he studied in Edinburgh

for only part of his undergraduate medical education, with the rest of his learning and apprenticeship in Glasgow. There he established an impressive reputation as a clinician and teacher, but he was attracted back to Edinburgh as professor of Chemistry in 1755. His prowess as a teacher was recorded in the diaries and letters of students at the time, but his clinical skills are notably demonstrated in the carefully preserved records of his extensive consultations by correspondence.[2,3]

Many of those writing were doctors seeking advice. Although renal disease was not clearly recognised at that time, beyond renal stones and infection, dropsy and anasarca (local or general fluid retention) were. *Ischuria renalis* (anuria) was recognised, but little intervention was possible if it was not caused by bladder outlet obstruction.

Cullen wrote famously, but gloomily, in 1784, on the dropsy suffered by the leading intellectual figure of Samuel Johnson.[3]

At the age of 74 Asthma and Dropsy are very insurmountable distempers … I am glad to observe that he is in the use of Laudanum as I believe it is the only means of rendering his life tolerably easy. The Vinegar of Squills I judge to be a medicine very well suited to both his Asthma and Dropsy. I hope the coming in of mild weather may be of service to him and if he is to live for another winter he should certainly pass it in a Climate much milder than that of England. I cannot help however telling you that I despair of his having the opportunity for I suspect he has not only water in his limbs but also in his breast.

Contemporary treatments were of limited effectiveness and often difficult to tolerate, relying on purgatives, emetics, and diaphoretics (to induce sweating) to remove fluid. Broom tops (*Genista*) were recommended as a diuretic by some, and Cullen recorded in his Materia Medica (1789) "some dropsies have been cured". Digitalis was now also reported to be an effective drug, based on work by Edinburgh graduate William Withering done in the Midlands of England and published in 1775.

Cullen's textbook *First Lines of the Practice of Physic*, and his *Materia Medica* (therapeutics), were standard texts for several decades. His textbook[4] shows that he understood hepatic, cardiac, and local causes for dropsy, and to some extent renal (dropsy caused by *ischuria renalis* is mentioned). However, his cases also show a thoughtful, sympathetic clinician, who knew not to treat when futile. He seems to have been the key medical opinion of his day. His distinction of insipid versus sweet diabetes is just one of his classic and lasting insights.[5]

3. THE BRIGHT ERA

There was little understanding of renal disease in Cullen's era, but in looking for antecedents of Richard Bright, one of those picked out is William Wells (1757–1815), a Scottish-American Edinburgh graduate working in London, who in 1812 described in great detail the oedema sometimes seen in scarlatina. He also made a number of tantalising observations around oedema and proteinuria, and kidney appearance at autopsy, and related some renal disease to exposure to mercury (prescribed for venereal infection). He was so near making a clear, saleable account, that some have wondered why Bright's story is the only one remembered.[6]

Richard Bright himself, widely credited for creating the specialty of Nephrology, studied in Edinburgh 1808–1810. His MD examination in 1813 including scrutiny (in Latin) of his thesis on erysipelas, as well as extended oral examination on clinical cases. But his 1827 "Reports of Medical Cases"[7] from Guy's Hospital reverberated around the world. He meticulously associated proteinuria and dropsy with shrunken kidneys, and the medical world was convinced. Suddenly everyone wanted to test for proteinuria.[8,9]

Bright's most notable colleagues at Guy's were two other Edinburgh graduates, Thomas Hodgkin (who introduced Laennec's stethoscope to London; Bright was an early adopter) and Thomas Addison, whose eponyms lasted even longer than Bright's. Bright's disease was widely used to describe kidney disease, and later more narrowly glomerulonephritis, into the 20th century.[8,9] Bright wrote an impressive textbook of medicine with Addison in 1839.[10]

4. POST-BRIGHT

Two key characters took Bright's work notably further. These were Robert Christison (1797–1882), professor of Medicine in Edinburgh, who received his Edinburgh MD 6 years after Bright in 1819, and Pierre Rayer (Paris). Each produced classic texts, in 1837 and 1839 respectively. The increasing recognition of acute renal disease, and greater understanding of nephritic (haematuric) renal disease from proteinuric, began here. Indeed this information was endorsed by Bright, and included in his 1839 textbook.[10]

Despite making some striking insights, and wide recognition at the time, as described by Cameron,[11] Christison's role in the development of nephrology has been relatively neglected since. Quietness about him seems almost certainly related to his campaign against permitting women to become doctors. He led internal opposition to the progression of the first female undergraduates in Britain, who had been admitted to study Medicine in Edinburgh

in 1869, and this 73-year-old man, 47 years since being appointed a professor, ultimately succeeded in preventing them from receiving medical degrees in Edinburgh. However honorary degrees were awarded to 7 of them in 2019, the 150th anniversary of their matriculation.[12,13] Though the columns of medical journals displayed views on both sides, Christison's stance seems to have been contrary to the prevailing public mood expressed in the wider press. Only a few years later the arguments were won, an 1876 amendment to the Medical Act clarifying that women should be eligible.[12,13] Women's schools sprang up, and it is fascinating that in 1889 Christison's own son Alexander, who had spent most of his medical life in India, took up presidency of Edinburgh's Medical College for Women, very publicly leading a cause that his late father had been prominently opposed to.

5. CHOLERA, INTRAVENOUS FLUIDS, AND BODIES

The profusion of medical students in Scottish cities led to a notorious shortage of bodies for dissection. This led first to grave-robbing, to sell bodies to anatomists, and culminated in the conviction of Burke and Hare, who found it more convenient to create their own bodies. They were believed to have murdered 16 citizens to sell the bodies to anatomists. Burke was hanged in 1828; Christison gave forensic evidence at the trial. The events aroused widespread scandal, and lasting mistrust. In 1831 the anatomy school in Aberdeen (colloquially known as the "Burkin hoose", after Burke) was burned to the ground,[14] and in Liverpool in 1832 "cholera riots" were triggered by the sight of cholera sufferers being taken to hospital, a rumour having spread that they were being abducted for their bodies.[14,15]

"Asian" cholera hit Britain in 1831–1832, but was also the subject of serious scientific enquiry. Based on science showing that red cells became concentrated in blood in cholera, in Leith (Edinburgh's port) in 1832, Dr Thomas Latta demonstrated that patients who were moribund from Asian cholera could be revived by intravenous injection of large volumes of salty water. This was the first reported successful use of intravenous fluids. The pages of the Lancet were filled with excitement and controversy for a short time, as this approach was the opposite of bleeding, which was recommended by some.[16,17]

"She had apparently reached the last moments of her earthly existence ... I feared that I should be unable to get my apparatus ready ere she expired. ... ounce after ounce was injected, but no visible change was produced. Still persevering, I thought she began to breathe less laboriously, soon the sharpened features, and sunken eye and fallen jaw, pale and cold ... began to glow with returning animation; the pulse, which had long ceased, returned to the wrist; at first small and quick, by degrees it became more and more distinct ... and in the short space of half an hour, when six pints had been injected ... her extremities were warm, and every feature bore the aspect of comfort and health."[18]

The debate died down with the epidemic. This was a discovery of much more immediate importance than Bright's, but was neglected for some decades, before returning as a treatment for haemorrhagic and other shock.[19]

6. THOMAS GRAHAM AND THE ROAD TO THERAPEUTIC DIALYSIS

Thomas Graham (1805–1869) meanwhile described the phenomenon of dialysis, distinguished and defined colloids and crystalloids, and semi-permeable membranes, in work commenced in Glasgow and completed in London, published 1830–1861. His 1861 paper described its application to urea in urine, laying the ground for the first attempts at therapeutic dialysis.[20] One of the steps required to implement it was control of blood clotting. Hirudin was purified from leeches by Edinburgh graduate John Haycraft (1857–1922), a physiologist working in Birmingham, England. Semi-permeable membrane (collodion) and hirudin were brought together by John Jacob Abel in Baltimore in 1913.[20] It was another 40 years before Willem Kolff found a way to harness the technique successfully.

7. DIALYSIS AND TRANSPLANTATION

The next hundred years were relatively quiet in Scottish nephrological output, although the astonishing longitudinal studies and impressive, humane *Glomerular Nephritis* (1948) of another Edinburgh graduate, Thomas Addis (1881–1949), working in Stanford, were a highlight.[21,22]

By 1960 selected academic centres around the world, including two in Scotland, picked up on the potential for of dialysis and even transplantation.

Dialysis for acute renal failure was introduced in Edinburgh and Glasgow in 1959. The first successful kidney transplant in the UK was undertaken between identical twins in Edinburgh in 1960 by surgeon Michael Woodruff. A period of leading research in immunology and immunopathology followed. The second use of Azathioprine in transplantation was in Edinburgh in 1962. Production and research into anti-lymphocyte serum followed. The survival in these early transplants was very poor; in the first 14 years, 129 transplants, Woodruff reported that patient survival at

6 months was 29%, but 28 (22%) had survived more than 2 years.[23] But the long term prospects on dialysis were uncertain during most of that period too.

Edinburgh and Glasgow shared many of the alarms and experiences around the potential of dialysis and transplantation. The affordability, uncertainty of long term viability, and new complications, including dialysis disequilibrium, aluminium toxicity, bone disease, and hepatitis.[24,25]

7. HEPATITIS AND HEPATITIS VACCINE

In 1969–1970, the world's worst dialysis-associated Hepatitis B outbreak occurred in Edinburgh.[26] Outbreaks had occurred intermittently in the UK, and similarly across Europe, since 1965. The Edinburgh epidemic killed 7 of 26 affected dialysis patients, and 4 of 12 members of staff, two transplant surgeons and two technicians.[27] The reason for the exceptionally high mortality in this epidemic is not known, but the events had a major impact on the new specialty locally, just at the time that the prospects for long-term patient survival were looking up. After a period of taking on no new patients, a move to more home rather than in-centre haemodialysis was driven by fears of hepatitis, as well as by economic factors.

There were no local presentations about the Edinburgh epidemic for 35 years, it seemed too sensitive a topic (R. Winney, personal communication). However a scurrilous, politically incorrect but darkly humorous novel "The Houseman's Tale" by Colin Douglas (pseudonym for Colin Currie, 1975) was set in a hospital with a hepatitis B outbreak spreading fear amongst its staff. Currie was an Edinburgh student at the time of the outbreak, when there was real concern about who might be affected next.[29]

The experience triggered a remarkable ensuing scientific project in one of the first of the new laboratories of Molecular Biology, that led to sequencing of the virus in 1979, and subsequent marketing of the recombinant vaccine Engerix B in 1986. The husband and wife team of Kenneth and Noreen Murray were central to this. The route to it included founding one of the first biotech companies, Biogen. The Murrays' income from the enormously successful vaccine was fed back into research and education, a benefit in addition to the health benefits for patients and staff everywhere.[28,29]

ΠΕΡΙΛΗΨΗ

Τριακόσια χρόνια Νεφρολογίας στη Σκωτία

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Μια αξιοσημείωτη άνθηση της επιστημονικής και φιλοσοφικής σκέψης, του Σκωτσέζικου Διαφωτισμού, έλαβε χώρα στο δεύτερο μισό του 1700, με επίκεντρο το Εδιμβούργο. Η νέα ιατρική σχολή της πόλης ωφελήθηκε, ανέπτυξε νέες ολοκληρωμένες μεθόδους διδασκαλίας, αναπτύχθηκε ραγδαία σε μέγεθος και έστειλε τους αποφοίτους της σε όλο τον κόσμο. Ένας εξ αυτών ήταν ο Richard Bright, ο δημιουργός της ειδικότητας της Νεφρολογίας. Ο Robert Christison, καθηγητής της Ιατρικής στο Εδιμβούργο, ήταν ένας από εκείνους που επέκτειναν εμφανώς τις παρατηρήσεις του Bright, αλλά η μόνιμη επιρροή του ήταν πιθανώς περιορισμένη από την αντίθεσή του προς τις γυναίκες γιατρούς. Σχεδόν ταυτόχρονα, ο απόφοιτος του Εδιμβούργου Thomas Latta περιγράφει την πρώτη χρήση ενδοφλέβιων υγρών για τη διάσωση ασθενών με κυκλοφορική καταπληξία από τη χολέρα. Εν τω μεταξύ, στη Γλασκώβη, ο Τόμας Γκράχαμ περιέγραφε τις αρχές της αιμοκάθαρσης. Η Σκωτία ξεκίνησε την αιμοκάθαρση και τη μεταμόσχευση ως θεραπείες για τη νεφρική ανεπάρκεια εκατό χρόνια αργότερα. Η αιμοκάθαρση για την οξεία νεφρική βλάβη από το 1959 και η πρώτη επιτυχημένη μεταμόσχευση στο Ηνωμένο Βασίλειο πραγματοποιήθηκαν στο Εδιμβούργο το 1960. Ιδρύθηκαν πρώιμες μονάδες για χρόνια αιμοκάθαρση και μεταμόσχευση, ακόμα σε μια εποχή που η βιωσιμότητα κανενός δεν ήταν εξασφαλισμένη. Η έρευνα επικεντρώθηκε στις επιπλοκές της αιμοκάθαρσης και στην ανοσοκαταστολή. Το Εδιμβούργο υπέστη καταστροφικό ξέσπασμα ηπατίτιδας που συνδέεται με την αιμοκάθαρση το 1969–1970. Αυτή ήταν μια σημαντική αλλά προσωρινή παύση της ανάπτυξης των υπηρεσιών. Ακολούθησε μια αξιοσημείωτη ερευνητική πρωτοβουλία που δημιούργησε ένα ορόσημο, πρώιμο εμπορικά επιτυχημένο προϊόν ανασυνδυασμένης πρωτεΐνης – εμβόλιο ηπατίτιδας Β.

Λέξεις ευρετηρίου: Ηπατίτιδα αιμοκάθαρση, Ιατρική εκπαίδευση Εδιμβούργο, Richard Bright, Robert Christison, Σκωτικός διαφωτισμός, Thomas Graham, Thomas Latta

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BIOGRAPHY
ΒΙΟΓΡΑΦΙΑ

Kidney diseases in the mediaeval work *"Michi Competit"* by Thomas of Wroclaw

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ΑΡΧΕΙΑ ΕΛΛΗΝΙΚΗΣ ΙΑΤΡΙΚΗΣ 2020, 37(Συμπλ 2):47–52

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Οι νεφρολογικές παθήσεις στο μεσαιωνικό έργο "Michi Competit" του Thomas του Wroclaw

Περίληψη στο τέλος του άρθρου

Key words

Kidney diseases
Middle Ages
Thomas of Wroclaw

Although mediaeval medicine is oft considered to suffer from many weaknesses, there is a lot of data against this view. These include the emergence of Europe's first universities, educating doctors such as Arnaldo De Villanova, in France and others. The next generation of outstanding doctors includes Thomas of Wrocław, born in the namesake Silesian town in 1297. At the age of 16, he started studying at the university in Montpellier, France where he met his renowned teachers: Peter Abano, Henry de Mondeville, and Bernard de Gordon. After completing his studies in Montpellier, he continued his scientific journey to Toledo (Spain), Salerno, Padua, Bologna and Rome (Italy) and to Oxford (England). Having earned a pan-European reputation, despite numerous job offers from universities, he returned to his homeland to become a court doctor for John of Bohemia and Charles IV, king of Bohemia and the Holy Roman Emperor. He died in Wrocław in 1378 and was buried at the nearby St. Vincent Abbey. Thomas is known to have written many works, yet *Mihi Competit,* completed at the age of 63, is the most prominent. It comprises four parts: *Regimen Sanitatis, Aggregatum, Antidotarium* and *Practica Medicinalis.* Modern nephrologists might find the last one the most interesting, as its chapters no 81–87 of part 112 refer to urinary tract diseases. The titles of the subsequent parts are: *De debilitate et dolore renum* (On Renal Disease and Pain), *De apostemate renum* (On Renal Abscess), *De ulceribus renum et vesice* (On Kidney and Bladder Ulcers), *De lapide renum et vesice* (On Kidney and Bladder Stone), *De difficultate mingendi* (On Problems with Urination), *De diampne* (On Urinary Incontinence) and *De diabete* (On Diabetes). There are no known translations of the Latin-written *Michi Competit* into modern languages. Finding some of the views depicted in the work historically interesting, the authors undertook to translate it, aiming to present it to a wider audience.

"If you would understand anything, observe its beginning and development"

Aristotle

1. INTRODUCTION

The central figure of this publication, Thomas of Wroclaw, is one of the beacons of the widely underestimated mediaeval medicine. By general consent, the switch from ancient to mediaeval medicine is believed to have happened in the late 4th and early 5th century or, as some want it, it is associated with the fall of the Roman Empire in 395 AD. At the other end, the publication of Andreas Vesalius' monumental work on anatomy *De humani corporis fabrica libri septem* in 1543 marks the end of mediaeval medicine. In the popular mind, the Middle Ages were shaped by the great thinkers and humanists of the time like Thomas Aquinas, Albertus Magnus, Dante Alighieri or Francesco Petrarca. However, alongside philosophy, literature, architecture and painting it was the time when medicine started to grow in the first medical schools and universities, which were also open for women. Moreover, the Middle Ages saw the development of sacral medicine and the early steps of hospital-based treatment. Healthcare development remained under the inevitable influence of political changes and turmoil of the time leading to the emergence of a variety of medical schools. Consequently, we can distinguish between the Byzantine school of medicine, represented by Oribasius of Pergamon or Paul of Aegina, Arabic medicine with Rhazes or Avicenna and Western or Latin medicine, practised by Benedict of Nursia, Constantine

the African, Arnaldo de Villanova and others. Mediaeval Poland was not deprived of its renowned doctors such as Nicholas of Poland, Vitello, John of Grodkow, Jan Radlica and Thomas of Wroclaw to name but a few.

2. LIFE

Thomas of Wroclaw (1297–1378) was born into a Silesian bourgeois family, most probably in the city of Wroclaw, although, according to some researchers, it was in Tilbury, England. We strongly believe, however, that the latter probability is considerably lower. Thomas' education started in a local parish school and continued in a cathedral school. Then, with the financial support from the Norbertines, at the age of 16, he made his way to France to study medicine at the University of Montpellier, famous for its renowned lecturer – Arnaldo de Villanova. The stay in France offered Thomas a chance to meet a number of outstanding doctors of the time such as Peter Abano, Henry de Mondeville and Bernard de Gordon. It was during his time in Montpellier that he also started a friendship with the future professor of the University of Paris, the famous anatomist and surgeon Guy de Chauliac. Having completed his studies in France, Thomas continued his training at the famous ophthalmology centre in Toledo, Spain and subsequently visited some of Europe's greatest universities. These include the Italian Salerno with its remarkable botanical garden, Padua, where he studied anatomy through post-mortem examinations performed under the supervision of Nicolas Bertruccia, Bologna with Mondino de Luzzi and, last but not least, the English Oxford University where alongside William Meerle he investigated the medicinal use of herbs.

Despite proposals to become professor at various European universities, Thomas decided to finish his 17-year-long peregrination and return to his hometown of Wroclaw. Those days, the total number of medical doctors in Poland stood at a rather modest figure of 30 individuals, mostly educated at Italian and French universities and practising medicine in the towns and cities of Krakow, Wroclaw, Raciborz, Brzeg, Wloclawek and Poznan. Thomas quickly became court doctor of Silesian princes and the Czech king John of Bohemia and, finally, the emperor Charles IV. He focused his work on the struggle against epidemics, caring for the lepers in lazarets and patients in the Wroclaw hospitals of Holy Spirit, St. Elisabeth and Corpus Christi. In recognition of his achievements, Pope Clement VI granted him the title of Bishop of Sarepta, a Phoenician city near Sidon in Asia Minor, in modern Lebanon. After his death in 1378, Thomas was buried in St. Vincent Abbey near Wroclaw.[1–6]

3. WORK

Despite a 17-year-long peregrination spent studying and working in Western Europe, Thomas of Wroclaw's life and professional activity have mostly been investigated only by Polish researchers. His most important works include *Alphabetum sive Collectorium, Regulae, De phlebotomia et de indiicis cruoris, De urinis* and, especially, his *opus magnum,* titled *Michi Competit* also known as "Avicenna's Silesian Canon". *Michi Competit*, published in 1360, when its author was already 63, includes the biggest number of references to urinary tract diseases (fig. 1).[7,8] The work comprises the following parts: *Regimen sanitatis* (on maintaining the human body in good health), *Aggregatum* (on simple medicines), *Antidotarium* (on complex medicines) and *Practica medicinalis* – a compendium including descriptions of diseases and treatment methods. A commented edition of the *Practica medicinalis* was published in 1989 (fig. 2). Originally written in Latin, the work has probably never been translated into any other language with the exception of one chapter (no. 39) *De debilitate cordis et syncopi* (on heart disease and fainting).[9–11]

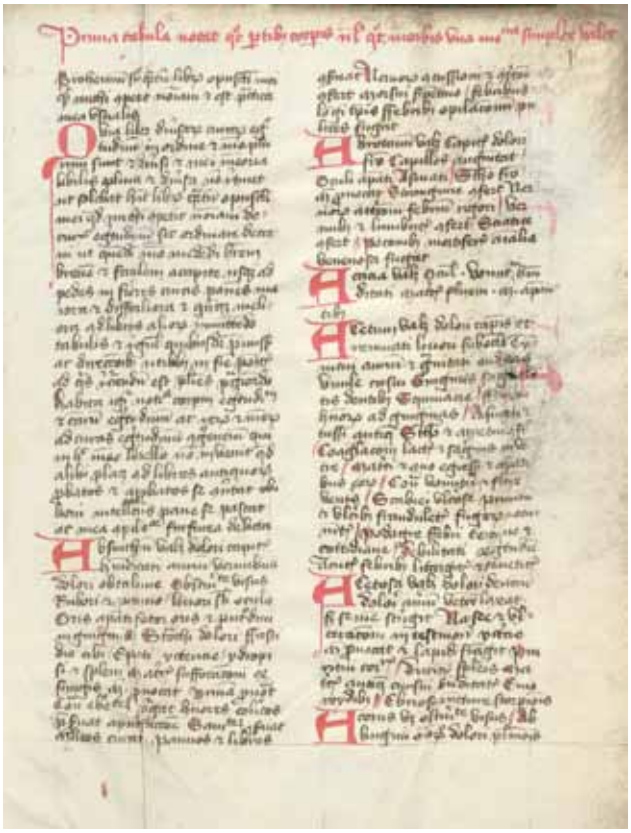
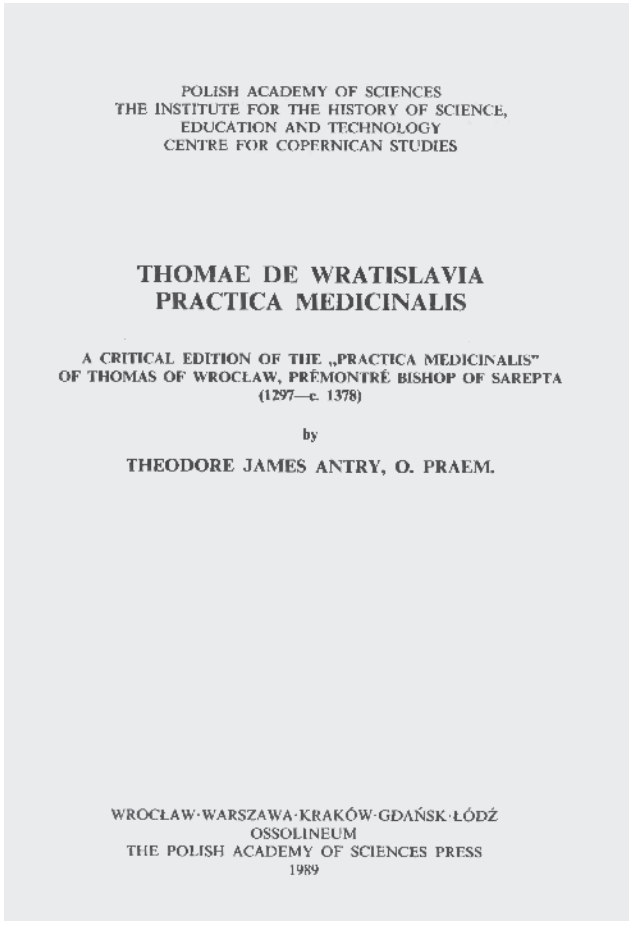


Figure 1. Title page of *Michi Competit* by Thomas of Wroclaw (courtesy of Lower-Silesian Digital Library in Wroclaw).



POLISH ACADEMY OF SCIENCES
THE INSTITUTE FOR THE HISTORY OF SCIENCE,
EDUCATION AND TECHNOLOGY
CENTRE FOR COPERNICAN STUDIES

THOMAE DE WRATISLAVIA
PRACTICA MEDICINALIS

A CRITICAL EDITION OF THE „PRACTICA MEDICINALIS"
OF THOMAS OF WROCŁAW, PRÉMONTRÉ BISHOP OF SAREPTA
(1297—c. 1378)

by

THEODORE JAMES ANTRY, O. PRAEM.

WROCŁAW·WARSZAWA·KRAKÓW·GDAŃSK·ŁÓDŹ
OSSOLINEUM
THE POLISH ACADEMY OF SCIENCES PRESS
1989

Figure 2. Title page of *Thomae De Vratislavia Practica medicinalis*, edited by Polish Academy of Science in 1989.

Seven of the 112 chapters describing a variety of ailments and diseases are devoted to urinary tract malfunctions (fig. 3). These are chapters 81–87, titled:

- Chapter 81: *De debilitate et dolore renum* (on renal disease and pain) (fig. 4)
- Chapter 82: *De apostemate renum* (on renal abscess) (fig. 5)
- Chapter 83: *De ulceribus renum et vesice* (on kidney and bladder ulcers)
- Chapter 84: *De lapide renum et vesice* (on kidney and bladder stone)
- Chapter 85: *De difficultate mingendi* (on problems with urination)
- Chapter 86: *De diampne* (on urinary incontinence)
- Chapter 87: *De diabete* (on diabetes).

In Chapter 81, Thomas wonders whether appropriate medical treatment can improve the functioning of the kidneys, which might be regarded as the mediaeval origin

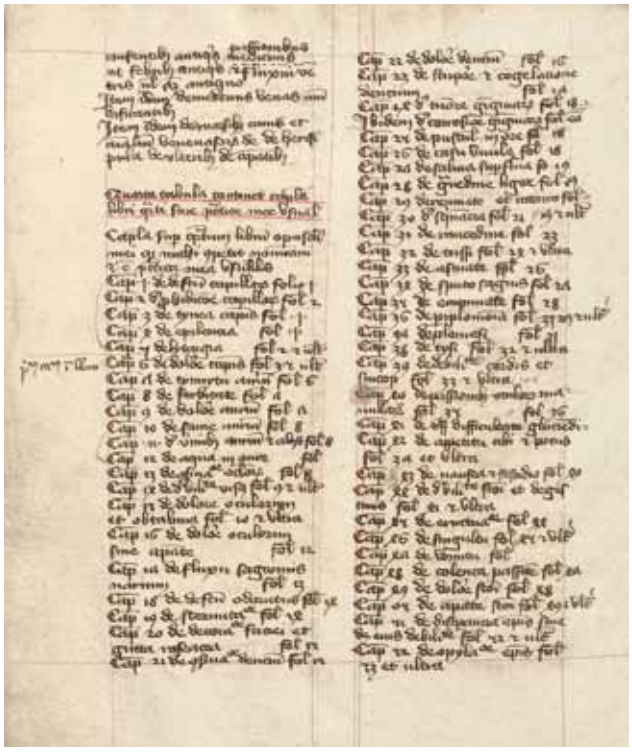


Figure 3. Part of the table of contents from *Michi Competit* (courtesy of Lower-Silesian Digital Library in Wroclaw).

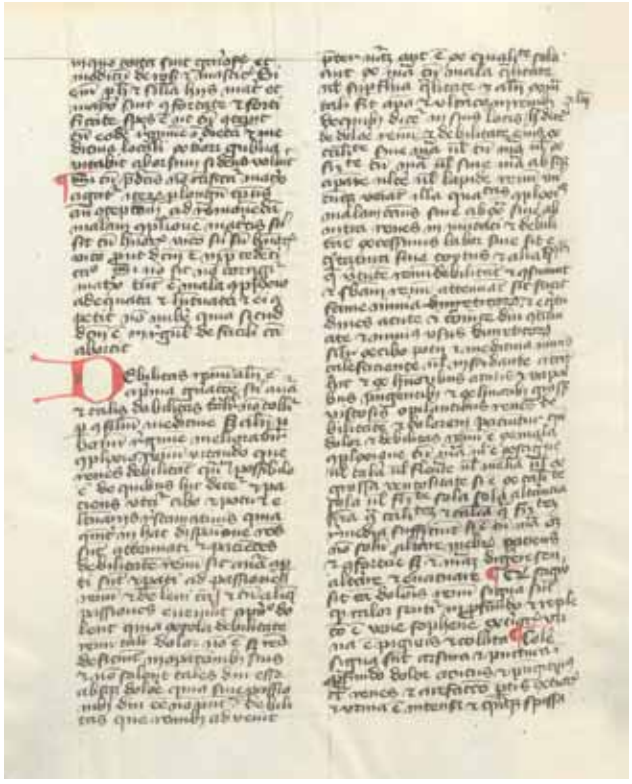


Figure 4. Chapter no 81 of *Michi Competit* (courtesy of Lower-Silesian Digital Library in Wroclaw).

Figure 5. Chapter no 82 of *Michi Competit* (courtesy of Lower-Silesian Digital Library in Wroclaw).

of preventive medicine. According to Thomas, kidneys are vulnerable to a number of internal (humor balance disturbances) and external (excessive work and bodily effort, chronic stress and malnutrition, excessive use of diuretics) factors. In the part devoted to pain he says*: "[…] I believe, however, that even in case of severe pain, painkillers should be administered very carefully and in moderate amounts. Therefore, if the root-cause is of hot character I use cold from the outside and give poppy milk, a drink popular in Poland for its hydrating, cooling, soporiferous and, hence, pain-soothing properties […]"*.

In Chapter 82, he claims that kidney abscesses result from accumulation of humors, which cannot be released due to the "weakness" of the organ. Abscesses tend to occur in different parts of the organ, on the outside and the inside. Moreover, frequently they are found in both kidneys at the same time. The occurrence of abscesses can be accompanied by fever, pain, nausea and emesis. This fragment has the following wording: *"[…] when pus with blood appears the fever and pain diminish giving the patient a chance to rest better, yet the feeling of heaviness in the place of the abscess remains. And then, nature permitting, the abscess breaks to the benefit of the sick. If, however, nature is reluctant, it must be helped. The patient is ordered to go up and down uneven steps, and if possible, jump. Such movements frequently help the abscess to break leading to big improvement in the patient's health […]"*.

In Chapter 83, Thomas indicates that kidney ulcers are a painful consequence of kidney abscesses, although, he points out, they can also concern the bladder and the tract between the kidneys and the bladder, that is the ureter. The symptoms they produce are similar to those described in the previous chapter. To use Thomas' words: *"[…] the common symptoms of ulceration in these three places is the extraction of blood and blood with pus through the urinary tract. If the ulcer is located in the bladder pus precedes urine and pain is felt in the bladder and the pubococcygeus muscle and urination is troublesome. If, however, the ulcer is placed in the kidneys or in the tract between the kidneys and the bladder, the urine is mixed with blood and pus […]"*.

Chapter 84 is by far the longest in the entire *Michi Competit*; this is not surprising, considering how common urolithiasis is in modern society as well. Thomas states that urinary stones affect the entire spectrum of the population and occur in various places of the urinary tract, in both sexes and all age groups. The stones can also assume a variety of shapes. As for their causes, Thomas indicates excessive amounts of slimy substance, small urine volumes due to dehydration and ureterostenosis. Regarding the last point, he makes an interesting observation: *[…] there is many a man and woman who do not have a stone in the bladder due to their high extraction potency and a wide duct through which the slimy matter can be released with the urine, especially women, whose neck of the urinary bladder is broad and very short […]"*.

In Chapter 85, Thomas takes a leaf out of his master's book, claiming that problematic urination can be attributed to the coincidence of urolithiasis, excessive amounts of humors, presence of abscesses and other warts or excrescences in the neck of the urinary bladder. He teaches that a total and prolonged obstruction of urine is lethal. He suggests the following treatment: *"[…] in the said illnesses enemas, baths and compresses of humour-soothing herbs and diuretics prove helpful in opening the urinary tract […]"*.

Chapter 86 investigates incontinence, especially in boys (nocturia) and intoxicated adult individuals. Thomas attributes this to the cold and the consequent paralysis of the urinary bladder: "*[…] some urinate at night in their bed due to dreaming about being in the place where they usually urinate. It is the power of imagination that causes urination […]*".

Chapter 87 is the last one on urinary tract ailments and concerns unstoppable urination in large volumes. Referring to modern medicine, it might be argued that it touched upon *diabetes insipidus*. The author of *Practica medicinalis* describes it as follows: "*[…] it is evident, then, that diabetes insipidus is not a disease of the kidneys or bladder but is rather caused by cold and a weak liver. What makes it different from incontinence (diampne) is the fact that in the case of diabetes insipidus urine is involuntarily passed in much larger volumes. In diampne, however, the volume is much smaller. It both cases, though, passing of urine is very frequent […]*".

Thomas' recommendation for treatment of these urinary tract diseases include a proper diet, simple and complex medicines mostly of plant, animal or mineral origin, phlebotomy, simple surgical interventions and purging the organism through induced emesis or the use of enemas. A detailed discussion of such procedures, including bleeding, however, requires a separate elaboration.[12–14]

ΠΕΡΙΛΗΨΗ

Οι νεφρολογικές παθήσεις στο μεσαιωνικό έργο "Michi Competit" του Thomas του Wroclaw

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Παρόλο που η μεσαιωνική ιατρική συχνά θεωρείται ότι πάσχει από πολλές αδυναμίες, υπάρχουν πολλά στοιχεία κατά της άποψης αυτής. Αυτά περιλαμβάνουν την εμφάνιση των πρώτων πανεπιστημίων της Ευρώπης, την εκπαίδευση των ιατρών όπως ο Arnaldo De Villanova, στη Γαλλία και άλλους. Η επόμενη γενιά εξαιρετικών ιατρών περιλαμβάνει τον Thomas από το Βρότσλαβ, που γεννήθηκε στην ομώνυμη πόλη της Σιλεσίας το 1297. Στην ηλικία των 16 ετών, άρχισε να σπουδάζει στο πανεπιστήμιο του Μονπελιέ της Γαλλίας, όπου συναντήθηκε με τους διάσημους δασκάλους του: Peter Abano, Henry de Mondeville, και Bernard de Gordon. Αφού ολοκλήρωσε τις σπουδές του στο Μονπελιέ, συνέχισε την επιστημονική του πορεία στο Τολέδο (Ισπανία), το Σαλέρνο, την Πάντοβα, την Μπολόνια και τη Ρώμη (Ιταλία) και στην Οξφόρδη (Αγγλία). Έχοντας κερδίσει μια πανευρωπαϊκή φήμη, παρά τις πολυάριθμες προσφορές εργασίας από πανεπιστήμια, επέστρεψε στην πατρίδα του για να γίνει γιατρός στην αυλή του Ιωάννη της Βοημίας και του Κάρολου IV, βασιλιά της Βοημίας και του Αυτοκράτορα της Αγίας Ρωμαϊκής Αυτοκρατορίας. Πέθανε στο Βρότσλαβ το 1378 και θάφτηκε στη μονή του Αγίου Βικέντιου της γύρω περιοχής. Είναι γνωστό πως ο Thomas έχει γράψει πολλά έργα, όμως το έργο *Mihi Competit,* που ολοκλήρωσε στην ηλικία των 63 ετών, είναι το πιο εξέχον. Περιλαμβάνει τέσσερα μέρη: *Regimen Sanitatis, Aggregatum, Antidotarium* και *Practica Medicinalis*. Οι σύγχρονοι νεφρολόγοι μπορεί να βρουν το τελευταίο πιο ενδιαφέρον, καθώς τα κεφάλαια του 81-87 του μέρους 112 αναφέρονται σε ασθένειες του ουροποιητικού συστήματος. Οι τίτλοι των επόμενων μερών είναι: *De debilitate et dolore renum* (Περί νεφρολογικής ασθένειας και πόνου), *De apostemate renum* (Περί νεφρολογικού αποστήματος), *De ulceribus renum et vesice* (Περί ελκών νεφρού και ουροδόχου κύστης), *De lapide renum et vesice* (Περί πέτρας νεφρού και ουροδόχου κύστης), *De difficultate mingendi* (Περί με προβλημάτων ούρησης), *De diampne* (Περί ακράτειας ούρων) και *De Diabete* (Περί διαβήτη). Δεν υπάρχουν γνωστές μεταφράσεις του λατινικού *Michi Competit* σε σύγχρονες γλώσσες. Βρίσκοντας μερικές από τις απόψεις που παρουσιάζονται στο έργο ενδιαφέρουσες ιστορικά, οι συγγραφείς ανέλαβαν να το μεταφράσουν, με στόχο να το παρουσιάσουν σε ένα ευρύτερο κοινό.

Λέξεις ευρετηρίου: Μεσαίωνας, Νεφρολογικές παθήσεις, Thomas του Wroclaw

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BIOGRAPHY
ΒΙΟΓΡΑΦΙΑ

Vincenzo Diamare (1871–1966) and the priority for the discovery of the endocrine function of the pancreas (1895)

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ΑΡΧΕΙΑ ΕΛΛΗΝΙΚΗΣ ΙΑΤΡΙΚΗΣ 2020, 37(Συμπλ 2):53–56

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From 1895 to 1908, Vincenzo Diamare (1871–1966), made innovative studies related to the function of the non-acinar cells of the pancreas, which were described by Paul Langerhans in 1869. Through comparative anatomy and physiology studies, he established their endocrine function and their regulation of glucose metabolism in man. His data were confirmed by E. Laguesse, W. Schulze, E. Sauerbeck, N. Minkowski and many others, including J.J.R. McLeod. When in 1923, the Nobel Prize for Medicine and Physiology was awarded to Frederick Grant Banting and John James Rickard Macleod, his name was neglected. The Nobel committee also neglected not only Charles Best and Bertrand Collip, belonging to the Toronto Group of investigators, but also N. Paulescu, G.L. Zuelzer, S.S. Kleiner and E. Lancereux. Diamare did not protest. Throughout his life, he continued to investigate the topic and at the age of 85 he even contributed a ponderous review (85 pages), thoroughly discussing the ideas of his supporters and opponents without acrimony.

Vincenzo Diamare (1871–1966) και η προτεραιότητα για την ανακάλυψη της ενδοκρινικής λειτουργίας του παγκρέατος (1895)

Περίληψη στο τέλος του άρθρου

Key words

Discovery of insulin
Endocrine function of the pancreas
Insulin
Paul Langerhans
Vincenzo Diamare

1. INTRODUCTION

In the thesis *Beiträge zur mikroscopischen Anatomie der Bauchspeicheldrüsen*, in 1869, German pathologist, physiologist and biologist Paul Langerhans (1847–1868) described the pancreatic islet, without advancing an hypothesis on their function. Diamare (1871–1966) –a scientist who was born and died in Naples, where he was professor of Histology, General Physiology and Embryology (1923–1944) – was innovative and successful in understanding islet function. From 1895 to 1908, he performed comparative studies in teleosts (mainly in *Lophius*), reptiles, mammals, amphibia and birds, utilising the facilities of the Marine Station founded by Anton Dohrn (1840–1909) and those at the Comparative Anatomy Institute of the University of Naples.[1–11] He demonstrated that:

- The cells of Langerhans are epithelial structures different from zymogenic cells and may be considered vascular glands
- These cells produce a granular substance stained fuchsia –which is different from that produced by the zymogenic acinar cells of the pancreas– and is secreted in blood vessels (endocrine function)
- These cells, found in humans and vertebrates, are independent of the zymogenic acinar cells of the pancreas cells

- The islets of Langerhans have an endocrine function in connection with the metabolism of glucose: hyperglycaemia and diabetes are associated with their inadequate functioning.

2. THE 1923 NOBEL PRIZE IN MEDICINE AND PHYSIOLOGY AND THE MANY MISTAKES OF THE NOMINATING COMMITTEE

In 1923, the Nobel Prize for Physiology and Medicine was given to Frederick Grant Banting –an unknown practicing physician– and to John James Rickard McLeod, Director of the Physiology Department at the University of Toronto, for the discovery of insulin.[12–14] Charles Best, a medical student, and the Biochemist Bertrand Collip, Professor at the University of Alberta who had been working in the Canadian team, were excluded although Collip had a purified extract. McLeod shared with Collip the money from the Nobel prize, as did Banting with Best. Vincenzo Diamare was not even mentioned but accepted the Nobel Committee's decision calmly. Nicolae Paulescu (Bucharest, 1869–1931) was also not mentioned by the Nobel Committee. Paulescu had started his research on pancreatic secretions in Paris under the guidance of Prof Etienne Lancereaux at Hotel Dieu and of Albert Dastre at the Sorbonne. Lancereaux was the first to provide evidence of the existence of two types of diabetes. Back in Bucharest, Paulescu did significant work on the action of insulin.[15,16] He was not mentioned, although his studies had been cited by the Canadian Group and he had personally patented insulin (patent no 6254 of the Romanian Ministry for Industry and Trade). Nicolae Paulescu protested, but without result. However, the truth came out and, in 1969, the Nobel Committee admitted the mistake in a letter by Professor Arne Tiselius, President of the Nobel Committee, written to Professor Iahn Murray, vice-president of the British Diabetic Association.[17,18] The Canadian Group[12] had even quoted Paulescu's paper (but wrongly).[15] The Nobel Committee also failed to acknowledge the work of Zuelzer,[19] Kleiner[20] and Lancereaux.[21]

3. VINCENZO DIAMARE'S PRIORITY RECOGNISED

After the prestigious Nobel Prize for 1923 was bestowed to Banting and Best, E. Laguesse wrote to Diamare: "Vous avez donc beaucoup fait preparer la découvert de Banting!".

W. Schulze in 1901 wrote *"Finally for the year 1899 we shall quote the comparative anatomy studies performed by Diamare, who confirmed the presence of the islets in all animals with a pancreas. He identifies their function as typical of ferments and describes them as vascular glands. I can confirm his findings on the basis of my personal experience, based on studies performed before the publication of his work"*.[22] Ernst Sauerbeck in 1904 in a classical study[23] wrote *"Diamare proposed already in 1899 on the basis of comparative anatomy studies the modern theory of the islets, where he sees the islet as an organ that through internal secretions influences sugar regulation"*. In 1908, N. Minkovski stated *"I consider that the merit of Diamare is more important for the development of the doctrine of the hormonal function and the final discovery of insulin"*.[24]

The 1923 Nobel Prize Winner John James Rickard McLeod in a famous book on insulin[25] wrote *"The great majority of anatomists have leaned to the view first expressed by Diamare [1895] and endorsed by Rennie[26] and Schafer [Lancet 1905, ii:321] [that the islets are structures distinct from the rest of the pancreas with the specific function of producing and internal secretion. […] Diamare states definitely that the islets of Langerhans have an endocrine function in connection with glucose metabolism in the body and that hyperglycaemia and diabetes are associated with their inadequate functioning [1905]"*.

4. COMMENT

Diamare, a great investigator who worked until the last day of his life, was not obsessed by the idea of the lost Nobel Prize. He knew that he had not been supported from Italy. However, he defended his work and debated his priority and continued to investigate the topic until the very end of his life. A great example is the paper *Il Pancreas Endocrino (endocrine pancreas)*, where he discussed the real contribution of his competitors.[27] At that time, he was 85 years old.

5. SHORT BIOGRAPHY OF DIAMARE

Vincenzo Diamare (1871–1966) was born in Naples on 3 April 1871. He started his medical studies at the University of Naples and received the MD in 1986. As a medical student, he was an internal fellow at the Anatomy Department of the Faculty of Science and at the Marine Station directed by Anton Dohrn. At the time, A.E. Dziesch, J. Apathy and A. Bethe worked there. Under their guidance, he started work on Cestods. After receiving the MD, he was nominated investigator of the Chair of Anatomy and Physiology. His creativity and productivity were so outstanding that in 1902 he received an invitation to teach Zoology and Anatomy at the University of Camerino. Later, he taught at the Universities of Perugia, Pisa and Siena. Finally, from 1923 to 1942,

he taught –as successor of Vincenzo Paladino– Histology, General Physiology and Embryology at the University of Naples. In 1951, Diamare received the Gold Medal of the Ministry of Education and Science and the prestigious Feltrinelli Prize from the Lincean Academy in Rome for his studies on the discovery of insulin. He died on 20 January 1966. A street in the quarter of the great hospitals in Naples bears his name.

ΠΕΡΙΛΗΨΗ

Vincenzo Diamare (1871–1966) και η προτεραιότητα για την ανακάλυψη της ενδοκρινικής λειτουργίας του παγκρέατος (1895)

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Από το 1895–1908, ο Vincenzo Diamare (1871–1966) έκανε καινοτόμες μελέτες σχετικά με τη λειτουργία των μη λοβιωδών κυττάρων του παγκρέατος, τα οποία περιγράφει ο Paul Langerhans το 1869. Μέσω συγκριτικών ανατομικών και φυσιολογικών μελετών, καθόρισε την ενδοκρινική τους λειτουργία και τη ρύθμιση του μεταβολισμού γλυκόζης στον άνθρωπο. Τα στοιχεία του επιβεβαιώθηκαν από τους E. Laguesse, W. Schulze, E. Sauerbeck, N. Minkowski και πολλούς άλλους, μεταξύ των οποίων ο J.J.R. McLeod. Όταν το 1923 απονεμήθηκε το βραβείο Νόμπελ Ιατρικής και Φυσιολογίας στους Frederick Grant Banting και John James Rickard McLeod, το όνομά του δεν αναφέρθηκε. Η Επιτροπή Νόμπελ παραμέλησε επίσης όχι μόνο τον Charles Best και τον Bertrand Collip που ανήκαν στην Ομάδα Ερευνών του Τορόντο, αλλά και τους N. Paulescu, G.L. Zuelzer, S.S. Kleiner και E. Lanceraeux. Ο Diamare δεν διαμαρτυρήθηκε. Καθ' όλη τη ζωή του, συνέχισε να ερευνά το θέμα και στην ηλικία των 85 ετών συνέγραψε μια σημαντική ανασκόπηση (85 σελίδων), αναφέροντας σχολαστικά τις ιδέες των υποστηρικτών και των αντιπάλων του, χωρίς δριμύτητα.

Λέξεις ευρετηρίου: Ανακάλυψη ινσουλίνης, Ενδοκρινική λειτουργία του παγκρέατος, Ινσουλίνη, Paul Langerhans, Vincenzo Diamare

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BIOGRAPHY
ΒΙΟΓΡΑΦΙΑ

The Seldinger technique – the vascular access method Nephrology application

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ΑΡΧΕΙΑ ΕΛΛΗΝΙΚΗΣ ΙΑΤΡΙΚΗΣ 2020, 37(Συμπλ 2):57–62

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Η τεχνική Seldinger – η μέθοδος αγγειακής προσπέλασης: Νεφρολογική εφαρμογή

Περίληψη στο τέλος του άρθρου

Key words

Dialysis access
Interventional radiology
Seldinger technique

The Swedish radiologist Sven Ivar Seldinger (1921–1998) was born in Mora, a small town in northern Sweden. Following the completion of his medical studies at the Karolinska Institute in Stockholm, he started his career at the Department of Radiology, Karolinska University Hospital in 1950. His special interest was angiography. In those days, the intravascular administration of contrast media involved catheterisation after a surgical incision of the vessels, either through a small polyethylene catheter placed in the needle or by direct needle puncture. Complications were common and the contrast medium could only be injected relatively slowly. In April 1952, Seldinger had "a severe attack of common sense". He realised the sequence in the procedure of catheter introduction to the vessel should be: needle in – guide-wire in through the needle – needle out – catheter in over the guide-wire – guide-wire out. This revolutionised the vascular access procedure and became widely used in interventional radiology, as well as in other clinical applications in Scandinavia and gradually spread to other clinical settings worldwide. Ever since the introduction of haemodialysis in the 1940s, vascular access had been the method's "Achille's heel", especially as the need for dialysis was continuously increasing. The most important steps in the improvement of haemodialysis were the creation of the Quinton–Scribner shunt in 1960 and later the Cimino–Brescia arteriovenous fistula in 1966. However, an easy method of vascular access for acute therapeutic needs or investigation was missing. The Seldinger technique solved this problem and was unrivalled thanks to its simplicity, quickness, and low risk of complications. Stanley Shaldon introduced this technique in dialysis in 1961. Since then, it has been used for all extracorporeal procedures in dialysis departments, when no other vascular accesses are attainable. Seldinger used this method to perform many interventions, such as catheterisation of the renal artery and selective renal angiography (1955). He returned to Mora in 1966 and worked at the local hospital until his retirement in 1986.

1. EARLY YEARS

Sven Ivar Seldinger (fig. 1) was born on 19 April 1921 in the small town of Mora in the northern Swedish province of Dalecarlia. A member of his mother's family worked with fine mechanics, making the famous Mora clocks. His great-grandfather, Djos Matts, while sitting in his Mora Mechanical Workshop, was painted (oil on canvas) by the renowned painter Anders Zorn in 1906 (fig. 2). Young Sven Ivar often visited his grandfather's workshop and observed him as he used precision tools. He attended primary school in Mora and high school in the nearby town of Falun. As a 17-year-old high school student, he went on a bicycle tour in Germany and sent a series of reports, which were published in the local Mora Newspaper, where, after graduating, he served for half a year as a volunteer. In 1940, he applied for technical and medical universities, was admitted to both but chose medical studies at the Karolinska Institute in Stockholm. After graduation in 1948, followed by an internship at hospitals in Stockholm, he obtained a residency in the Department of Radiology at Karolinska Hospital in 1950, where he joined the angiography group and assisted in the procedures.[1,2] He quickly earned a reputation for being highly intelligent, independent and at times drastic in expressing himself.[3]

Figure 1. Sven Ivar Seldinger, 1950s (reproduced by permission of Seldinger's family).

Figure 2. Sven Ivar Seldinger's great-grandfather Dios Matts painted by Anders Zorn 1906. Reproduced by permission of the Zorn collections, Mora, Sweden.

2. RESIDENCY, DEPARTMENT OF RADIOLOGY, KAROLINSKA HOSPITAL, STOCKHOLM

At this time, the three main methods of blood vessel access for angiography were:[1–4]

- Surgical incision to expose venous and arterial vessels before catheterisation, often followed by resuturing or ligature of the vessel
- Percutaneous puncture using a needle with a catheter inside (catheter-through-needle) where small or large bore needles were used. In case of small calibre of the catheter the flow and amount of administered contrast was limited
- Direct needle-puncture of vessels (e.g. the carotid and femoral artery, the lumbar artery) and organs (the heart) and injection of contrast media through the needle.

These methods were relatively traumatic, time-consuming and involved a substantial risk of blood loss, damage to the vessel walls, nerves, infection and other complications. Some parts of the vascular bed like the visceral arteries were not accessible to investigation.

Technically oriented Seldinger was well aware of these disadvantages of the existing methods of vascular access. He intended to improve the catheter insertion technique and initially modified the Cournand's puncture method using an inner sharp needle in an outer blunt cannula, the edge of the needle exceeding the cannula by 1–2 mm.[5] It was difficult to operate with the longer needle and Seldinger inserted the needle in the side hole of the catheter with the tip protruding 1–2 mm beyond the catheter end. After introducing the needle and the catheter into the vessel, the needle was removed and a piano string wire was inserted into the catheter to make it rigid enough to be pushed along the vessel (fig. 3). Later, the string was replaced by an actual guide wire (long semi-flexible metal wire tightly coiled on a central wire core) constructed in cooperation with Stille-Werner company in Stockholm. This method was, however, imperfect and one day in April 1952, during his second year of residency, when he was standing depressed at the table with the needle, guide wire and catheter in his hands, making several attempts to place a catheter into a frozen cadaver aorta,[6] he was struck by what he himself described as a "severe attack of common sense". He realised that he should use these three items in another sequence (fig. 4): (a) Needle in; (b) guide wire in through the needle; (c) needle out; (d) catheter in over wire; (e) guide wire out.[4] With "beginner's luck" he successfully used this new technique the following day in a brachial artery puncture to get access to the subclavian artery for visualisation of a parathyroid adenoma.[7]

3. SELDINGER TECHNIQUE ACCEPTED WORLDWIDE

In June 1952, the Seldinger technique was presented by his professor Knut Lindbom at the Nordic Association

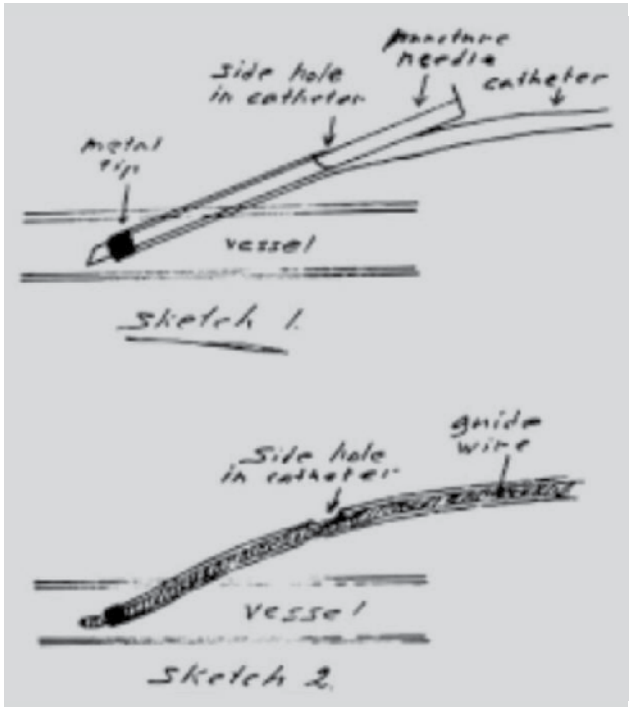

Figure 3. Seldinger's line drawings of two stages in the development of his method of introducing a catheter into an artery. Reproduced by permission from letter to Doby T., published in *AJR Am J Roentgenol* 1984, 142:2.

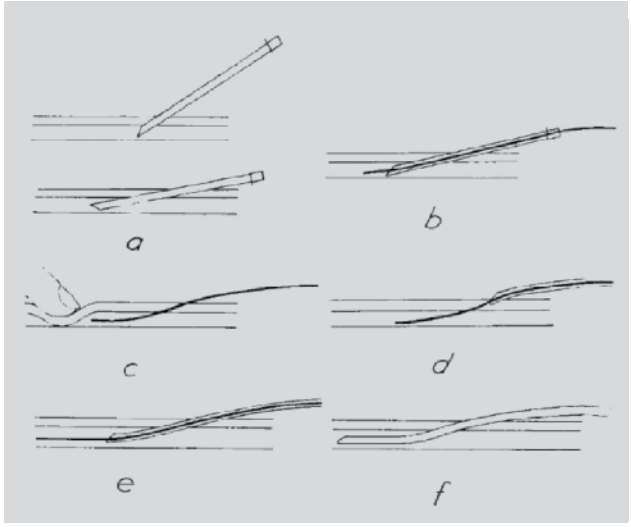

Figure 4. Steps in the Seldinger technique of vessels catheterization. Reproduced by permission from the original paper by Seldinger in *Acta Radiol* 1953, 39:370.

of Medical Radiology in Helsinki, Finland (Seldinger stayed in the hospital doing the routine work) and in 1953 it was published in *Acta Radiologica*.[4] It described 40 cases of angiographies, without severe complications and proved to be a new method for quick, simple and easy access for catheterisation of peripheral and central arterial and venous vessels. Seldinger wrote: *"This technique is simpler than appears on paper and after a little practice should present no difficulties"*. The Seldinger technique was introduced in Sweden as early as 1952 and soon gained in popularity across Europe and later in the United States.

Seldinger showed on a cadaver's aorta that with his access technique all aortic branches could be catheterised by the femoral route[1] and applied this method in many interventions, such as catheterisation of the renal artery and selective renal angiography (1955) using a pre-shaped bent polyethylene catheter of the same size as the needle or somewhat larger (fig. 5).[8,9] He performed transhepatic and transsplenic catheterisations of the portal vein for venography and studies of hemodynamics, also for cholangiography via percutaneous puncture of the bile duct.[10,11] The position, the course of the vessels and all pathological abnormalities, for example in extremities, could now be visualised.[12] This ingenious invention was a medical milestone, used widely in all interventional vascular and nonvascular procedures in radiology, neurology, oncology (arterial cytostatic treatment), urology and nephrology (haemodialysis treatment), cardiology and treatment of vascular diseases.[13,14] The Seldinger technique fully contributed to the development of cardiovascular catheterisation (investigation of cardiac hemodynamics, coronary angioplasty, endovascular stent-graft placement). Cournand, Forssmann and Richards were awarded the Nobel Prize in Physiology or Medicine in 1956 for the work in this field.

Figure 5. Steps in introducing a catheter into the renal artery (selective renal angiography). Reproduced by permission from *Acta Radiol* 1956, 45:16.

As estimated according to the number of sold guide wires, by 1984, this technique had been used in as many as 50 million patients up from just 6 million in 1983.[15]

4. THE SELDINGER TECHNIQUE IN NEPHROLOGY

Access to vessels in haemodialysis treatment had been an important problem since the early 1940s. Initially, only acute cases were treated and access to a peripheral artery and vein was obtained through exposure of the vessels and insertion of glass or plastic cannulae. After each treatment, the cannulae were removed and the vessels tied – consequently after several treatments the possibility to obtain access was lost.

In the late 1950s, when treatment of chronic renal failure started, the access problem became especially crucial as a patient needed to be connected to a dialyser over 100 (nowadays 150) times in one year. The situation changed in 1960 when the Quinton-Scribner arteriovenous shunt was introduced and further in 1966 when the Cimino-Brescia arteriovenous fistula was implemented. Both required simpler operative procedures and were inadequate in acute cases when haemodialysis had to be started immediately (due to e.g. hyperkalemia, overhydration, intoxication), in patients with failure of the existing accesses or waiting for access operation.

In 1961, Shaldon from London (UK), unable to find a surgeon to expose the vessels and insert a catheter for haemodialysis, used the Seldinger technique for placing catheters via the femoral artery and vein.[16] He was also able to use femoral venous catheters for single or repeated dialyses in intermittent treatment when chronic haemodialysis was started in 1961. Currently, the Seldinger technique is an irreplaceable method of catheterisation in emergency access situations in many haemodialysis departments, especially those that deal with different forms of extracorporeal circulation. It takes about 20 minutes between the decision for catheter insertion via the femoral vein and connection to the proper machine.

In the Department of Nephrology in Lund, Sweden, this percutaneous access procedure for catheter insertion is used for haemodialysis, continuous arteriovenous (venovenous) haemofiltration, haemoperfusion, plasmapheresis, protein A immunoabsorption and other extracorporeal procedures. The femoral veins may be used alternatively many times by an experienced person. The size of the double lumen catheter´s internal diameters allows blood flow of up to 300 mL/min. A single lumen catheter with a smaller external diameter can be used in continuous blood circulation if double pump equipment is available. Complications like bleeding or puncture of an artery may happen but nerve damage or femoral stenosis are very rare.

5. EPILOGUE

Sven Ivar Seldinger defended his doctoral thesis "Percutaneous Transhepatic Cholangiography" in 1966[17] and moved to the Radiology Department at the University of Gothenburg where he got the position of Associate Professor. After spending one year there, he returned to his home town of Mora to become Head of the Radiology Department at the local hospital until his retirement in 1986 at the age of 65. He died 12 years later, on 21 February 1998 in his home in Mora. He was survived by his wife, an artist. They had three daughters.

Sven Ivar Seldinger published 32 clinical articles, eight of which refer to nephrology. Worldwide acknowledgement of Seldinger's contribution was proved by many awards and honours that he received. Herbert Abrams (a prominent radiology professor at the Harvard Medical School and the Stanford University School of Medicine, Nobel Peace Prize 1985), wrote: *"…probably no single contribution has weighed more heavily than the technique developed by Sven Seldinger… His contribution moved the field into a new and exciting direction and left permanent imprint on medical imaging, diagnostic and therapeutic medicine"*.[18] His close Swedish friend and colleague Torgny Greitz wrote: *"We who know him learned soon to appreciate his sincerity, honesty, and solicitude for others. He was a good and reliable friend"*.[3]

His name is preserved in the Swedish Seldinger Society of Vascular and Interventional Radiology, established in 1992.

Honorary member: Central African Congress of Radiology, Bulawayo 1963; South African Congress of Radiology, Johannesburg 1968; International Radiology Congress, Madrid 1973; The New York Academy of Medicine, Section of Urology, New York 1975; The Angiography Course, Massachusetts General Hospital, Boston 1981; European Radiology Congress, Lisbon 1987; International Symposium of Interventional Radiology and New Vascular Imaging, Hakone, Japan 1988; International Radiology Congress, Paris 1989; The Atherectomy Symposium, Coronary Interventions, San Francisco 1990; The Annual Meeting of the British Society of Interventional Radiology, Sheffield 1991; Asian Oceanian Congress of Radiology, New Delhi 1992; Annual Meeting of the Society of Cardiovascular and Interventional Radiology, Washington DC 1992.

Honorary memberships: Swedish Society of Radiology,

1979; The American Society of Neuroradiology, 1986; The Radiological Society of North America, Chicago 1991; The American Society of Cardiovascular and Interventional Radiology, 1992; Seldinger Society of Vascular and Interventional Radiology, 1993; Swedish Society of Neuroradiology, 1993; Doctor Honoris causa – Uppsala University, 1984.

Awards: Valentine Award, New York Academy of Medicine, Section of Urology, for "distinguished contributions to urology", 1975; Korrespondierende Mitglied in Deutsche Röntgengesellschaft, 1976; Theodore and Jean Castle Professor of Radiology (the first holder of this professorship), Case Western University, Cleveland, Ohio USA, 1991; the first recipient of the "Pioneer in Interventional Radiology Award" by the American Society of Cardiovascular and Interventional Radiology, 1992; The Royal Swedish Academy of Science, Hilda och Alfred Eriksson award, 1993.

ΠΕΡΙΛΗΨΗ

Η τεχνική Seldinger – η μέθοδος αγγειακής προσπέλασης: Νεφρολογική εφαρμογή

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Ο Σουηδός ακτινολόγος Sven-Ivar Seldinger (1921–1998) γεννήθηκε στη Μόρα, μια μικρή πόλη στη βόρεια Σουηδία. Μετά την ολοκλήρωση των ιατρικών του σπουδών στο Ινστιτούτο Καρολίνσκα στη Στοκχόλμη, ξεκίνησε την καριέρα του στο Τμήμα Ακτινολογίας, στο Πανεπιστημιακό Νοσοκομείο Καρολίνσκα το 1950. Επέδειξε ιδιαίτερο ενδιαφέρον στην αγγειογραφία. Εκείνη την εποχή, η ενδαγγειακή χορήγηση σκιαγραφικών μέσων περιλάμβανε καθετηριασμό μετά από χειρουργική τομή των αγγείων, είτε μέσω ενός μικρού καθετήρα πολυαιθυλενίου τοποθετημένου στη βελόνα είτε με άμεση διάτρηση από βελόνα. Οι επιπλοκές ήταν συχνές και το σκιαγραφικό μέσο μπορούσε να εγχυθεί σχετικά αργά. Τον Απρίλιο του 1952, ο Seldinger είχε «μια σοβαρή επίθεση της κοινής λογικής». Συνειδητοποίησε ότι η ακολουθία στη διαδικασία εισαγωγής του καθετήρα στο αγγείο πρέπει να είναι: βελόνα μέσα – οδηγός-σύρμα μέσα από τη βελόνα – βελόνα έξω – καθετήρας μέσα πάνω από τον οδηγό-σύρμα – οδηγός-σύρμα έξω. Αυτό έφερε την επανάσταση στη διαδικασία αγγειακής πρόσβασης και χρησιμοποιήθηκε ευρέως στην Επεμβατική Ακτινολογία, καθώς και σε άλλες κλινικές εφαρμογές στη Σκανδιναβία και σταδιακά εξαπλώθηκε σε άλλα κλινικά περιβάλλοντα σε όλο τον κόσμο. Από την εισαγωγή της αιμοκάθαρσης τη δεκαετία του 1940, η αγγειακή πρόσβαση ήταν η «αχίλλειος πτέρνα» της μεθόδου, ειδικά καθώς η ανάγκη για αιμοκάθαρση αυξανόταν συνεχώς. Τα σημαντικότερα βήματα στη βελτίωση της αιμοκάθαρσης ήταν η δημιουργία παροχέτευσης Quinton-Scribner το 1960 και αργότερα του αρτηριοφλεβικού συριγγίου του Cimino-Brescia το 1966. Ωστόσο, έλειπε μια εύκολη μέθοδος αγγειακής πρόσβασης για οξείες θεραπευτικές ανάγκες ή έρευνα. Η τεχνική Seldinger λύνει αυτό το πρόβλημα και ήταν απαράμιλλη χάρη στην απλότητα, την ταχύτητα και τον χαμηλό κίνδυνο επιπλοκών. Ο Stanley Shaldon εισήγαγε αυτή την τεχνική στην αιμοκάθαρση το 1961. Από τότε, έχει χρησιμοποιηθεί για όλες τις εξωσωματικές διαδικασίες σε τμήματα αιμοκάθαρσης, όταν δεν είναι εφικτές άλλες αγγειακές προσβάσεις. Ο Seldinger χρησιμοποίησε αυτή τη μέθοδο για να εκτελέσει πολλές παρεμβάσεις, όπως ο καθετηριασμός της νεφρικής αρτηρίας και η επιλεκτική νεφρική αγγειογραφία (1955). Επέστρεψε στη Μόρα το 1966 και εργάστηκε στο τοπικό νοσοκομείο μέχρι τη συνταξιοδότησή του το 1986.

Λέξεις ευρετηρίου: Επεμβατική Ακτινολογία, Παρακέντηση, Αιμοκάθαρση, Τεχνική Seldinger

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BIOGRAPHY
ΒΙΟΓΡΑΦΙΑ

Ludwik Hirszfeld (1884–1954) – Pioneer of blood type testing
Significance for organ transplants

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ΑΡΧΕΙΑ ΕΛΛΗΝΙΚΗΣ ΙΑΤΡΙΚΗΣ 2020, 37(Συμπλ 2):63–67

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Ludwik Hirszfeld (1884–1954) – Πρωτοπόρος των εξετάσεων τύπου αίματος. Μεγάλης σημασίας για τις μεταμοσχεύσεις οργάνων

Περίληψη στο τέλος του άρθρου

Proper selection of the organ to be transplanted requires a series of tests and determines the effectiveness of the treatment. The selection is preceded by a series of tests performed between the donor and recipient: pre-selection according to blood group, human leukocyte antigens (HLA), panel reactive antibody (PRA) and crossmatch. Of course, the first condition is the compliance of blood types between the donor and the recipient. In 1901, Karl Landsteiner discovered that human blood had different properties and distinguished three blood groups: A, B, and C. In 1910–1911, Emil von Dungern and Ludwik Hirszfeld discovered the Mendelian inheritance of blood types. Their division into four basic groups A, B, AB and O has been used since 1928. The same researchers found subtypes A1 and A2 within type A. Ludwik Hirszfeld (1884–1954) was born in Warsaw and studied medicine in Würzburg. In 1907, he received a doctorate at the University of Berlin and moved to the Cancer Research Centre in Heidelberg and, in 1911, to the University of Zurich. As a volunteer in World War I in Serbia, he fought a typhus epidemic. In 1918–1919, with his wife Hanna, he researched and described the uneven distribution of blood type features that reflects the diverse evolutionary adaptations of humans. In the 1920s, he co-founded the National Institute of Hygiene in Warsaw. During World War II, he spent two years in the Warsaw ghetto, where he fought infectious diseases, typhus and tuberculosis. After the war, he headed the Department of Medical Microbiology at Maria Skłodowska-Curie University in Lublin. In 1945, he worked in Wrocław as the Head of the Department of Microbiology. He died in Wroclaw. Ludwik Hirszfeld was an outstanding medical doctor, researcher and community activist. The importance of Hirszfeld's contribution to our knowledge of the blood type system was confirmed by Karl Landsteiner in his Nobel Address, by choosing Hirszfeld to the Presidency of the Blood Group of the Second International Congress of Blood Transfusion in Paris in 1937 and by naming after him the Institute of Immunology and Experimental Therapy of the Polish Academy of Sciences in Wrocław.

Key words

Blood type
Ludwik Hirszfeld
Organ transplant

1. INTRODUCTION

Beyond doubt, the ultimate solution for those suffering from end-stage renal disease is renal transplant. The first attempts at transplanting kidneys date back to the early 20th century, yet for a long time the success of the surgery depended on the then-unknown mechanisms of transplant rejection. A good, yet sorry example is made by a series of unsuccessful organ transplants resulting from the lack of knowledge about the mechanisms of immune response after the introduction of a foreign tissue or organ into the system. Nowadays, the selection of organs to be transplanted is preceded by a series of tests performed between the donor and recipient: pre-selection according to blood group, human leukocyte antigens (HLA), panel reactive antibody (PRA) and crossmatch. The first and foremost condition for correct selection is matching for ABO blood groups.[1] The discovery of blood groups is owed to the research carried out by the Austrian Karl Landsteiner, working at the Anatomical Pathology Department at the University of Vienna. It was in 1901 when he divided blood into three groups, depending on its properties: A, B and a

third one, today known as group 0. One year later, in 1902, Sturli and von Decastelo described the fourth and rarest of them all – group AB. In 1930, for his discoveries, Landsteiner received the Nobel Prize in the field of physiology and medicine. In 1910-1911, Emil von Dungern and Ludwik Hirszfeld from the Cancer Research Centre in Heidelberg, Germany discovered and described Mendelian inheritance of blood type and introduced the marking of blood groups A, B, AB and O, which was officially accepted in 1928. They also discovered subgroups A_1 and A_2 within the A type.[2–4] Being representatives of Western Europe, Karl Landsteiner and Emil von Dungern are very well known to readers of English and German-language publications. So remarkable was the significance of these discoveries that the presentation of the third one, Ludwik Hirszfeld from Eastern Europe, seems necessary.

2. LIFE

Ludwik Hirszfeld was born on 5th August 1884 in a Polonised Jewish family (fig. 1). His parents were Stanisław, a merchant and industrialist and Jenny nee Ginsberg. The Hirszfelds were strongly rooted in Polish culture. Ludwik's uncle was a chemist and a community activist and his sister's husband, Władysław Sterling, was a renowned Polish neurologist. Due to financial problems, the Hirszfelds moved to the city of Łódź where, in 1902, Ludwik graduated from a secondary school, majoring in Arts and Humanities. Followed on from that, he went to Germany which, at that time, was one of the most popular destinations for young Poles wishing to study at a university. First, he studied medicine in Würzburg and then in Berlin, where he obtained the title of doctor of medicine. Then, in 1907, the young doctor moved to the Cancer Research Institute in Heidelberg, to be taken on as an assistant in the Parasitology Department and then in Serology. This is where he came into contact with Emil von Dungern; their cooperation, in 1910, resulted in the establishment of blood types and the principles of their inheritance. The following year, Hirszfeld moved to the University of Zurich, Switzerland where he was habilitated in the field of hygiene and the science of immunity. In Zurich, he also investigated the issue of endemic goitre in Switzerland and worked as a full-time associate professor, lecturing on infectious diseases and serology.[5–7]

Figure 1. Ludwik Hirszfeld (photo courtesy of the National Digital Archive in Warsaw).

After the outbreak of World War I, in 1915 he volunteered to go to Serbia where he was shortly joined by his wife. During his visit to the Balkans, he was involved in fighting a huge epidemic of typhus typhoid in the town of Valiewo. Extraordinary measures having been applied, the epidemic was brought under control. In stunningly primitive conditions, Hirszfeld managed to set up a small scientific centre there. Before the end of the war, the Hirszfelds were evacuated out of Serbia with the retreating army, as part of the hospital formation. The daunting route led through the Albanian mountains from where they made a sea crossing to Italy and finally managed to get back to Switzerland. There, for a while, Hirszfeld continued his work on the application of kitchen salt in patients with haemorrhagic shock only to move to Corfu, Greece where his wife, Hanna, ran her own department and he conducted statistical research on the incidence of major blood groups among different races and nations.[8,9]

After the end of World War I, the Hirszfelds returned to Warsaw, Poland, where Ludwik became Director of the Serum Research Department of the Department of Bacteriology and Experimental Medicine of the emerging National Institute of Hygiene, headed by Ludwik Raichman, the founder of UNICEF. In Warsaw, Hirszfeld also lectured on bacteriology and immunology at the Free Polish University, in the Medical and Pharmaceutical Departments of the University of Warsaw and at the School of Hygiene (fig. 2).

After the outbreak of World War II, due to his origin, he could not continue working in the National Institute of Hygiene and, in 1941, he and his family were transferred to the Warsaw Ghetto. There, he fought the typhoid fever epidemic with the use of a typhoid vaccine smuggled out of Lviv by another Polish researcher, Rudolf Weigel. He was also involved in underground university teaching. In August 1942, the Hirszfeld family managed to get out of the ghetto

Figure 2. Ludwik Hirszfeld (photo courtesy of the National Digital Archive in Warsaw).

and were hiding under a changed name in many places in German-occupied Poland. After the war, Hirszfeld was one of the organisers of Maria Skłodowska-Curie University in Lublin, being the head of the Department of Medical Microbiology and simultaneously acting as the university's Vice Rector. However, the following year, in August 1945, he arrived in Wrocław to organise the Medical Department of the University of Wrocław, since 1950 known as the Medical Academy, where he headed the Department of Microbiology and, for one year, held the position of Dean. In 1954, he became head of the Blood Group Department of the Institute of Immunology and Experimental Therapy of the Polish Academy of Sciences, which today is named after him. He died of a heart attack on 7 March 1954 in Wrocław and was buried in the cemetery of St. Lawrence. Professor Ludwik Hirszfeld's wife was Hanna Kassmann, after World War II professor of paediatrics at the University of Warsaw and later Medical University in Wrocław. The Hirszfelds had one daughter, who died in 1943 at the age of 23.[10,11]

3. WORK

Ludwik Hirszfeld's scientific achievements are impressive. The most important publications include papers written together with Emil von Dungern on Mendelian blood group differentiation A, B, AB, O adopted worldwide in 1928, as well as the discovery of subgroups within type A. In 1917, he described erythrocyte sedimentation (ESR), independently of Edmund Biernacki. Working with his wife in 1918–1919, he described the uneven distribution of blood group features that reflect diverse adaptations of the human species in the course of evolution. In 1919, he presented the bacteria of paratyphoid, which he had discovered, today named *Salmonella hirszfeldi*. Also important is his work on serological conflict between mother and foetus, as well as in the field of forensic medicine and genetics.[12–14]

He also wrote four books: *Konstitutionsserologie und Blutgruppenforschung* (fig. 3), *Blood groups in biology, medicine and law* (fig. 4);[15,16] *Affiliation in the Light of Blood Grouping*, and *General Immunology*. His autobiography *The Story of*

Figure 3. The title page of the book *Konstitutionsserologie und blutgruppenforschung* (*Constitution Serology and Blood Group Research)*.

Figure 4. The title page of the book *Grupy krwi w zastosowaniu do biologii, medycyny i prawa (Blood Groups in Biology, Medicine and Law).*

One Life, first published in 1946, and later renewed several times, sheds a lot of light on Professor Ludwik Hirszfeld. For his scientific achievements, in 1950, he was a Noble Prize nominee. He also received numerous awards, including honorary doctorates at the Universities of Prague (Czechoslovakia) and Zurich (Switzerland). He was also an honorary member of the Academy of Sciences in New York (USA). He was awarded numerous Polish and foreign state decorations.

Paweł Kisielow presented crucial Hirszfeld's characteristics with the following words: *"[…] for many he remains an icon of science, not only Polish. He embodies a large-scale scholar, researcher, teacher, doctor, community activist, organiser and humanist of well-earned international fame. His reputation was earned thanks to his wide array of talents and original scientific discoveries and concepts which greatly added to the development of a number of branches: immunogenetics, haematology, microbiology and immunology of neoplastic diseases, forensic medicine, transfusiology and, above all, research on blood types […]"*. On the other hand, research on blood types had a significant impact on the development of transfusion medicine and transplantology, including kidney transplants. The authors of this study strongly agree with the opinion presented by the author of the above-cited publication.[17]

ΠΕΡΙΛΗΨΗ

Ludwik Hirszfeld (1884–1954) – Πρωτοπόρος των εξετάσεων τύπου αίματος. Μεγάλης σημασίας για τις μεταμοσχεύσεις οργάνων

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Αρχεία Ελληνικής Ιατρικής 2020, 37(Συμπλ 2):63–67

Η σωστή επιλογή του προς μεταμόσχευση οργάνου απαιτεί σειρά εξετάσεων και καθορίζει την αποτελεσματικότητα της θεραπείας. Η επιλογή προηγείται από μια σειρά εξετάσεων που διεξάγεται μεταξύ του δότη και του λήπτη: προεπιλογή σύμφωνα με την ομάδα αίματος, τα αντιγόνα ανθρώπινων λευκοκυττάρων (HLA), τα αντισώματα αντιδραστικής ομάδας (PRA) και τη διασταύρωση. Φυσικά, η πρώτη προϋπόθεση είναι η συμβατότητα των τύπων αίματος μεταξύ του δότη και του λήπτη. Το 1901, ο Karl Landsteiner ανακάλυψε ότι το ανθρώπινο αίμα είχε διαφορετικές ιδιότητες και διέκρινε τρεις ομάδες αίματος: Α, Β και Γ. Το 1910–1911, ο Emil von Dungern και ο Ludwik Hirszfeld ανακάλυψαν τη μεντελική κληρονομιά των τύπων αίματος. Η διαίρεσή τους σε τέσσερις βασικές ομάδες Α, Β, ΑΒ και Ο χρησιμοποιείται από το 1928. Οι ίδιοι ερευνητές βρήκαν υποτύπους Α1 και Α2 εντός του τύπου Α. Ο Ludwik Hirszfeld (1884–1954) γεννήθηκε στη Βαρσοβία και σπούδασε Ιατρική στο Würzburg. Το 1907, έλαβε διδακτορικό δίπλωμα στο Πανεπιστήμιο του Βερολίνου και μετακόμισε στο Κέντρο Έρευνας για τον Καρκίνο στη Χαϊδελβέργη και το 1911 στο Πανεπιστήμιο της Ζυρίχης. Ως εθελοντής στον Α΄ Παγκόσμιο Πόλεμο στη Σερβία, καταπολέμησε μια επιδημία τύφου. Το 1918–1919, με τη σύζυγό του Hanna, διερεύνησε και περιέγραψε την ανομοιόμορφη κατανομή των χαρακτηριστικών του αίματος που αντικατοπτρίζει τις ποικίλες εξελικτικές προσαρμογές των ανθρώπων. Στη δεκαετία του 1920 συνίδρυσε το Εθνικό Ινστιτούτο Υγιεινής στη Βαρσοβία. Κατά τη διάρκεια του Β΄ Παγκοσμίου Πολέμου, πέρασε δύο χρόνια στο γκέτο της Βαρσοβίας, όπου καταπολέμησε μολυσματικές ασθένειες, τύφο και φυματίωση. Μετά τον πόλεμο, ηγήθηκε του Τμήματος Ιατρικής Μικροβιολογίας στο Πανεπιστήμιο Maria Skłodowska-Curie στο Λούμπλιν. Το 1945 εργάστηκε στο Βρότσλαβ ως Επικεφαλής του Τμήματος Μικροβιολογίας. Πέθανε στο Βρότσλαβ. Ο Ludwik Hirszfeld ήταν εξαιρετικός ιατρός, ερευνητής και ακτιβιστής της κοινότητας. Η σημασία της συμβολής του Hirszfeld στη γνώση μας για το σύστημα τύπων αίματος επιβεβαιώθηκε από τον Karl Landsteiner στην Απονομή του Νόμπελ, επιλέγοντας τον Hirszfeld στην Προεδρία της Ομάδας Αίματος του Δεύτερου Διεθνούς Συνεδρίου Μετάγγισης Αίματος στο Παρίσι το 1937 και δίνοντας το όνομά του στο Ινστιτούτο Ανοσολογίας και Πειραματικής Θεραπείας της Πολωνικής Ακαδημίας Επιστημών στο Βρότσλαβ.

Λέξεις ευρετηρίου: Ludwik Hirszfeld, Μεταμόσχευση οργάνου, Τύπος αίματος

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Precursor of Nephrology in Poland

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ΑΡΧΕΙΑ ΕΛΛΗΝΙΚΗΣ ΙΑΤΡΙΚΗΣ 2020, 37(Συμπλ 2):68–73

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Καθηγητής Andrzej Biernacki – Πρόδρομος της Νεφρολογίας στην Πολωνία

Περίληψη στο τέλος του άρθρου

It was in the mid-20th century that nephrology started to emerge as an independent specialty and Professor Witold Orłowski is regarded as its father. His remarkable successor was Professor Andrzej Biernacki (1903–1963). Born in Lublin, Andrzej Biernacki graduated from the Medical Department of Warsaw University. During university times, he worked at the National Hygiene Institute headed by Ludwik Hirszfeld and trained at the Pasteur Institute in Paris. Then he went to a Polish colony in Brazil to study the health conditions there. On returning from Brazil, he accepted a post in the 2nd Department of Internal Medicine in Warsaw, headed by Witold Orłowski. In the 1930s, he did an internship in Vienna in Professor Wilhem Neuman's clinic and at the Forlanini Institute in Rome, and later in Davos and Paris. Staying in Italy and Germany, he could sense the atmosphere of the war lurking behind the corner. Back in Poland, he continued his work at Orlowski's clinic. During WWII, he fought in the resistance and worked in the Second Department of Internal Medicine at the University's Secret Medical Department. After the war, he organised the 1st Department of Internal Medicine. As a WHO scholarship holder, he trained in the USA in 1947. Already a professor, in 1958 as the chairman of the Nephrology Development Committee at the Ministry of Health, whose members were also Prof Jan Roguski and Prof Tadeusz Orłowski, he brought 2 Alwall's artificial kidneys to Poland. At his clinic in 1959, the team headed by Tadeusz Orłowski performed the first dialysis session in Warsaw. Biernacki's portfolio includes 75 own works and over 400 conceived under his supervision. The issues investigated concerned lung diseases, including pulmonary tuberculosis, and cardiology. However, his work on nephrology deserves special attention. It deals with key problems of division of hypertension, its malignant phase with changes in the kidneys and pharmacological and balneological treatment. He also describes the case of paroxysmal haemoglobinuria, genitourinary tuberculosis. Additionally, his work concerns the symptoms of uraemia in kidney amyloidosis, the problem of the circadian rhythm of urine production depending on the circulatory capacity and later also the possibility of haemodialysis treatment, including the treatment of mercury poisoning. Nephrology-related topics raised by A. Biernacki were continued by his co-workers and students. Andrzej Biernacki had numerous non-medical interests. He was an expert on music and husband to Grażyna Bacewicz, the outstanding Polish composer and violinist.

Key words

Andrzej Biernacki
History of dialysis in Poland
History of Nephrology in Poland

1. INTRODUCTION

Around the mid-twentieth century, a new, independent medical specialty, denoted as nephrology, started to emerge from the more general science of internal medicine, in both the USA and Europe. The late 1940s and early 1950s saw the creation of Europe's first clinics of this new discipline in the Swedish town of Lund and in the French capital Paris. They were established and headed by the legendary Nils Alwall and Jean Hamburger respectively. In Poland, despite numerous earlier references to urinary tract diseases in medical publications, these are Professor Witold Orłowski, the distinguished internist, and his successors, Profs. Andrzej Biernacki and Tadeusz Orłowski who, by general consent are regarded as the fathers of Polish nephrology. Witold Orłowski and his son Tadeusz have already been given nu-

merous accounts in international medical journals making them well-recognised figures for all those interested in the history of nephrology. This paper, then, shall set to present the life and work of Witold Orłowski's direct successor at the Clinic of Internal Medicine in Warsaw, Prof. Andrzej Biernacki, who in post-war Poland played a remarkable role in the development of the discipline that later was to become known as nephrology. In turn, his work was continued by the famous Tadeusz Orłowski, Alfred Siciński and others.

2. LIFE

Born in the Polish town of Lublin on 14 March 1903, Andrzej Biernacki was the son of the renowned Polish doctor and community activist Mieczysław Biernacki and his wife Zofia Anna Weysflog (fig. 1). After the young Biernacki's graduation from Lublin Vetter secondary school, the family moved to Warsaw in 1921. Seven years on, in 1928, Biernacki graduated from the Medical Department at the University of Warsaw, obtaining the title of *doctor medicinae universae*. Still a student, A. Biernacki was engaged in voluntary work (1924–1925) in one of the departments at Infant Jesus Hospital ran by Władysław Janowski and then worked at the National Institute of Hygiene in the Department of Experimental Medicine (1925–1927) headed by Prof Ludwik Hirszfeld, the famous Polish serologist and immunologist. At the same time, he served as a demonstrator in the Faculty of Pharmacy at the university. It was in 1925 when the National Institute of Hygiene decided to send the promising student to Luis Pasteur Institute in Paris to learn the *Neisseria meningitides* serum titration method. There, over the summer months, he worked at the departments headed by Professors Jan Danysz and Dujarrio de la Riviere.[1,2] Back in Poland, after graduating in 1928, Biernacki started working at St. John's Hospital in Lublin, yet a few months later, in September 1929, he went to Brazil to work as a doctor for the Polish colony "White Eagle" in the state of Espirito Santo (fig. 2). He stayed there until December 1930 and in January 1931, he accepted a post at Instituto Oswaldo Cruz in Rio de Janeiro, funded by this well-known epidemiologist.[3] During his stay there, which lasted until May 1931, he developed the material collected in the colony. The results were later published right before the outbreak of the Second World War in the Polish journal *Medycyna* (*Medicine)*. Biernacki left Brazil and on 1 November 1931, he became a voluntary assistant in the 2nd Clinic of Internal Medicine at the University of Warsaw, headed by Witold Orłowski. Having been granted a one-year Potocki scholarship in 1935, Biernacki made his way to Vienna and Rome. In the Austrian capital, he

Figure 1. Professor Andrzej Biernacki (courtesy of Dr. Zbigniew Fałda).

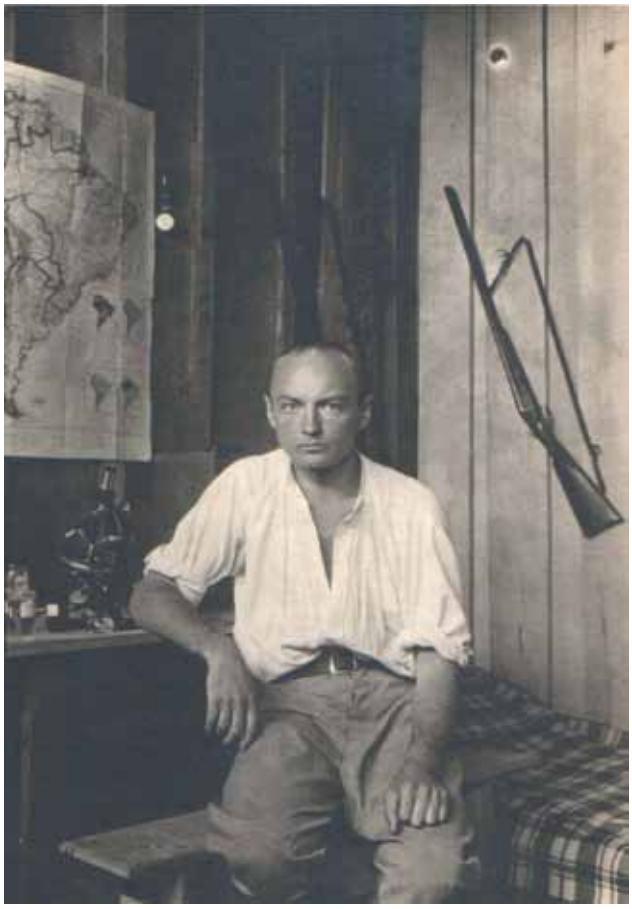


Figure 2. Andrzej Biernacki in the colony in Brazil (courtesy of Joanna Sendłak).

worked at the clinic headed by Prof. Wilhelm Neuman's, the outstanding Austrian internist specialising in TB treatment and then trained in an X-ray department headed by Prof. Felix Fleischner, the Austrian radiologist later working in the USA. After short training stays in Paris, Berlin and Szczecin, Biernacki arrived at Carlo Forlanini Institute in Rome, one of the world's greatest centres of TB treatment and research. Opened in 1934, the Institute was initially named after Benito Mussolini; it was later renamed into Carlo Forlanini – the discoverer of a new TB treatment method with pneumothorax. It comprised a few departments: the hospital, sanatorium znd research centre and the clinics of internal medicine, surgery, orthopaedics, obstetrics, paediatrics and laryngology.[4]

The training having finished, Biernacki returned to Poland to continue work at the 2nd Clinic of Internal Medicine as the Head of the TB Outpatient Clinic and the TB Department.[5] After the outbreak of WWII, during the September campaign, he worked as Head of the Infectious Diseases and Internal Medicine Department in Złoczów. Then, after a short stay in Lviv, he went back to Warsaw to be taken on as a Senior Assistant, and since 1943 as an Assistant Professor in the Clinic. During the Nazi German occupation, he was involved in the system of underground education and was a soldier of the underground Home Army. He was also a member of the Board of the Health Section of the Warsaw Social Self-Help Committee. On the eve of the Warsaw Uprising, he obtained a habilitation (*the circulatory system in pulmonary tuberculosis*). During the uprising, he worked in the hospital in Lviv st. and after the fall of the uprising he stayed in a camp in Pruszków. Subsequently, he worked in Grodzisk Mazowiecki in an evacuated Clinic.

After the war, Andrzej Biernacki organised and then managed the Department of Internal Medicine at Infant Jesus Hospital. In 1948, he transformed the Department into the 1st Clinic of Internal Medicine at the Medical Academy in Warsaw.[6,7] In 1947, he became *Professor Extraordinarius* and in 1956 a full professor. In October 1947, with a WHO scholarship in his hand, he made his way to the USA, where for the next 4 months he worked in New York, Boston, Baltimore and Chicago. He was a Correspondent Member of the Polish Academy of Arts and Sciences and of the Polish Academy of Sciences, Chairman of the 1st Committee of Clinical Sciences of the Polish Academy of Sciences, the Poznań Society of Friends of Science, the Polish Society of Internal Medicine, the International Society of Internal Medicine and the International Society of Haematology (fig. 3).

In recognition of his remarkable scientific and organisational achievements, Andrzej Biernacki received many awards of national, ministerial and university character. Notably, apart from medicine, Biernacki was interested in a wide range of subjects and fields of human activity. He was a classical music connoisseur and himself a talented pianist. He was very knowledgeable about literature and art and a keen skier and mountain hiker. He was married to the renowned Polish composer and violinist, Grażyna Baczewska with whom had a daughter, Alina.[8] Professor Andrzej Biernacki died on 30 July 1963.

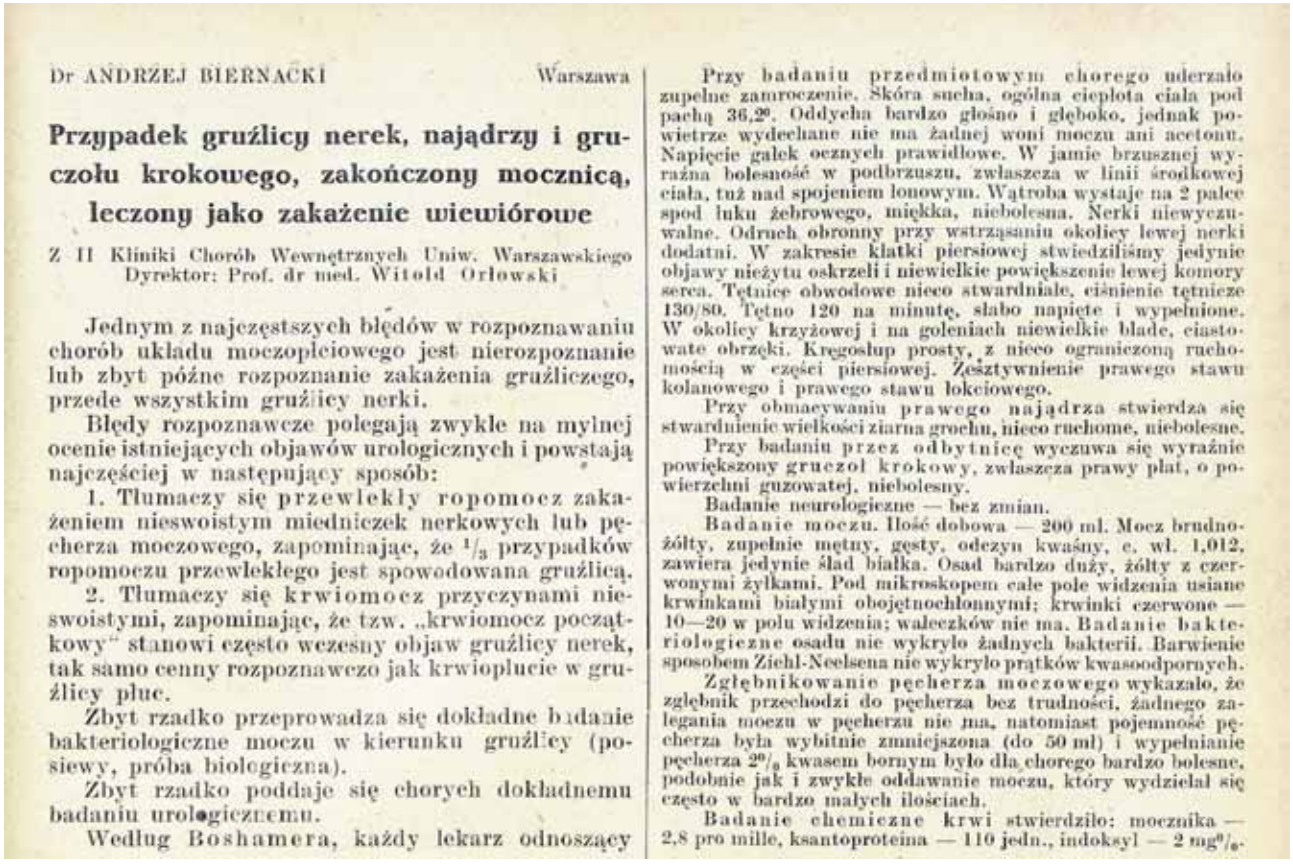
Figure 3. First left: Prof. Andrzej Biernacki, prof. Walenty Hartwig (courtesy of Dr. Zbigniew Fałda).

3. WORK

The fruit of Professor Andrzej Biernacki's scientific activity is 75 own works and over 400 prepared under his supervision. Among his own works, 28 publications in the field of lung diseases and tuberculosis deserve special recognition as they present the importance of this issue in a variety of aspects. He also published on cardiovascular disease, haematology and angiology. He also dealt with and published on issues of organisation of scientific institutions. He presented, among others, a plan of the 6th Faculty of Medicine of the Academy of Sciences regarding the creation of the Institute of Experimental and Clinical Medicine of the Academy.[9–13] He also proposed a plan of scientific research in the fields crucial for the country's

economy. These included virology, struggle with circulatory system and oncological diseases and research on new medicines. His first publication, titled *On Scleroma* was published in *Warszawskie Czasopismo Lekarskie (Warsaw Doctors' Journal)* in 1927.[14] What is especially striking is a substantial number of publications on the newly-emerging discipline –Nephrology– which deserve a brief discussion.

Back in 1936, *Medicine* published Biernacki's paper on a rare case of paroxysmal haemoglobinuria. Only approximately 200 cases of this illness had been described before 1921. In 1945, in *Przegląd Lekarski (Doctors' Review)* he published his work titled *A case of tuberculosis of the kidneys, epididymis and prostate, ending in uraemia, treated as…* in which he emphasises frequent errors in the diagnosis of tuberculosis of the genitourinary system, which consist mainly in considering chronic pyuria and haematuria as a cause of inflammatory infections, ignoring the possibility of tuberculosis (fig. 4).[15] In *Doctors' Review,* he published the paper *On the form of nitrogenous kidney amyloidosis*. There, he states that uraemia in the course of renal amyloidosis may arise as a result of amyloidal changes in the glomeruli (they destroy the glomeruli and reduce the amount of active parenchyma), amyloidal lesions in the vessels and retrograde lesions in the renal tubules. Those days it was tuberculosis that was the most common cause of amyloidosis.[16] In 1954, the journal *Polish Doctors' Weekly* published Biernacki's paper *Diuresis during sleep and after waking up in cases of circulatory efficiency and inefficiency.* The work indicates that in normal circumstances the amount of urine passed during the day exceeds that which is passed during the night, the cause of which might nest in the circadian rhythm and changes in neuro-humoral mechanisms. This same subject was also investigated in Poland by Mieczysław Fejgin and Tadeusz Orłowski.[17] In 1953 and 1956, *The Polish Archive of Internal Medicine* published two papers: *Clinical division of hypertensive disease* and *On the so called malignant hypertension*. In the first, Biernacki proposes the most important classifications of hypertension on the basis of Soviet Russian research (Łang, Zelenin, Miasnikow).[18] He also presents the Project of the Committee for the Unification of Cardiological Terminology, which is based on the following periods: initial period, period of unstable hypertension, fixed and end hypertension. In the latter work, he discusses the malignant stage of hypertension or



Dr ANDRZEJ BIERNACKI Warszawa

Przypadek gruźlicy nerek, najądrzy i gruczołu krokowego, zakończony mocznicą, leczony jako zakażenie wiciórowe

Z II Kliniki Chorób Wewnętrznych Uniw. Warszawskiego
Dyrektor: Prof. dr med. Witold Orłowski

Jednym z najczęstszych błędów w rozpoznawaniu chorób układu moczopłciowego jest nierozpoznanie lub zbyt późne rozpoznanie zakażenia gruźliczego, przede wszystkim gruźlicy nerki.

Błędy rozpoznawcze polegają zwykle na mylnej ocenie istniejących objawów urologicznych i powstają najczęściej w następujący sposób:

1. Tłumaczy się przewlekły ropomocz zakażeniem nieswoistym miedniczek nerkowych lub pęcherza moczowego, zapominając, że $^1/_3$ przypadków ropomoczu przewlekłego jest spowodowana gruźlicą.

2. Tłumaczy się krwiomocz przyczynami nieswoistymi, zapominając, że tzw. „krwiomocz początkowy" stanowi często wczesny objaw gruźlicy nerek, tak samo cenny rozpoznawczo jak krwioplucie w gruźlicy płuc.

Zbyt rzadko przeprowadza się dokładne badanie bakteriologiczne moczu w kierunku gruźlicy (posiewy, próba biologiczna).

Zbyt rzadko poddaje się chorych dokładnemu badaniu urologicznemu.

Według Boshamera, każdy lekarz odnoszący

Przy badaniu przedmiotowym chorego uderzało zupełne zamroczenie. Skóra sucha, ogólna ciepłota ciała pod pachą 36,2°. Oddycha bardzo głośno i głęboko, jednak powietrze wydechane nie ma żadnej woni moczu ani acetonu. Napięcie gałek ocznych prawidłowe. W jamie brzusznej wyraźna bolesność w podbrzuszu, zwłaszcza w linii środkowej ciała, tuż nad spojeniem łonowym. Wątroba wystaje na 2 palce spod łuku żebrowego, miękka, niebolesna. Nerki niewyczuwalne. Odruch obronny przy wstrząsaniu okolicy lewej nerki dodatni. W zakresie klatki piersiowej stwierdziliśmy jedynie objawy nieżytu oskrzeli i niewielkie powiększenie lewej komory serca. Tętnice obwodowe nieco stwardniałe, ciśnienie tętnicze 130/80. Tętno 120 na minutę, słabo napięte i wypełnione. W okolicy krzyżowej i na goleniach niewielkie blade, ciastowate obrzęki. Kręgosłup prosty, z nieco ograniczoną ruchomością w części piersiowej. Zęsztywnienie prawego stawu kolanowego i prawego stawu łokciowego.

Przy obmacywaniu prawego najądrza stwierdza się stwardnienie wielkości ziarna grochu, nieco ruchome, niebolesne.

Przy badaniu przez odbytnicę wyczuwa się wyraźnie powiększony gruczoł krokowy, zwłaszcza prawy płat, o powierzchni guzowatej, niebolesny.

Badanie neurologiczne — bez zmian.

Badanie moczu. Ilość dobowa — 200 ml. Mocz brudnożółty, zupełnie mętny, gęsty, odczyn kwaśny, c. wł. 1,012, zawiera jedynie ślad białka. Osad bardzo duży, żółty z czerwonymi żyłkami. Pod mikroskopem całe pole widzenia usiane krwinkami białymi obojętnochłonnymi; krwinki czerwone — 10—20 w polu widzenia; waleczków nie ma. Badanie bakteriologiczne osadu nie wykryło żadnych bakterii. Barwienie sposobem Ziehl-Neelsena nie wykryło prątków kwasoodpornych.

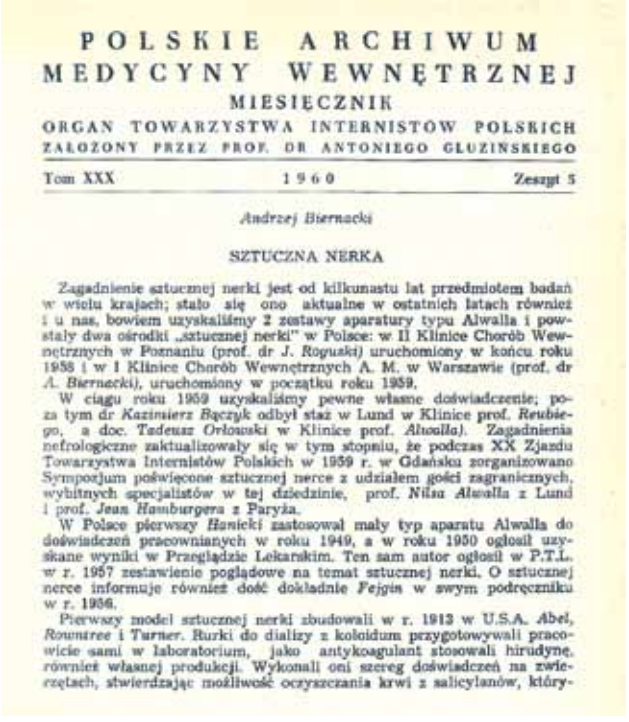
Zgłębnikowanie pęcherza moczowego wykazało, że zgłębnik przechodzi do pęcherza bez trudności, żadnego zalegania moczu w pęcherzu nie ma, natomiast pojemność pęcherza była wybitnie zmniejszona (do 50 ml) i wypełnianie pęcherza 2% kwasem bornym było dla chorego bardzo bolesne, podobnie jak i zwykłe oddawanie moczu, który wydzielał się często w bardzo małych ilościach.

Badanie chemiczne krwi stwierdziło: mocznika — 2,8 pro mille, ksantoproteina — 110 jedn., indoksyl — 2 mg%.

Figure 4. Title page of *A case of tuberculosis of the kidneys, epididymis and prostate, ending in uraemia, treated as…*

hypertensive emergency characterised by acute impairment of several organs, including the kidneys, fundus or systems like the central nervous or circulatory ones. Citing the work performed in the clinic headed by Prof. Jakub Penson in Gdańsk, Biernacki[19] states that malignant hypertension accounts for about 5.5% of hypertension cases. In his paper *Treatment of hypertensive disease* published in *Polish Doctors' Weekly* in 1961, he emphasises that the prerequisite for rational treatment is proper diagnosis.[20] He believes that a significant number of cases of hypertension are of renal origin, mainly in the course of pyelonephritis. As for the treatment methods, he suggests the use of balneotherapy, pharmacological and surgical treatment. At the same time, however, he states that hypertension in old age often does not require any treatment. It is worth adding here that in the 1950s Biernacki organised a Scientific and Research Centre in Ciechocinek spa to deal with hypertension spa treatment, including balneotherapy.

Already as the Chairman of the Commission for the Development of Dialysis Treatment at the Ministry of Health, he published in the *Polish Archives of Internal Medicine* in 1960 a review work entitled *Artificial kidney*, in which he presented the history of the creation of the haemodialysis apparatus, principles of dialysis and presented a brief history of treatment in Poland, emphasising the fact that the first haemodialysis session in Poland was performed in 1958 by the team led by Professor Kazimierz Bączyk, and then in early 1959 in Warsaw in Prof Tadeusz Orłowski's clinic (fig. 5).[21] In his article *Acute mercury poisoning. Treatment with extracorporeal dialysis* published in 1963 also in the *Polish Archives of Internal Medicine*, of which he was editor-in-chief, he described 22 cases of mercury poisoning with acute renal failure in 1959–1960 in Poland.[22]



POLSKIE ARCHIWUM MEDYCYNY WEWNĘTRZNEJ

MIESIĘCZNIK

ORGAN TOWARZYSTWA INTERNISTÓW POLSKICH
ZAŁOŻONY PRZEZ PROF. DR ANTONIEGO GŁUZIŃSKIEGO

Tom XXX 1960 Zeszyt 5

Andrzej Biernacki

SZTUCZNA NERKA

Zagadnienie sztucznej nerki jest od kilkunastu lat przedmiotem badań w wielu krajach; stało się ono aktualne w ostatnich latach również i u nas, bowiem uzyskaliśmy 2 zestawy aparatury typu Alwalla i powstały dwa ośrodki „sztucznej nerki" w Polsce: w II Klinice Chorób Wewnętrznych w Poznaniu (prof. dr J. *Roguski*) uruchomiony w końcu roku 1958 i w I Klinice Chorób Wewnętrznych A. M. w Warszawie (prof. dr *A. Biernacki*), uruchomiony w początku roku 1959.

W ciągu roku 1959 uzyskaliśmy pewne własne doświadczenie; poza tym dr *Kazimierz Bączyk* odbył staż w Lund w Klinice prof. *Reubiego*, a doc. *Tadeusz Orłowski* w Klinice prof. *Alwalla*). Zagadnienia nefrologiczne zaktualizowały się w tym stopniu, że podczas XX Zjazdu Towarzystwa Internistów Polskich w 1959 r. w Gdańsku zorganizowano Symporjum poświęcone sztucznej nerce z udziałem gości zagranicznych, wybitnych specjalistów w tej dziedzinie, prof. *Nilsa Alwalla* z Lund i prof. *Jean Hamburgera* z Paryża.

W Polsce pierwszy *Hanicki* zastosował mały typ aparatu Alwalla do doświadczeń pracowianych w roku 1949, a w roku 1950 ogłosił uzyskane wyniki w Przeglądzie Lekarskim. Ten sam autor ogłosił w P.T.L. w r. 1957 zestawienie poglądowe na temat sztucznej nerki. O sztucznej nerce informuje również dość dokładnie *Fejgin* w swym podręczniku w r. 1958.

Pierwszy model sztucznej nerki zbudowali w r. 1913 w U.S.A. *Abel, Rowntree* i *Turner*. Rurki do dializy z kolodium przygotowywali pracowicie sami w laboratorium, jako antykoagulant stosowali hirudynę, również własnej produkcji. Wykonali oni szereg doświadczeń na zwierzętach, stwierdzając możliwość oczyszczania krwi z salicylanów, który-

Figure 5. Title page of *Artificial kidney.*

ΠΕΡΙΛΗΨΗ

Καθηγητής Andrzej Biernacki – Πρόδρομος της Νεφρολογίας στην Πολωνία

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Ήταν στα μέσα του 20ού αιώνα όταν η νεφρολογία άρχισε να αναδύεται ως ανεξάρτητη ειδικότητα και ο καθηγητής Witold Orłowski θεωρείται πατέρας της. Ο αξιοσημείωτος διάδοχός του ήταν ο Καθηγητής Andrzej Biernacki (1903–1963). Γεννημένος στο Λούμπλιν, ο Andrzej Biernacki αποφοίτησε από το Ιατρικό Τμήμα του Πανεπιστημίου της Βαρσοβίας. Κατά τη διάρκεια των πανεπιστημιακών χρόνων, εργάστηκε στο Εθνικό Ινστιτούτο Υγιεινής με επικεφαλής τον Ludwik Hirszfeld και εκπαιδεύτηκε στο Ινστιτούτο Pasteur στο Παρίσι. Στη συνέχεια πήγε σε μια πολωνική αποικία στη Βραζιλία για να μελετήσει τις συνθήκες υγιεινής εκεί. Επιστρέφοντας από τη Βραζιλία, αποδέχθηκε θέση στο 2ο Τμήμα Παθολογίας στη Βαρσοβία, με επικεφαλής τον Witold Orłowski. Στη δεκαετία του 1930 έκανε πρακτική άσκηση στη Βιέννη στην κλινική του Καθηγητή Wilhem Neuman και στο Ινστιτούτο Forlanini στη Ρώμη, και αργότερα στο Νταβός και στο Παρίσι. Διαμένοντας στην Ιταλία και τη Γερμανία, μπορούσε να αισθανθεί την ατμόσφαιρα του πολέμου να παραμονεύει στη γωνία. Πίσω στην Πολωνία, συνέχισε την εργασία του στην κλινική του Orlowski. Κατά τη διάρκεια του Β΄ Π.Π., πολέμησε στην αντίσταση και εργάστηκε στο 2ο Τμήμα Παθολογίας στο Μυστικό Ιατρικό Τμήμα του Πανεπιστημίου. Μετά τον πόλεμο, οργάνωσε το 1ο Τμήμα Παθολογίας. Ως κάτοχος υποτροφιών του ΠΟΥ, εκ-

παιδεύτηκε στις ΗΠΑ το 1947. Ήδη καθηγητής, το 1958 ως πρόεδρος της Επιτροπής Νεφρολογικής Ανάπτυξης στο Υπουργείο Υγείας, των οποίων τα μέλη ήταν επίσης ο Καθηγητής Jan Roguski και ο Καθηγητής Tadeusz Orłowski, έφερε δύο τεχνητούς νεφρούς του Alwall στην Πολωνία. Στην κλινική του το 1959, η ομάδα με επικεφαλής τον Tadeusz Orłowski πραγματοποίησε την πρώτη συνεδρία αιμοκάθαρσης στη Βαρσοβία. Το χαρτοφυλάκιο του Biernacki περιλαμβάνει 75 δικά του έργα και πάνω από 400 που καταρτίστηκαν υπό την εποπτεία του. Τα θέματα που εξετάστηκαν αφορούσαν παθήσεις των πνευμόνων, συμπεριλαμβανομένης της πνευμονικής φυματίωσης, και της καρδιολογίας. Ωστόσο, το έργο του για τη νεφρολογία αξίζει ιδιαίτερη προσοχή. Ασχολείται με βασικά προβλήματα διαίρεσης της υπέρτασης, της κακοήθους φάσης της με μεταβολές στα νεφρά και φαρμακολογικής και υδροθεραπευτικής αντιμετώπισης. Περιγράφει, επίσης, την περίπτωση της παροξυσμικής αιμοσφαιρινουρίας, της φυματίωσης του ουροποιογεννητικού. Επιπρόσθετα, η εργασία του αφορά τα συμπτώματα της ουραιμίας στην αμυλοείδωση των νεφρών, το πρόβλημα του κιρκάδιου ρυθμού της παραγωγής ούρων ανάλογα με την κυκλοφορική ικανότητα και αργότερα επίσης τη δυνατότητα της θεραπείας αιμοδιάλυσης, συμπεριλαμβανομένης της θεραπείας της δηλητηρίασης από υδράργυρο. Τα ζητήματα που σχετίζονται με τη νεφρολογία, τα οποία θίγει ο A. Biernacki, συνεχίστηκαν από τους συναδέλφους και τους μαθητές του. Ο Andrzej Biernacki είχε πολλά μη ιατρικά ενδιαφέροντα. Ήταν ειδικός στη μουσική και σύζυγος της Grażyna Bacewicz, εξαιρετική Πολωνή συνθέτης και βιολίστρια.

Λέξεις ευρετηρίου: Andrzej Biernacki, Ιστορία της αιμοδιάλυσης στην Πολωνία, Ιστορία της Νεφρολογίας στην Πολωνία

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BIOGRAPHY
ΒΙΟΓΡΑΦΙΑ

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Leonard George Rowntree (1883–1959)
A near-forgotten father of North American nephrology

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Leonard George Rowntree (1883–1959): Ένας σχεδόν ξεχασμένος πατέρας της βορειοαμερικανικής Νεφρολογίας

Περίληψη στο τέλος του άρθρου

Canadian physician Rowntree's crucial participation in the first *in vivo* haemodialysis in 1913 at the Johns Hopkins Hospital Baltimore US, under the direction of John Jacob Abel, was only one of Rowntree's several major contributions to Nephrology. He had already pioneered, aided by John T. Geraghty, a renal function test using injection of phenolsulphonephthalein (PSP) and its detection in the urine, which was used clinically for half a century. Rowntree used a dye dilution technique also to study plasma volume in normal circumstances and in patients, including those with renal disease. He moved to Minneapolis in 1915 and there worked on water overload and hyponatraemia, and on the hydrogen ion concentration in the blood using a buffer method that he set up. Then, late in the First World War, he worked in France on aviation medicine, assessing physiological and psychological suitability in potential pilots. After the war, of several choices, he accepted the chair of medicine in the prestigious Mayo Clinic, to supervise and set up new clinical research programmes. There, early on, he participated with Osborne in the first use of iodide to obtain X-ray images of functioning kidneys (the intravenous urogram, IVU), which is still in use, later studying the clotting of blood in extracorporeal circuits, described the histology of acute lupus nephritis with Norman Keith, and worked on oedema in renal and other patients. Finally, he did early work on adrenal cortex extracts and was a pioneer of the treatment of Addison's disease, hitherto fatal. During this time at the Mayo Clinic from 1921 to 1932, he used his experience from the Johns Hopkins Hospital to organise and staff eight subspecialty medical units, including one in renal medicine, all of whose contributions remain outstanding today. However, he fell out with the Mayo clinic, left in 1931 and returned to Philadelphia University, near where he had started from. During the Second World War, he served as director of a unit assessing men for service in the armed forces as well as their rehabilitation – work for which he received a Presidential citation from Harry S. Truman in 1946. Throughout his whole working life, he continued to publish steadily on clinical and research subjects, for example the more than 100 papers in the 1920s whilst at the Mayo clinic, a remarkable record for the period. His last paper appeared shortly before his death in 1959, 50 years after he had first published as a general practitioner in Camden, New Jersey.

Key words

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Aviation medicine
History haemodialysis
Intravenous urography
Leonard George Rowntree
Phenolsulphonephthalein injection
Renal function tests

1. INTRODUCTION

The founders of 20th century North American renal medicine can be debated, but the names of Osler, van Slyke, Christian, Fishberg, Addis and of course Homer Smith come to mind. But one individual who has perhaps the right to join the pantheon is almost never mentioned – Canadian Leonard George Rowntree (1883–1959).

Rowntree wrote a rambling, diffuse, part-autobiography part history of early 20th century medicine, which is a major source of information about him, but obviously biased and not impartial.[1] Others have hitherto provided only brief biographies.[2,3]

2. LIFE AND WORKS

Rowntree was born on April 10th 1883 into a family of eight children of a successful businessman in London,

Ontario in Canada. He was educated locally in Medicine at the University of Western Ontario, graduating in 1905 with the gold medal. Very early his wide curiosity and considerable ability was evident, but at the suggestion of an uncle, a community physician in Camden, New Jersey (a suburb of Philadelphia across the river Delaware) Rowntree joined him, and then practised there solo. The account in his autobiography of his time in general practice is vivid,[1] with infections dominating practice – his first paper in 1908 was on endocarditis.[4] He however acquired an attachment to treating patients rather than diseases, and at heart remained a general practitioner throughout his working life, as reflected in the broad range of his lifelong interests and contributions.

But he became dissatisfied with general practice *"I was so immersed in general practice I had no time to think"*[1] and also wanted to do clinical laboratory research. His life changed when, in 1907, he approached the famous fellow Canadian (Sir) William Osler for advice about his career, after Osler, on a visit to the USA from Oxford, had spoken to a local medical society. Osler wrote and suggested Rowntree go to the Johns Hopkins Hospital in Baltimore (where Osler had been chair of medicine from 1889 to 1905) and study – for 6 years. During this time, he would not be paid, but Osler judged *"if you have brains… and enough cash to keep you floating – which I believe you to have"*[1] it could be a success. Rowntree accepted with alacrity and after a short period of biochemistry working on guanine nucleotides, began work in the Laboratory of pharmacologist John Jacob Abel (1858–1935) in 1909 (fig. 1).

Figure 1. Leonard George Rowntree as a young man, at the Johns Hopkins Hospital around 1910. Later he habitually wore eyeglasses (Rowntree family photograph; photographer unknown).

Abel suggested *"as medicine needs a new … laxative"*[1] that he study a promising group of new compounds, the phenolsulphonephthaleins. With the help of John T. Geraghty, he dived into this project, assessing their lack of toxicity, then absorption and elimination of PSP (as the compound's unwieldy name was abbreviated). Apart from its use as a laxative, which persists today, he realised that it was almost exclusively and rapidly excreted by renal tubular secretion, and could be measured simply by adding alkali, which produced a ruby red colour, easily quantitated photometrically. He realised that they had an easy, cheap and safe renal function test completed in as little as half an hour, and the "PSP test" or "Rowntree test"[5,6] was used clinically worldwide for the next half century.

Meanwhile, Rowntree also studied the elimination of phenoltetrachorphthalein (PTCP), which turned out to be almost exclusively excreted through the liver. In parallel with the studies on renal function using PSP, he also designed a test of hepatic function using PTCP. This did not last as long as the PSP test, since the dye Congo red proved equally specific and easier to measure in body fluids. However, this gave Rowntree a lifelong interest in hepatic function and diseases, which persisted through his time at the Mayo clinic and beyond.

Abel started Rowntree on a salary after the successful work of phthaleins, and had sent him to Europe and to visit Strauss in Berlin, von Pirquet, van Noorden, and the incomparable Friedrich von Müller in Munich, who became a sort of long-distance guru for Rowntree. Amongst other influences, August Krogh of Copenhagen played a similar role as well.

This summer working holiday European trip was repeated in each of the following four years, with variations, and accompanying family members including sisters and cousins. 1913 however was different. This time he was accompanied by Abel himself, and their "vividiffusion" apparatus,[7] which they demonstrated in London at an international medical meeting, and in Groningen in the Netherlands – the first *in vivo* haemodialysis. This was called in London by an anonymous newspaper reporter of the London *Times* of August 11th 1913 an "artificial kidney". This important story I and others have related elsewhere, and will not repeat it all here, except to quote Rowntree himself *"Dr Turner made the glass fittings, I made the collodion tubes, the leech extract, and conducted the experiments. Dr Abel conceived the idea, and made the chemical analysis"*.[1]

In his autobiography, unfortunately Rowntree –the only clinician in the team– didn't elaborate as to the potential

value of haemodialysis in clinical renal failure. Certainly, in 1913 in London and elsewhere Abel presented the apparatus as a means of isolating and analysing amino-acids and other solutes in the blood. But equally in their earliest written account of their work, in the Transactions of the presentation to the American College of Physicians (ACP) meeting[7] that same year (1913), held in Washington DC on May 5–8 1913, and thus earlier than the visit to London on August 11th, the preamble to the paper clearly states the potential value of blood purification in disease states such as renal failure. This perhaps indicates that Rowntree and not Abel (a pharmacologist and chemist) may have written and given this oral paper, being a member of the ACP, and was better aware than his mentor of its wide applications. Later, Abel followed this trend and referred to dialysis as a treatment for renal failure, but only after it had been done in humans during the 1920s in Germany.

In the 1911 and 1912 trips, finding *"time on my hands"* in London, Rowntree undertook a study of the surgeon James Parkinson, at that time a man of mystery and of whom still no authentic portrait has been identified. The paper he published[8] still remains one of the principal sources of information on Parkinson.

Following on the renal function study, with Norman Keith (also Canadian), he used a dye again, this time to measure blood volumes in normal circumstances and in patients,[9] and later wrote a book on the subject.[10] Again, this test was a standard in clinical medicine, until radioactive isotopes replaced the dye. Meanwhile, Abel's interest in haemodialysis had waned and returned to earlier experiments of withdrawing blood and then returning it. Rowntree and Turner again performed the experiments on dogs,[11] showing how the blood could be centrifuged, and the plasma modified *in vitro*. Abel called this procedure "plasmapheresis" a name which, unlike "vivdiffusion" has survived.

Now with salary as an attending physician at the Johns Hopkins, summer work back in Camden in general practice, and family resources, he felt able to marry, to Katherine Campbell of Camden NJ in 1914. They had 44 years together.

In 1916, ever restless and ambitious, now 32 and seeking promotion, he left the Hopkins and took a Chair of medicine post in Minneapolis, despite a decided deficit in the local facilities for clinical research. Even so, there he began a lifelong interest in water metabolism, studying polyurias and water intoxication,[12] and perhaps stimulated by Krogh, he also designed a buffer indicator method to measure hydrogen ion concentrations in dialysates of blood that he studied,[13] including during renal failure. He wrote a book on this subject, which ran to 16 editions.

Then World War I intervened for Americans, and he spent the latter two years of the war in the military studying aviation medicine and assessing service pilots, serving in the Allied Expeditionary Force in France through most of 1917–1918. This subject again remained a lifelong interest. Demobilised, rather than return to Minneapolis he was in the happy position of having several offers of chairman posts to choose from. He chose the Mayo Clinic, the graduate school of the University of Minnesota, rather than one of several other universities eager to have him, and went to Rochester, Min in 1920. He was now 37 years old. His thirteen years at the Mayo were his apogee.

Rowntree had reason to be grateful to the Mayo brothers. He had had a number of ailments throughout his life[1] suffered with an almost Panglossian cheerfulness, but a perforated gastric ulcer in 1918 threatened his life. He was operated on by William J Mayo, who saved him.

Rowntree's responsibilities at the Mayo were vast, as chief of medicine and Professor of medicine. By 1922, he was elevated to Chief of the Department of Medicine. His task was to add laboratory and clinical investigation in medicine of world quality to the unparalleled clinical service provided by the clinic, which started with surgery as its predominant activity but spread to internal medicine under his aegis. To achieve this, he had in his mind the images of the great clinics he had seen in Europe, such as that of Friedrich von Müller, as well as his experience from the Johns Hopkins.

He persuaded and appointed men of talent (no women of that standing were available to him in the early 1920s) to form a stellar team incorporating almost every area of medicine, amongst the first being his fellow Canadian Norman Keith to head a division in what would later be called Nephrology. Alongside them were two other colleagues from the Hopkins – Dr Samuel Amberg of Chicago and Dr Reginald Fitz of Boston. Henry Helmholz was attracted to head up paediatrics. Gastroenterologist Walter Alvarez of San Francisco and Nobel winner-to-be rheumatologist Philip Hench also joined the team, along with Drs Russell Wilder already on the staff, George Brown, Stanley McVicar, George Brown, Carl Greene, Jay Bargen and Albert Snell. Each was given space and postgraduate students from the university, and recruited further talent from within and outside Mayo. Rowntree headed 8 divisions, all doing clinical investigation as well as clinical medicine, and Dr Henry Plummer (still with the title also of Chief of Medicine) seven.

What of Rowntree's personal contribution to clinical and investigational medicine during his time at the Mayo? During his time there, he published 107 papers in medical journals. Nor did he simply put his name on work done in his many departments; each was a personal contribution. He continued the major interests of his Hopkins days in liver disease,[14] kidney disease, plasma volume and oedema and acidosis, writing a book on plasma volume in health and disease with colleagues at the Clinic Drs George Brown and GM Roth *The volume of the blood and plasma*.[10] He returned to study directly clotting of blood in artificial circuits made from collodion, and pointed to the involvement of platelets in this process, as well as the inability of hirudins and the newly introduced heparin to totally arrest this process.[15]

But there were also new projects to pursue. Early in his time at the Mayo Clinic, in 1923 he collaborated with Osborne, a pioneer of the use of iodide in radiology, using urinary excreted iodide as a tool for imaging the anatomy of the kidney and the urinary tract.[16] This became known as the intravenous urogram (IVU), and is still in use today, using improved contrast media. With Norman Keith, he gave the first detailed description of severe lupus nephritis, including photomicrographs.[17] His work on the adrenal cortex later in the 1920s was groundbreaking, and led to a further book, *A clinical study of Addison's disease*[18] with Dr Albert Snell, which included data on the first successful use of adrenal extracts to maintain patients with Addison's disease long-term.

Newly developed interests included hypertension, for which at that time there were few ineffective medicines, although salt restriction was clearly important. Rowntree was probably the first who set out deliberately, in 1925, to follow Leriche and do lumbar sympathectomy for severe hypertension with success,[19] but did not follow this early attempt with long-term studies although further cases were treated, although it remained a standard method of treating severe hypertension for more than three decades. He did however also persuade "his" surgeon Dr Alfred Adson to do in addition a nephrectomy in a patient with unilateral renal disease and severe hypertension, again with success. This was before the experiments of Golblatt were performed.

However, his time at the Mayo Clinic ended somewhat acrimoniously in 1931–1932. John Graner, an alumnus[20] suggests that the Mayo tradition of maintaining a generalist stance in medicine –an idea which Rowntree himself advocated lifelong– became incompatible with the increasingly specialist interests of the "Rowntree group", who drifted apart as their many individual contributions blossomed. Rowntree himself also spent less and less time seeing patients whilst pursuing and supervising the many projects his departments were engaged in. Graner remarks *"Rowntree never became assimilated into the Mayo Clinic's structure and routine"* and his new academic style did not suit many of the existing, more senior, staff. Rowntree also in his autobiography felt that he was *"losing control of his time"*,[1] and his personal life was affected adversely with overwork. Moreover, other members of his staff were *"suffering from chronic exhaustion"*.[1]

He resigned, but was invited to stay on by W.J. Mayo (as he emphasises strongly in his autobiography), with an increased salary – but with conditions and restrictions, including a public guarantee never to leave the Clinic; Rowntree declined this offer, and so he left after 13 ½ very successful years. Graner[20] quotes Dr Nelson Barker *"Perhaps Leonard Rowntree's greatest contribution was the fact that he stimulated in his associates, first assistants and fellows a strong and lasting interest in clinical investigation and research"*. The clinic remains a centre of excellence with a worldwide reputation for both clinical medicine and clinical investigation and innovation. Much of this was begun by Leonard Rowntree.

He left for a less demanding role in his adopted home town of Philadelphia, becoming Director of the Philadelphia Institute for Medical Research. Nevertheless, in the next few years he published a further 37 papers on his several interests. He became more interested in endocrinology after his success with the adrenal cortex, but sadly achieved little with both pineal and thymus extracts and implants.

His medical career was then interrupted by the entry of the USA into World War II. Rowntree volunteered, wishing to continue his work in aviation medicine begun in the previous conflict. Probably because he was nearing 60 and had enormous administrative and medical experience, he was appointed instead as head of the Medical Service of the Selective Service System (popularly known as "the draft") in August 1940. He quickly became an expert in public health and constantly revised and improved criteria for clinical assessment for service in the armed forces.[21] For this work, he was awarded a Presidential Citation in 1946 by US President Harry S. Truman.[22]

After the war, he retired with his wife to Florida, but was far from inactive, helping to set up the University of Miami School of Medicine in 1952. His last publication, in 1958, was a case report in JAMA, just 50 years after his first paper. In that year, he also had the pleasure of watching a dialysis done for acute renal failure in a patient under the care of Dr George W. Schreiner of Georgetown University. He died aged 76 in 1959.[23]

Like all too many individuals who contributed notably to medicine and medical science and were not recognised Rowntree's contribution has been largely lost to notice. Only at the Mayo Clinic has he been remembered. In Nephrology, he is now only known –if at all– as part of the *"et al."* in Abel's landmark work on *in vivo* haemodialysis, to which he contributed so much. Perhaps this article can help to alter this neglect by medical historians.

ΠΕΡΙΛΗΨΗ

Leonard George Rowntree (1883–1959): Ένας σχεδόν ξεχασμένος πατέρας της βορειοαμερικανικής Νεφρολογίας

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Η κρίσιμη συμμετοχή του Καναδού ιατρού Rowntree στην πρώτη *in vivo* αιμοκάθαρση το 1913 στο νοσοκομείο Johns Hopkins της Βαλτιμόρης των ΗΠΑ, υπό την καθοδήγηση του John Jacob Abel, ήταν μόνο μία από τις σημαντικές συνεισφορές του Rowntree στη Νεφρολογία. Ήταν ήδη πρωτοπόρος, με τη βοήθεια του John T. Geraghty, στη χρήση μιας δοκιμασίας νεφρικής λειτουργίας με έγχυση φαινολοσουλφονυλοφθαλεΐνης (PSP) και την ανίχνευσή της στα ούρα, η οποία χρησιμοποιήθηκε κλινικά για μισό αιώνα. Ο Rowntree χρησιμοποίησε μια τεχνική αραίωσης χρωστικών για να μελετήσει τον όγκο πλάσματος σε κανονικές συνθήκες και σε ασθενείς, συμπεριλαμβανομένων εκείνων με νεφρική νόσο. Μετακόμισε στη Μινεάπολη το 1915 και εκεί εργάστηκε πάνω στην υπερφόρτωση ύδατος και την υπονατριαιμία καθώς και στη συγκέντρωση ιόντων υδρογόνου στο αίμα, χρησιμοποιώντας μια μέθοδο ρυθμιστικών που δημιούργησε. Στη συνέχεια, προς τα τέλη του Πρώτου Παγκοσμίου Πολέμου, εργάστηκε στη Γαλλία στον τομέα της αεροπορικής ιατρικής, αξιολογώντας τη σωματική και ψυχολογική καταλληλότητα υποψήφιων πιλότων. Μετά τον πόλεμο, μεταξύ πολλών προτάσεων που του έγιναν, δέχθηκε την έδρα της Ιατρικής στην περίφημη Κλινική Mayo, με στόχο την επίβλεψη και δημιουργία νέων προγραμμάτων κλινικής έρευνας. Εκεί, από νωρίς, συμμετείχε με τον Osborne στην πρώτη χρήση ιωδιδίου για τη λήψη ακτινολογικών εικόνων των λειτουργικών νεφρών (ενδοφλέβιο ουρογράφημα, IVU), το οποίο εξακολουθεί να χρησιμοποιείται και σήμερα. Αργότερα, μελέτησε την θρόμβωση του αίματος σε εξωσωματικά κυκλώματα, περιέγραψε την ιστολογία οξείας νεφρίτιδας του λύκου μαζί με τον Norman Keith και εργάστηκε πάνω στο οίδημα σε ασθενείς με νεφρικές παθήσεις και άλλους. Τέλος, ήταν ένας από τους πρώτους που ασχολήθηκαν με τα εκχυλίσματα φλοιού των επινεφριδίων και ήταν πρωτοπόρος στη θεραπεία της νόσου του Addison, που ήταν θανατηφόρα μέχρι τότε. Κατά τη διάρκεια αυτής της περιόδου στην Κλινική Mayo, από το 1921 έως το 1932, χρησιμοποίησε την εμπειρία του από το Νοσοκομείο Johns Hopkins για να οργανώσει και να στελεχώσει οκτώ ιατρικές μονάδες υποειδικοτήτων, συμπεριλαμβανομένης μιας στη νεφρική Ιατρική, οι συνεισφορές των οποίων παραμένουν εξαιρετικές και σήμερα. Ωστόσο, καθώς οι σχέσεις του με την Κλινική Mayo ψυχράθηκαν, αποχώρησε το 1931 και επέστρεψε στο Πανεπιστήμιο της Φιλαδέλφειας, κοντά στον τόπο από όπου είχε αρχίσει. Κατά τη διάρκεια του Β΄ Παγκοσμίου Πολέμου, υπηρέτησε ως διευθυντής μονάδας αξιολόγησης ανδρών για θητεία στις ένοπλες δυνάμεις καθώς και για την αποκατάστασή τους - έργο για το οποίο έλαβε Προεδρική μνεία από τον Χάρι Σ Τρούμαν το 1946. Καθ' όλη την επαγγελματική του ζωή, συνέχισε σταθερά να κάνει δημοσιεύσεις για κλινικά και ερευνητικά θέματα. Επί παραδείγματι, δημοσίευσε περισσότερες από 100 εργασίες τη δεκαετία του 1920, όντας ακόμα στην Κλινική Mayo, ένα αξιοσημείωτο ρεκόρ για την περίοδο. Η τελευταία του εργασία δημοσιεύθηκε λίγο πριν από τον θάνατό του το 1959, 50 χρόνια μετά την πρώτη του δημοσίευση ως γενικός ιατρός στο Κάμντεν του Νιου Τζέρσεϋ.

Λέξεις ευρετηρίου: Αεροπορική Ιατρική, Δοκιμασίες νεφρικής λειτουργίας, Έγχυση phenolsulphonephthalein, Ενδοφλέβιος πυελογραφία, Ιστορία αιμοκάθαρσης, Leonard George Rowntree, Νόσος του Addison

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PHILOSOPHY
ΦΙΛΟΣΟΦΙΑ

Nephrology: a prototype of a discipline evolving into complexity
The border with philosophy

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ΑΡΧΕΙΑ ΕΛΛΗΝΙΚΗΣ ΙΑΤΡΙΚΗΣ 2020, 37(Συμπλ 2):80–84

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Νεφρολογία: Πρότυπο ενός κλάδου που εξελίσσεται στην πολυπλοκότητα: Τα σύνορα με τη Φιλοσοφία

Περίληψη στο τέλος του άρθρου

In the last quarter of the twentieth century, there has been a growing opposition to reductionism, driven by individual disciplines which however have given solutions to many practical problems of our times. Opposition grew along with a quest for unity of culture and the adoption of a complexity-based method. The movement was nurtured by Morin, Nicolescu and de Freitas who, in 1994, wrote and signed the *Charter of transdisciplinarity*. Complexity is therefore seen as an indispensable tool for the effective, harmonious, appropriate, timely and long lasting advancement of science. The old debate about basic and practical science has lost some of its appeal. Nephrology, born in the 1950s, is now charged with meeting the needs of more than 10% of the world population. It holds all the characteristics of a discipline born in the fertile world of complexity and continuously expanding into the boundaries of other disciplines. It is characterised by a unique exponential growth of generated information and by the capability of matching the challenges of big data algorithms and omics platforms. Chronic Kidney Disease (CKD) –a complex disease– is now amenable to cure.

Key words

CKD
Complexity
DKD
Nephrology
Omic techniques
Transdisciplinarity

1. INTRODUCTION

At the beginning of the 13th century in Europe, teaching was based on: (a) the *trivium* (literally the place where 3 roads meet), which included Grammar, Rhetoric and Dialectic and (b) the *quadrivium* (the place where 4 roads meet), which included Arithmetic, Geometry, Music and Astronomy, as described in the 7th book of Plato's *Republic* and represented the so-called liberal arts. These disciplines represented the basic curriculum for studying Theology, Medicine, Philosophy.

According to Basarab Nicolescu, there was "a big bang" and the number of disciplines increased to 8,000 in 2012. The fragmentation is erroneous, since our world is marked by the rapid advance of communications and a connected world is driven by complexity. "The new education has to invent new methods of teaching, founded on new logics. The old classical binary logic, that of "yes" and "no", i.e. the logic of the excluded middle, is no more valid in the context of complexity".[1]

The Webster Dictionary notes that "Discipline" is derived from the Latin *disciplina* meaning (a) teaching, learning, a subject that is taught; (b) a field of study; (c) training that moulds or perfects; (d) rules governing conduct or activity, and (e) control gained by enforcing obedience.

In Roman times, *Disciplina* was a minor goddess that was a personification of discipline and the patron of soldiers living at the Empire's borders.

We have discussed elsewhere "the process leading to birth, life, progress and death of disciplines and that one could well recount the history of humankind by analysing the lifespan of various disciplines".[2]

Le Goff pointed out that *"disciplines are often talked in an abstract way, as if they were ideas wandering around the world and possessing a scientific classification behind which are social organisations. Behind the division of knowledge there were the leaders of universities and schools who organised the discipline into subdivisions"*. He also stressed that scientists can protect their disciplines by participating in the debate on the media, after being appropriately trained in their use. The growing number of disciplines is directly linked to the schizophrenia of subdividing science into smaller and smaller tesserae, which is also a sign of the high subjectivity of the world's present inhabitants.[2,3] Ceruti pointed out that *"Specialties have generated new knowledge that however does*

not allow to solve multidimensional problems. The separation of disciplines makes us unfit to capture complexity. The fragmentation of thought allows experts and specialists to provide high performance within their areas and collaborate in non-complex sectors of knowledge. However, it makes us blind to inter- and retro-actions and circular causality".[4,5]

The history of science from Archilocus of Parsos (680–640 BC) to the Higgs boson (God's particle) adopted the method of reductionism for solving complex problems. Archilocus made a distinction between the fox that knows many things and the hedgehog that knows only one big thing, thus indicating that the fox is more creative and finds many tricks to escape hunters and dogs whereas the hedgehog knows one big thing which however in many occasions serves to save its life. The hedgehog has identified only one possible way and uses it in all occasions. In the same 7th century BC, Thales (born 636 BC) identified water as the universal principle.

2. THE QUEST FOR COMPLEXITY

In the last quarter of the last century, along with a quest for unity of culture, a growing opposition to specialisation emerged. A new method of teaching, not based on disciplines, but between disciplines and crossing disciplines was proposed; this adopted complexity. The method also flourished thanks to (a) the foundation in 1984 of the Santa Fe Institute in New Mexico, inspired by Murray Gellman and (b) the publication in 1994 of the *Charter of Transdisciplinarity,* signed by Lima de Freitas, Edgar Morin and Basarab Nicolescu. Complexity emerged from three main streams: cybernetics, general systems theory and dynamical system theory. It is now regarded as an indispensable tool for advancing science without losing the advantages of specialisation, which are of paramount importance for solving practical problems.

Disciplines play a great role in disseminating and furthering knowledge. "They are born –without aiming to eternity– in order to warrant the originality of the scientists who existed, exist and will exist in the future. Investigators attempt to achieve original findings with the hidden desire to be indicated as originators of ideas. Theirs is a battle to find an own role in the scientific enterprise, to be recognised; thus they scrape smaller niche disciplines and topics [...]. Disciplines however are like fractals; their boundary regions are zones where exchanges are wider than those occurring in the internal zones".[6,7]

We have now finally discovered the limits of reductionism; in the quest for transdisciplinarity, complexity has emerged. Thus for Morin we have "to substitute the method which drives to know by disjunction and reduction with a new method obliging us to know by distinction and conjunction" (Introduction to complex thinking). However, we have to be aware that we are not yet in the society of knowledge, but rather in the society where knowledge is fragmented, and consists of various *tesserae*, each separated from the others. Such separation does not allow us to bind them in order to understand the fundamental and global problems related to our personal lives as well as to our collective destinies".[8] So it means that "we have to do different things and we have to do things differently" and inject new blood into academia in order to create a new cadre of scientists.[9,10] Indeed Morin's efforts are devoted to introducing complexity in primary school.

3. PRESERVING THE BENEFITS OF REDUCTIONISM (SPECIALTIES) IN THE ERA OF COMPLEXITY

Specialisation may provide the best medical care. These benefits should be protected without renouncing the advantages of complexity. This can be achieved through a highly specialised workforce, meaning that the quality of students enrolled for university studies must necessarily increase.

This can be easily understood through the experience of a great leader of the industry, Tadahiro Sekimoto (1926–2007). As a young student, Sekimoto had prepared his Bachelor of Science under the mentorship of Kazuhiko Nishjijma, a candidate Nobel physicist, in 1960 and 1961. Sekimoto considered himself unfit for the academy so decided to work for NEC, where he became chairman of the board of directors.

In an interview to the *Asahi Evening News* on 9 April 1997, Sekimoto presented some rules for identifying the best employees at NEC, defining the "V" shaped collaborators. What did he mean? When you drill deeply in pursuit of your specialty the earth around the hole you dig crumbles on itself making drilling easier, allowing you to move further ahead in your specialty. A cross-sectional view of this hole resembles the letter V. They are the best specialists. However, success in one's profession requires the attitude of the ants climbing a bamboo tree. The tree has joints and ants cannot see what lies beyond the joint. To move ahead they have to move over the joint. When they clear it they run up against the next joint". Thus, complexity preserving the role of the best specialists is possible.[2–11] It is also telling about the quality of the people who must be enrolled. However, teaching complexity should start in primary school and

last until completion of high school. Once the process is in motion, all medical university students would be able to profit from the method.

4. NEPHROLOGY: A PROTOTYPE OF A DISCIPLINE GENERATED BY COMPLEXITY

Nephrology is a young discipline that effectively "entered the parlance of medicine in 1961", the year of the birth of its International Society. However, "it was the advent of maintenance dialysis that fuelled its growth after the 1970".[12,13]

Nephrology has been characterised[13] by "the exponential information overload being generated. The pattern began in the 1960s, has continued and been magnified by the specialty journals that have appeared since then. As shown in table 1, over the years since their inauguration, the number of pages in the leading journals in the field has doubled for some *(Journal of the American Society of Nephrology, JASN)*, quadrupled *(Kidney Int)* and quintupled *(Nephrology Dialysis Transplantation, NDT)* for others. But then, each of those journals has spawned new publications *(Nature Review Nephrology*, *Advances in Chronic Kidney Disease*, *NDT Plus*, and *Clinical JASN* additional information).

Systems biology is the last fruitful approach that drives the present progress of nephrology. Many omics databases have been published, which can be used for diagnostic purposes and to generate new hypotheses for clinical intervention as well as in research on IgA nephropathy and diabetic nephropathy.[14–16]

However, we have shown that the most successful steps of nephrology were driven by two main ideas: (a) the classification of Chronic Kidney Disease (CKD) based on the estimated glomerular filtration rate (eGFR) and (b) the identification of CKD and uraemia as systemic diseases.[17]

Table 1. Nephrology journals, showing the upwards trend in pages since their respective inauguration. Modified from Eknoyan.[13]

Year	Journal	Inaugural issue (pages)	June 2011 issue (pages)	% increase
1964	*Nephron*	72	219*	304
1972	*Kidney Int*	65	233	358
1981	*AJKD*	51	161	315
1986	*NDT*	63	309	490
1990	*JASN*	125	193	149

AJKD: American Journal of Kidney Diseases; Kidney Int: Kidney International; NDT: Nephrology Dialysis Transplantation; JASN: Journal of the American Society of Nephrology

*As of January 2003 Nephron has been divided into three separately edited sections, i.e., Clinical Practice, Experimental Nephrology and Physiology

5. CHRONIC KIDNEY DISEASE AND URAEMIA: SYSTEMIC DISEASES AMENABLE TO CURE

The complex and systemic nature of CKD was demonstrated by Zoccali et al.[18,19] Their studies revealed the limits of the reductionist approach. Thus, a systems biology approach was identified as potentially capable of exploring the pathophysiology of this systemic disease and unravelling critical pathways that can be targeted for CKD prevention and therapy. Those studies address the effects of CKD on (a) the energy-immunity link, (b) metabolism, bone and heart, (c) the gut-kidney link, (d) the lung-kidney link and (e) the link of the kidney with the nervous system.[18–20] However, recently real progress has been made, which may be conducive to the postponement of death and dialysis.[21–23] A new tool should also take into consideration "an age-adapted definition" of CKD.[24]

That means that nephrology is rooted in complexity, grows through interdisciplinarity; it will be continuously shaped by analysing big data and the use of algorithms. This will allow taking care of an increasing number of patients guided by guidelines emerging from complex analysis of a huge number of publications, which no nephrologist could read/analyse personally. eGFR is a strong tool derived from a complex process and we can soon expect other tools to explain the increase of cardiovascular death in patients with CKD as well to find the key to advance the now stagnant survival of kidney transplanted patients.

6. THE LINK WITH PHILOSOPHY

Science needs philosophy.[25] As nephrologists, we can remember that Empedocles of Acragas in the 5th century BC put forward a theory of a world made of air, water, fire, and earth, governed by love and hate. By observing body tissues, he strove to demonstrate that they consisted of four elements assembled at different mathematical ratios (*logos*). Blood was the most perfect tissue, because the ratio between elements is one. Bone was a very unusual tissue because it is made of 2 parts of earth, 2 parts of water, and 4 parts of fire.[26,27]

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ΠΕΡΙΛΗΨΗ

Νεφρολογία: Πρότυπο ενός κλάδου που εξελίσσεται στην πολυπλοκότητα: Τα σύνορα με τη Φιλοσοφία

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Κατά το τελευταίο τέταρτο του 20ού αιώνα, υπήρξε μια αυξανόμενη αντιπαράθεση στον αναγωγισμό, που προωθήθηκε από μεμονωμένες επιστήμες, οι οποίες όμως έδωσαν λύσεις σε πολλά πρακτικά προβλήματα της εποχής μας. Η αντιπαράθεση αναπτύχθηκε μαζί με την αναζήτηση της ενότητας του πολιτισμού και της υιοθέτησης μιας μεθόδου με βάση την πολυπλοκότητα. Το κίνημα καλλιεργήθηκε από τους Morin, Nicolescu και de Freitas οι οποίοι, το 1994, έγραψαν και υπέγραψαν τον *Χάρτη της διεπιστημονικότητας*. Επομένως, η πολυπλοκότητα θεωρείται αναντικατάστατο εργαλείο για την αποτελεσματική, αρμονική, κατάλληλη, έγκαιρη και μακροχρόνια πρόοδο της επιστήμης. Η παλιά συζήτηση για τη βασική και την πρακτική επιστήμη έχει χάσει μέρος της γοητείας της. Η Νεφρολογία, που γεννήθηκε στη δεκαετία του 1950, είναι τώρα επιφορτισμένη με την κάλυψη των αναγκών άνω του 10% του παγκόσμιου πληθυσμού. Διαθέτει όλα τα χαρακτηριστικά μιας επιστήμης που γεννάται στον εύφορο κόσμο της πολυπλοκότητας και συνεχώς διευρύνεται στα όρια άλλων επιστημών. Χαρακτηρίζεται από μια μοναδική εκθετική ανάπτυξη των παραγόμενων πληροφοριών και από την ικανότητα αντιστοίχισης των προκλήσεων των μεγάλων αλγορίθμων δεδομένων και των ομικών πλατφορμών. Η χρόνια νόσος των νεφρών –μια σύνθετη ασθένεια– επιδέχεται πλέον θεραπεία.

Λέξεις ευρετηρίου: Διεπιστημονικότητα, CKD, DKD, Νεφρολογία, Ομικές τεχνικές, Πολυπλοκότητα

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PHILOSOPHY
ΦΙΛΟΣΟΦΙΑ

The Emperor's new clothes in nephrology Past and present

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Τα καινούργια ρούχα του αυτοκράτορα στη Νεφρολογία: Παρόν και παρελθόν

Περίληψη στο τέλος του άρθρου

Evidence-based Medicine has been described as the integration of information from best available evidence with the doctor's experience and the patient's point of view. If it is replaced by Guidelines-based Medicine it resembles the Hans Christian Andersen's fairy tale the "Emperor's New Clothes" where the Emperor (our Healthcare) is naked and nobody dares to cry it out. History has made circles since "Authority" based Medicine of the Past has been replaced by "Guidelines", if followed blindly. We searched for such examples in the Past and the Present in the field of Nephrology. Galen's and Aristotle's sayings were not contradicted by their successors, in the "shadow" of their prestige and their "Authority», even though ironically both actively encouraged experimentation and the questioning of established theory. In the present treatment of hyperphospatemia with Phosphate binders and dyslipidemia with statins in Dialysis patients are two examples where in clinical practice the doctor and the patient are not in the centre of the decision process. In conclusion we should hear the voices that cry out "the Emperor is naked" and as a recurring historical cycle turn to Hippocrates' Oath ordering us to apply the best possible treatment to our patients.

Key words

Emperor New Clothes' syndrome
Evidence based medicine
Nephrology

1. INTRODUCTION

The Emperor' New Clothes' Syndrome, based on the tale by the Danish writer Hans Christian Andersen (1835), first described by Gross F,[1] can be considered as a parody of the way we currently practice Medicine. As Tebala GD stated "The Emperor is healthcare, the way we treat our patients. His 'new clothes' are what we consider modern Evidence-Based Medicine (EBM). Ministers and knights – and the crowd gathered for the procession – are those who pretend to practice the best up-to-date medicine. The innocent young kid represents the whistle-blower of a potentially failing system".[2] Scientists often do not challenge data with which they might not agree, or conclusions that are perhaps overblown or overstated for various reasons. In that sense "modern" EBM is equivalent to Guidelines-Based Medicine where doctors are gradually becoming only passive executors of someone else's decisions. Modern Healthcare is dangerously heading back to "Authority-based Medicine", i.e. based on a leader as in the ancient science.

1.2. Aim

We aimed to search for examples of the syndrome of "The Emperor's new clothes" in the field of Nephrology from the past and the present, in order to find reasons and possible solutions. "Present" is defined as Medicine from the 19th century onwards. At that time, the "Germ theory of disease" by Robert Koch and Louis Pasteur marked the beginning of "Modern Medicine" and a shift from "patient-centred" to "evidence-based" medicine.

2. RESULTS

Past: Aristotle (384-322 BC) challenged the method of teaching biological sciences based on theories. He strongly suggested using direct observation via experiments and dissections and opposed the aversion to them. Nevertheless, he made some "mistakes" based on his observations.[3,4] He incorrectly observed the absence of kidneys in fish and birds and deduced that they were not essential for the existence of a living organism. He stated that the kidneys are "assistants" to the work of the bladder: "pre-purify the blood and send the filtrate to the bladder where it is turned to clear urine and excreted". He believed that "the aorta sends similar branches to each kidney, but none to the liver or spleen", and that "the kidneys also lie in the same position in all creatures that possess them" (study on a dead cow).

Galen (130–210 AD) was the father of the experimen-

tal method. He dissected animals in his quest to understand how the body functions. He regarded medicine as an interdisciplinary field best practiced by using theory, observation, and experimentation in conjunction. Galen challenged his students and anyone else to conduct the same experiments in order to check the accuracy of his observations. "For I have already shown thousands of times the twin (organs) that intercede the spermatic cords from the outer horns to the inside of the uterus (…). And this must be shown by anyone (that follows the same experimental method) after I and my pupils have died". Despite the above, he made some mistakes based on his observations, which persisted because of his "authority".[5] He described Diabetes as a disease specific to the kidneys because of a weakness in their retentive faculties. Matthew Dobson (1732–1784) showed that "sweet" urine was so because it contained sugar and was preceded and accompanied by sugar in the blood. Although diabetes then came to be ascribed to increased sugar in the blood, the presence of sugar in urine continued to be attributed to the decreased retentive properties of the kidneys. Galen's medical works were regarded as authoritative until well into the Middle Ages. Galen left a physiological model of the human body that became the mainstay of the medieval physician's university anatomy curriculum, but it suffered greatly from stasis and intellectual stagnation as some of Galen's ideas were incorrect; he did not dissect a human body.[6] Greek and Roman taboos meant that dissection was unusual in ancient times, but in the Middle Ages this gradually changed.[7]

2.1. Present

The patient is regarded as a cluster of different diseases - each demanding a specific treatment, governed by "guidelines" from expert committees. In Nephrology, this task is covered by the Kidney Disease Improving Global Outcomes (KDIGO) initiative, founded in 2003 to fulfil a need for international cooperation and consolidation in the development and implementation of clinical practice guidelines.[8]

Regarding hyperphosphatemia, the KDIGO 2017 update states:[9] "In patients with CKD G3a-G5D, we suggest lowering phosphate levels toward the normal range (2C)". "In patients with CKD G3a-G5D, we suggest limiting dietary phosphate intake in the treatment of hyperphosphatemia alone or in combination with other treatments (2D). It is reasonable to consider phosphate source (e.g. animal, vegetable, additives) in making dietary recommendations (not graded)". The article states that decisions about a phosphate-lowering treatment should be based on progressively or persistently elevated Serum Phosphate (Ph) (not graded). This emphasises the perception that early "preventive" Ph-lowering treatment is currently not supported by data. The broader term "Ph-lowering treatment" is used instead of Ph binding agents since all possible approaches (i.e. binders, diet, dialysis) can be effective, Ph migration from bone may contribute to serum levels. In a review article,[10] Professor Vervloet states that "It is difficult to establish when an intervention should be considered as a "preventive" or as a "therapeutic" measure, as hyperphosphatemia is not a disease.

Despite the "suggestion" and the accompanying "low quality of evidence" for the use of phosphate binders in the CKD population, in the real world the corresponding pill burden (average number 19) represents a major burden for patients[11] and the Health Care System.[12]

Regarding dyslipidaemia, in the general population statins are a mainstay in the secondary prevention of atherosclerotic cardiovascular disease.[13] The relative decrease in cardiovascular risk by statins diminishes as kidney function declines, even after allowing for the smaller reductions in LDL cholesterol obtained in more advanced CKD. In patients on maintenance dialysis, several large randomised trials and high-quality meta-analyses revealed that statins have little or no effect on cardiovascular outcome, despite significant LDL cholesterol lowering.[14] These counter intuitive findings have been attributed to the poor association of LDL cholesterol with cardiovascular risk in the dialysis population, owing to the predomination of non-traditional risk factors (e.g., mineral and bone metabolism disorder and oxidative stress) and non-atherosclerotic cardiac events (e.g., arrhythmia and heart failure) drowning out classic atherosclerotic disease.[15]

The 2014 Kidney Disease Improving Global Outcomes Lipid Work Group suggests that statins should not be initiated in patients on dialysis, but that statins can be continued in patients already receiving them at the time of dialysis initiation.[16] Despite the proven lack of meaningful gains and concerns about costs, polypharmacy and side effects, statins are currently still widely prescribed to patients on dialysis and viewed as safe and effective agents by most nephrologists.[17] A recent observational study in patients on RRT revealed that the use of statins correlated with a higher baseline coronary artery calcification (CAC) score, independent of age, sex, and diabetes, as well as a more rapid progression of the CAC score in a longitudinal evaluation compared to no treatment with statins.[18]

3. DISCUSSION

Hippocrates (460–370 B.C.) is considered the Greek

Father of medicine, who began the scientific study of Medicine. He instructed doctors to review and analyse all existing data before embarking on any research. This method of Inquiry being "the only acceptable way of finding answers in medicine, as it helps physicians with good training and an inquisitive mind to focus their attention on what had not been discovered". This clear Hippocratic instruction brings to mind today's call for systematic reviews. But at the same time Hippocratic doctors considered each person to be unique and therefore adapted their advice paying attention to the characteristics of each person (age, gender, appearance and physique) their daily habits, the place they lived in and the season of the year. They were helped to decide on their prescribed treatment by their past experience on treating similar cases.[19]

In ancient times, Galen's and Aristotle's sayings were not contradicted by their successors, in the "shadow" of their prestige and their "Authority". There is a great irony in Galen's and Aristotle's posthumous fate. Although they actively encouraged experimentation and the questioning of established theory, those who followed were prohibited from questioning theirs. They went so far as to claim that the human body had changed over the centuries, accounting for the dissimilarity.

The first clear definition of Evidence-Based Medicine (EBM) comes from the late Professor Sackett: "Evidence-based medicine is the conscientious, explicit and judicious use of current best evidence in making decisions about the care of individual patients. The practice of evidence-based medicine means integrating individual clinical expertise with the best available external clinical evidence from systematic research".[20] But as Professor Ioannidis states "Evidence-based medicine has been hijacked". In many places, medicine and healthcare are wasting societal resources and becoming a threat to human well-being. Science denialism and quacks are also flourishing and leading more people astray in their life choices, including health. EBM still remains an unmet goal, worthy to be attained.[21]

Now, there are voices implying a form of judgment in the interpretation of Guidelines. Regarding Hyperphosphatemia in CKD,[10] as Vervloet states "Presently there is no definite proof of a beneficial effect of phosphate lowering on patient-level outcome. Moreover, both dietary intervention and phosphate binder therapy may have side effects. Despite these limitations, treating hyperphosphatemia in CKD still appears appropriate but should be paralleled by ongoing research to further underpin this approach and improve therapeutic strategies".

Regarding Dyslipidaemia treatment with statins in CKD and in particular in dialysis patients, the evidence supporting a beneficial effect of statins in patients on dialysis is moot, but this has not discouraged physicians to prescribe these drugs. However, as Professor de Vriese suggests the insight that statins potentially accelerate vascular calcifications in patients on dialysis may persuade nephrologists to ban statins from dialysis, pending hard data to supersede these assumptions.[14]

In the tale "The Emperor's new clothes", the emperor and courtiers were silent because they feared being revealed as stupid or incompetent. This attitude has been described 2400 years ago by Aristotle, who in his "Rhetoric' stated "But the hearers also are impressed in a certain way by a device employed *ad nauseam* by writers of speeches: "Who does not know?""Everybody knows"; for the hearer agrees, because he is ashamed to appear not to share what is a matter of common knowledge. (Aristotle, Rhetoric 3.7).

4. CONCLUSIONS

"Authority-based Medicine" is being substituted by "Guidelines-based Medicine" if the patient and the treating physician are not in the centre of the decision making process. We should hear the voices that cry out "the Emperor (our Healthcare) is naked" and as a recurring historical cycle turn to Hippocrates saying "make a habit of two things-to help or at least, to do no harm".

ΠΕΡΙΛΗΨΗ

Τα καινούργια ρούχα του αυτοκράτορα στη Νεφρολογία: Παρόν και παρελθόν

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Η Ιατρική βασισμένη σε αποδείξεις έχει περιγραφεί ως η συγχώνευση της καλλίτερα τεκμηριωμένης πληροφορίας με την εμπειρία του ιατρού και την προσωπική άποψη του ασθενή. Αν αντικατασταθεί από την Ιατρική των «Κατευ-

θυντήριων Οδηγιών» προσομοιάζει με το παραμύθι του Χανς Κρίστιαν Άντερσεν «Τα καινούργια ρούχα του Αυτοκράτορα» όπου ο Αυτοκράτορας (Σύστημα Υγείας) είναι γυμνός και κανείς δεν τολμάει να το φωνάξει. Η Ιστορία έχει κάνει κύκλους καθώς η Ιατρική βασισμένη στις «Αυθεντίες» του Παρελθόντος έχει αντικατασταθεί από τις «Κατευθυντήριες Οδηγίες», όταν αυτές ακολουθούνται τυφλά. Ερευνήσαμε παραδείγματα στο πεδίο της Νεφρολογίας στο Παρελθόν και στο Παρόν. Τα αποφθέγματα του Γαληνού και του Αριστοτέλη δεν αμφισβητήθηκαν από τους διαδόχους τους, στην «σκιά» της «Αυθεντίας» τους, παρόλο που ειρωνικά και οι δύο ενεργά ενθάρρυναν τον πειραματισμό και την αμφισβήτηση των καθιερωμένων θεωριών. Στο Παρόν η θεραπεία της υπερφωσφαταιμίας με δεσμευτικά του φωσφόρου και της δυσλιπιδαιμίας με στατίνες σε Αιμοκαθαιρόμενους ασθενείς αποτελούν δύο παραδείγματα όπου στην κλινική πράξη ο ιατρός και ο ασθενής δεν είναι στο κέντρο της θεραπευτικής απόφασης. Συμπερασματικά θα πρέπει να ακούμε τις φωνές «ο Αυτοκράτορας είναι γυμνός» και σε έναν επαναλαμβανόμενο ιστορικό κύκλο να επιστρέψουμε στον Όρκο του Ιπποκράτη.

Λέξεις ευρετηρίου: Ιατρική βασισμένη σε αποδείξεις, Νεφρολογία, Σύνδρομο «Τα καινούργια ρούχα του Αυτοκράτορα»

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PHILOSOPHY
ΦΙΛΟΣΟΦΙΑ

Nephrology history is alive and well and helps predict the future

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ΑΡΧΕΙΑ ΕΛΛΗΝΙΚΗΣ ΙΑΤΡΙΚΗΣ 2020, 37(Συμπλ 2):89–92

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If there can be "love in the time of cholera", then there can be history of kidney medicine in the time of COVID-19. In our article, we celebrate the history of nephrology, which unites curious young minds with the legacy built by senior figures of the discipline. Notably, technological advances such as the Internet have made nephrology history more accessible to a wide range of audiences, including young students and physicians in training. The interest that continues to prevail for the field ensures that the future of kidney medicine is bright and bound to expand in new directions. We can treat the past and the future with equal precision and rigor under the umbrella of history. One can describe a symmetrical timeline with 193 years back to Richard Bright's book in 1827, and 193 years forward to 2213 the point when some expect that human consciousness will be routinely uploaded to inorganic substrates. But for now, we shall seek to excavate the past to have a better idea of where we're going and how to achieve desired outcomes, which is especially important in a time of global health emergency, where we are all fighting a single enemy, COVID-19.

Η ιστορία της Νεφρολογίας είναι ζωντανή και παρούσα και βοηθά στην πρόβλεψη του μέλλοντος

Περίληψη στο τέλος του άρθρου

Key words

History of Nephrology
Medical education
Richard Bright
Technological singularity
The future

"History maketh a young man to be old, without either wrinkles or grey hairs; privileging him with the experiences of age, without either the infirmities or inconveniences thereof. Yea, it not only maketh things past, present; but enableth one to make a rational conjecture of things to come."

Thomas Fuller 1608–1661.[1]

INTRODUCTION

Despite the quotation at the head of this article, Dr. Eknoyan was pessimistic about the declining place of historical stories in medical education in his 2016 editorial.[1] However, in the opinion of young people who we speak to today, the history of nephrology is perhaps the most interesting history of any medical specialty. In contrast to the apparently reduced interest of medical journals, if one searches for "history of nephrology" or "history of transplantation" on social media, the resources found are pleasing and memorable, with images and videos that seem to jump off the page or screen to directly engage the senses (tables 1, 2). Yet, in the meetings of the International Association for the History of Nephrology, one gets the impression that it is a small niche discipline forgotten by the rest of the world.

In the world at large as seen by young people and the young at heart, the history of nephrology is vibrant and interesting, with new resources appearing all the time and accessed by many people (tables 1, 2). It is those connections to young people and the future that will ensure the success and longevity of the discipline.

Medical history is not a discrete set of archaic facts, but rather a relationship between medical historians in the present and the people and events of the past. From the beginning of historical writing, the endeavour has usually served two purposes: to answer the questions of the present about the past; and to account for the past in such a

Table 1. Popular history of nephrology resources readily found by searching.

https://www.youtube.com/playlist?list=PLS1ZP4out6bM__j9_rxTgy4V_aoTNPFpu Video Legacy playlist
https://ajkdblog.org/2017/03/07/nephmadness-2017-history-of-nephrology-region/
https://resident360.nejm.org/content_items/419
http://historyofnephrology.blogspot.com/2016/10/renal-biopsy-becomes-mainstream-1954.html
http://historyofnephrology.blogspot.com
http://historyofnephrology.blogspot.com/?view=flipcard
http://historyofnephrology.blogspot.com/?view=magazine
http://2.bp.blogspot.com/_X3TyLb9XrMM/SZ2lU7QzFaI/AAAAAAAAAAY/A8vPoB8Du6o/s1600-h/kidneyfactoryBethShorttA.jpg
https://hekint.org/2017/01/30/history-of-nephrology-modern-era/
https://hekint.org/2017/01/30/history-of-nephrology-beginnings/
https://web.archive.org/web/20190701170527/http://www.renalmed.co.uk/history-of-nephrology
https://www.kidney-international.org/article/S0085-2538(15)55080-1/fulltext
http://www.era-edta.org/history/A_Timeline_of_the_History_of_Nephrology.pdf

Table 2. Popular history of transplantation resources found by searching.

https://www.organdonor.gov/about/facts-terms/history.html
https://www.myast.org/about-ast/who-we-are/timeline History of AST
https://unos.org/transplant/history/
https://asts.org/about-asts/history#.XkbUZi0ZOjg
https://asts.org/docs/default-source/presidential-address/kahan-presidential-address.pdf?sfvrsn=2
https://www.youtube.com/user/ttscommunications/videos?view=0&sort=dd&shelf_id=1 TTS
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3684003/
https://futurism.com/images/a-timeline-of-organ-transplant-milestones
https://timelines.issarice.com/wiki/Timeline_of_organ_transplantation
https://www.amazon.com/History-Transplantation-Recollections-Paul-Terasaki/dp/0960460675
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3684003/ Clyde Barker History of Transplantation 2013
https://muse.jhu.edu/book/14856 David Hamilton History of Organ Transplantation 2012
https://asts.org/docs/default-source/about-asts/presidential-reminiscences.pdf?sfvrsn=2

way that it serves as a guide for the *future*, providing a set of exemplars to emulate and avoid as we face new challenges that resemble, in part, the challenges of the past.

Fundamentally, we need to think about how history connects the past to the present and to the future. If there are 193 years to account for between today and Richard Bright's 1827 book, we need to envision a symmetrical timeline where the 193 years back to Bright's book are balanced by 193 years into the predicted future. The history of nephrology must contemplate the question: where are we going? The first author Kim Solez successfully predicted the Translatotron in a presentation about Boundaries and Ethics in cyberNephrology[2] in February 2009 (tab. 5), and there are still many advances around the corner that can be understood in connection to the development of our discipline in the 19th and 20th centuries. Soon, we will have organs generated from the patient's stem cells, and this development should be understood by medical historians in continuity with the first "artificial kidneys" from decades ago.

Presentation is also important. At the meetings of the International Association for the History of Nephrology (such as the 2019 meeting in Larissa, tab. 3) dated PowerPoint templates are favoured, where the screen is mainly solid colours and the text then subtracts from the theme colours (tab. 4). This is quite the opposite of the more uplifting minimalist PowerPoint templates favoured by young

Table 3. Videos from IAHN meeting in Larissa, Greece in September 2019.

https://www.youtube.com/watch?v=GPACpUXJo4Q Solez
https://www.youtube.com/watch?v=j57MAprvPP4 Eknoyan
https://www.youtube.com/watch?v=rDXeBINRkAE Cameron
https://www.youtube.com/watch?v=lwwfvpjJL8Y George
https://www.youtube.com/watch?v=U68jnXDrlPY Stefanidis
https://www.youtube.com/watch?v=DnNDDqm3ZUE Phillips

Table 4. History of presentations. Before PowerPoint.

https://visme.co/blog/evolution-of-presentations/ 2020
https://www.youtube.com/watch?v=suRDUFpsHus Mad Men 2008 The Carousel
https://www.duarte.com/presentation-skills-resources/back-to-the-future-slides-before-powerpoint/
https://computerhistory.org/blog/slide-logic-the-emergence-of-presentation-software-and-the-prehistory-of-powerpoint/ 2016
https://archive.computerhistory.org/resources/access/text/finding-aids/102733943-Austin/102733943-Austin.pdf
https://www.robertgaskins.com/powerpoint-history/sweating-bullets/gaskins-sweating-bullets-webpdf-isbn-9780985142414.pdf 2012 (25th anniversary of PowerPoint)

Table 5. Translatotron links.

https://www.slideshare.net/ksolez/kim-solez-boundaries-and-ethics-of-cybernephrology-feb-2009-boundaries-ethics-2 First author predicts Translatotron in 2009 (slide 27)
https://ai.googleblog.com/2019/05/introducing-translatotron-end-to-end.html
https://google-research.github.io/lingvo-lab/translatotron/
https://bigthink.com/surprising-science/translatotron
https://www.youtube.com/watch?v=tKwK8GHLYOo
https://www.theverge.com/2019/5/17/18628980/google-ai-translation-tone-cadence-voice-translatotron
https://techcrunch.com/2019/05/15/googles-translatotron-converts-one-spoken-language-to-another-no-text-involved/
http://languagehat.com/translatotron/
https://medium.com/syncedreview/google-ai-translatotron-can-make-anyone-a-real-time-polyglot-e7b6d616f5d2
https://www.youtube.com/watch?v=38ZXwJj6j8k (June 20, 2019)
https://www.androidpolice.com/2019/05/16/google-introduces-direct-speech-to-speech-translation-technology-it-calls-translatotron/

people today, where most of the screen is white until text and graphics are added. Putting the history of nephrology into such new-style templates brings a much more positive feeling to the whole enterprise.

The way forward

Canadian author and musician Leonard Cohen's best-known song, "Hallelujah", contains these self-referential lines: "It goes like this, the fourth, the fifth, the minor fall, the major lift, the baffled king composing Hallelujah" in which the words describe exactly what the melody is doing. The song exalts the daily lives of flawed human beings in the present with reference to the legendary past of David, king of Israel, striving to please God. The history of nephrology attained a similar self-referential moment in 2016, when Dr. Diamandopoulos published "On the History of the History of Nephrology" in NDT in 2016,[3] where he attempted to articulate exactly how the field was linking the present to the past today, and how it had done so in previous years. Self-referentiality and a consciousness of the way we link present to past is bound to change, while addressing new questions about the future, and may bode well for the discipline. Hallelujah to the bright and expanding future of the history of nephrology.

Finally, if one is concerned about the promotion of the history of nephrology, either as an amateur or scholar in the field, one can play a positive role by openly sharing the passion for the history of nephrology with those around them. After all, passion in young people arises proportionately with the enthusiasm exuded by their mentors. Thus, all authors of this paper, in addition to the readers, have an important role to play as torchbearers in keeping alive the passion for nephrology's history, today, tomorrow and beyond into the future.

Figures 1 a, b, c. Images from Solez's presentation at the Larissa IAHN Meeting. Available at: https://www.youtube.com/watch?v=GPACpUXJo4Q.

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ΠΕΡΙΛΗΨΗ

Η ιστορία της Νεφρολογίας είναι ζωντανή και παρούσα και βοηθά στην πρόβλεψη του μέλλοντος

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Αν μπορεί να υπάρξει ένας «έρωτας στα χρόνια της χολέρας», τότε μπορεί να υπάρξει και η Ιστορία της Ιατρικής των νεφρών στην εποχή του COVID-19. Στο άρθρο μας αφηγούμαστε την ιστορία της Νεφρολογίας, η οποία και ενώνει διερευνητικά νεαρά μυαλά με μια επιστημονική παράδοση δημιουργημένη από τις πλέον έμπειρες προσωπικότητες της επιστήμης. Ιδιαίτερα νέες τεχνολογίες όπως αυτή του διαδικτύου έχουν πια κάνει την ιστορία της νεφρολογίας πολύ πιο προσβάσιμη σε ένα ευρύ φάσμα κοινού, συμπεριλαμβανομένων των νεαρών φοιτητών και των ασκούμενων ιατρών. Το ενδιαφέρον που συνεχίζει να κυριαρχεί στο πεδίο εγγυάται ότι το μέλλον της Ιατρικής των νεφρών θα είναι λαμπρό και θα επεκταθεί προς όλες τις κατευθύνσεις. Μπορούμε να αντιμετωπίσουμε τόσο το παρελθόν όσο και το μέλλον με ίση ακρίβεια και αυστηρότητα υπό τη σκέπη της ιστορίας. Μπορεί κανείς να φανταστεί μια συμμετρική πορεία ανάμεσα στα 193 χρόνια που μεσολάβησαν από την έκδοση του βιβλίου του Richard Bright το 1827 και το σήμερα και τα 193 χρόνια που θα μεσολαβήσουν από το σήμερα μέχρι το 2213, την εποχή που κάποιοι αναμένουν ότι η ανθρώπινη συνείδηση θα μπορεί πια να μεταφυτεύεται τακτικά σε ανόργανα υποστρώματα. Προς το παρόν, ωστόσο, πρέπει να «ανασκάψουμε» το παρελθόν ώστε να επιτύχουμε μια καλύτερη εικόνα για το πού πηγαίνουμε και για το πώς θα επιτύχουμε τα επιθυμητά αποτελέσματα, που είναι ιδιαίτερα σημαντικά στην εποχή μιας παγκόσμιας κατάστασης υγειονομικής έκτακτης ανάγκης, που όλοι πολεμούμε τον κοινό εχθρό, τον COVID-19.

Λέξεις ευρετηρίου: Ιατρική εκπαίδευση, Ιστορία της Νεφρολογίας, Richard Bright, Τεχνολογική μοναδικότητα, Το μέλλον

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PHILOSOPHY
ΦΙΛΟΣΟΦΙΑ

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ΑΡΧΕΙΑ ΕΛΛΗΝΙΚΗΣ ΙΑΤΡΙΚΗΣ 2020, 37(Συμπλ 2):93–96

Hippocrates' Aphorisms on nephrology and the application of his Spirit for caring renal patients

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Nephrology is one of the newest medical specialties that developed during the previous century. The earliest scientific approach to clinical nephrology, however, is attributed to Hippocrates, granting him the title "Father of clinical nephrology". The principal essence of renal medicine is in fact hidden within the Hippocratic theory of the four humors, as it remarkably resembles the main kidney function, which is the preservation of fluid and electrolyte homeostasis. Hippocrates excelled in the art of uroscopy for the diagnosis of nephrological conditions. Moreover, within the Hippocratic corpus there are many references to renal problems, such as kidney stones, gout, nephrotic syndrome, haematuria, and acute tubular necrosis. The writer provided a detailed description of their symptoms, accompanied with prognostic and therapeutic guidance. Nowadays renal patients' care has progressed far beyond the Hippocratic writings. Renal replacement therapy, biological treatments and organ transplantation have altered the natural course of renal disease. The modern nephrologist must face several dilemmas associated with a chronic terminal condition, such as end-of-life treatment, palliative care and support to both patients and their families. At this time, the Hippocratic Spirit emerges as an ethical guide and constant reminder of the moral responsibilities linked to medical profession, in the Spirit of the Hippocratic saying "benefit or do no harm".

Οι Αφορισμοί του Ιπποκράτους για τη Νεφρολογία και η εφαρμογή του Πνεύματός του στη φροντίδα των νεφροπαθών

Περίληψη στο τέλος του άρθρου

Key words

Aphorisms
Hippocrates
History nephrology
Medical ethics
Purging

1. INTRODUCTION

Nephrology is one of the newest medical specialties of the previous century. Its recognition as a distinct specialty and not as part of urology, internal medicine or clinical physiology was only possible after several revolutionary scientific advances, such as the analysis of glomerular filtrate by micropuncture in 1924 by Wearn and Richard, or the first successful haemodialysis session in 1945 by Kolff. A search for the earliest scientific approach to clinical nephrology, however, leads to Hippocratic medicine, granting Hippocrates the title "Father of clinical nephrology".

2. NEPHROLOGY IN THE HIPPOCRATIC COLLECTION

The contribution of Hippocratic medicine to nephrology is significant and involves several aspects of clinical practice. First of all, Hippocrates used many nephrological terms such as *nephros*, *nephritis*, *hematuria*, *dysuria*, *lithos* that are still in use.[1] In antiquity, there was limited knowledge of human anatomy and physiology. Despite that fact, he made correct observations regarding the shape and place of the kidneys as well as their relation to urine formation.[2] It is believed that Hippocrates was the first to conceive the fundamental principle of kidney function, which is preservation of volume and composition of the body fluids, or homeostasis.[3] In the humoral theory, he proposed that the human body is made up of four substances, called the humors. Each of these humors, phlegm, blood, yellow bile and black bile, was linked to an element in the universe and to a temperament. Perfect balance of the four humors of the body ensured ideal health whereas imbalance, or dyscrasia, was the direct cause of all disease. Therefore, medical efforts should always focus on preserving or restoring that balance.[4]

As a treatment, Hippocrates recommended the practice of "purging", which means intentionally removing from the body substances that are abundant or disturbing and cannot be removed otherwise. The similarity to the principles of modern renal replacement therapy is astonishing.

"In purging we should bring away such matters from the body as it would be advantageous had they come away spontaneously; but those of an opposite character should be stopped." [Aphorism IV, 2].
"If the matters which are purged be such as should be purged, it is beneficial and well borne; but if the contrary, with difficulty."[Aphorism IV, 3].[2]

Hippocrates excelled in the art of uroscopy. He believed that no other organ or system of the human body can provide so much diagnostic or prognostic information by its excretion as does the urinary tract.[5] In *Aphorism VII (67)*, he stated that the urine must be observed to see how far it resembles that passed in health.

"We must look to the urinary evacuations, whether they resemble those of persons in health; if not at all so, they are particularly morbid, but if they are like those of healthy persons, they are not at all morbid".

For example,

"Bubbles appearing on the surface of the urine indicate disease of the kidneys and a prolonged illness". [Aphorism VII, 34]

refers to the classic description of proteinuria.

"When small fleshy substances like hairs are discharged along with thick urine, these substances come from the kidneys". [Aphorism IV, 76]

is correspondent to red blood cell casts.

In the Hippocratic corpus there are more than 30 aphorisms of nephrological interest which included diagnostic, prognostic and therapeutic observations.[2]

"When the urine is transparent and white, it is bad; it appears principally in cases of phrenitis". [Aphorism IV, 72]

probably refers to a case of advanced renal failure with uremic encephalopathy. Other examples are descriptions of renal papillary necrosis, acute pyelonephritis and postinfectious glomerulonephritis.

"In cases where there is a spontaneous discharge of bloody urine, it indicates rupture of a small vein in the kidneys." [Aphorism IV, 78]
"When there is a farinaceous sediment in the urine during fever, it indicates a protracted illness." [Aphorism VII, 31]
"In those cases, in which the urine is thin at first, and the sediments become bilious, an acute disease is indicated." [Aphorism VII, 32].[2,6]

Gout, its epidemiology and its relation with sex hormones were described with surprising detail.

"Eunuchs do not take the gout, nor become bald". [Aphorism VI, 28].
"A woman does not take the gout, unless her menses be stopped". [Aphorism VI, 29].
"A young man [boy] does not take the gout until he indulges in coition". [Aphorism VI, 30].[2]

A significant contribution of Hippocrates is the pathophysiology of kidney stone formation and renal colic.

"Calculus forms in the bladder of those in whose urine sandy particles are deposited". [Aphorism IV, 79].
"When pure blood and clots are discharged with urine, strangury, pain at the bottom of the belly and in the perineum, likewise occurring, there exists disease in the bladder". [Aphorism IV, 80].

Moreover, he was the first to comment on the disease epidemiology and to address the importance of water quality. Many of his interpretations are considered accurate until today.[5]

The prognosis of renal disease in the Hippocratic writings is of great interest. Hippocrates observed that many of the disorders are long-standing and fatal.

"Diseases of the kidney and of the bladder are difficult to cure in the aged". [Aphorism VI, 6].[3]
"When cough and redness of the eyes succeed vomiting, the indication is bad". [Aphorism VII, 47]

referring to the uremic state.[6]

"When much urine is passed during the night, it indicates slight retreat of the disease". [Aphorism IV, 83].[2]

Therapeutically, Hippocrates believed that diet modifications and physical exercise are key elements for cure.[6,7] The purpose of treatment was to achieve normalisation of the constitution of the body fluids.

"Bodies not properly cleansed, the more you feed them the more you injure". [Aphorism II, 10].
"Diseases which arise from depletion are cured by depletion; and those that arise from depletion are cured by repletion; and in general, diseases are cured by their contraries". [Aphorism II, 22].

He also recommended use of herbal extracts and other remedies.

"Strangury and dysuria are cured by drinking pure wine [drunkenness], and venesection; open the vein on the inside". [Aphorism VII, 48].[2]

Hippocrates recommended surgery only in cases where other treatments failed.

"What drugs will not cure, the knife will". [*Aphorism VII, 87*].[3]

3. RENAL PATIENTS' CARE

Care of renal patients is particularly challenging due to the slow progression of chronic kidney disease, its debilitating nature, its inevitable outcome and the ethical issues that arise during its course. The modern nephrologist must face moral dilemmas that confound the life of a chronic patient, such as coping with everyday problems, dealing with end-of-life treatment, and providing support to patients and their families. During that time, the Hippocratic teachings can offer the struggling physician guidance, motivation and courage.

Hippocrates, as a physician-philosopher, suggested looking beyond the physical features of diseases and considering the patient as a unique psychosomatic entity, therefore treating the body and the soul.[8] He advised respect for the power of nature and consciousness in the use of medical treatments, along with wisdom and rationalism when practicing the art of medicine. Moreover, the Hippocratic writings summarised all the ethical principles that accompany medical practice throughout the centuries. Hippocratic medicine taught physicians to behave with integrity, discretion and honesty towards their patients, consideration for their fears and feelings but also adherence to the rules of their profession.[9] Many of the quotes of the Hippocratic collection, including the Oath, are dedicated to the moral code of medicine and the sacredness of the physician-patient relationship, which are highly applicable in modern nephrological practice.

"Life is short, the Art long; opportunity fleeting, experiment treacherous, judgment difficult".

"The physician must not only be prepared to do what is right himself, but also to make the patient, the attendants and the externals cooperate".

"The Medical Art has three actors: the physician, the patients and the disease. The physician and the patient must be allied against the disease in order to fight it".

"To cure sometimes, to relieve often, and to comfort always".

"The place of a physician is at the bedside of his patient".

"It is more important to know what sort of person has a disease than to know what sort of disease a person has".

"Science is the father of knowledge, but opinion breeds ignorance".

4. CONCLUSIONS

At this difficult time for mankind, the Hippocratic Spirit emerges as an ethical guide and reminder of the moral responsibilities linked to the medical profession. Through the study of the Hippocratic Corpus, the modern physician can appreciate the true meaning of the Hippocratic saying "benefit or do no harm" and apply it in everyday medical practice against moral pressures, affirming that Medicine is the greatest and most humane of all sciences.

ΠΕΡΙΛΗΨΗ

Οι Αφορισμοί του Ιπποκράτους για τη Νεφρολογία και η εφαρμογή του Πνεύματός του στη φροντίδα των νεφροπαθών

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Αν και η Νεφρολογία αποτελεί μια από τις νεότερες ιατρικές ειδικότητες, οι βάσεις της ανάγονται στην εποχή του Ιπποκράτη δίνοντάς του τον τίτλο του «Πατέρα της Κλινικής Νεφρολογίας». Η Ιπποκρατική θεωρία των 4 χυμών αντικατοπτρίζει τη θεμελιώδη αρχή της Νεφρολογίας που είναι η διατήρηση της ομοιοστασίας των υγρών και ηλεκτρολυτών στον οργανισμό. Ο Ιπποκράτης ανέπτυξε την τεχνική της ουροσκοπίας για τη διάγνωση νεφρικών παθήσεων. Επί πλέον, στο Ιπποκρατικό σώμα περιέχονται πολλές αναφορές σε νεφρικές διαταραχές, όπως λιθίαση, ποδάγρα, νεφρωσικό σύνδρομο, αιματουρία, οξεία σωληναριακή νέκρωση. Σε αυτές περιλαμβάνεται η αναλυτική περιγραφή των συμπτωμάτων, η πρόγνωσή τους και θεραπευτικές συστάσεις. Στη σύγχρονη εποχή, η φροντίδα των ασθενών με νεφρική νόσο έχει γίνει ιδιαίτερα απαιτητική, καθώς οι σύγχρονες θεραπείες και εξελίξεις στη θεραπεία έχουν με-

ταβάλει τη φυσική πορεία της πάθησης. Ο σύγχρονος νεφρολόγος έρχεται αντιμέτωπος με σοβαρά διλήμματα τα οποία σχετίζονται με μια χρόνια ανίατη νόσο, όπως τη διαχείριση του τέλους της ζωής, την παρηγορητική φροντίδα, την υποστήριξη του ασθενή και των οικείων του. Ακριβώς σε αυτή τη στιγμή, το Ιπποκρατικό πνεύμα αναδεικνύεται ως ο ηθικός οδηγός, σύμβουλος και υπενθυμιστής του υψηλού ιατρικού φρονήματος στο πνεύμα της Ιπποκρατικής ρήσης «Ωφελέειν ή μη βλάπτειν».

Λέξεις ευρετηρίου: Αφορισμοί, Ιατρική ηθική, Ιπποκράτης, Ιστορία Νεφρολογίας, Υποκλυσμοί

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LABORATORY PROCEDURE
ΕΡΓΑΣΤΗΡΙΑΚΗ ΜΕΘΟΔΟΣ

Urine specific gravity according to ancient and medieval Greek sources

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ΑΡΧΕΙΑ ΕΛΛΗΝΙΚΗΣ ΙΑΤΡΙΚΗΣ 2020, 37(Συμπλ 2):97–103

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Το ειδικό βάρος των ούρων σύμφωνα με αρχαίες και μεσαιωνικές ελληνικές πηγές

Περίληψη στο τέλος του άρθρου

The original relevant works by Hippocrates, Galen, Anonymi Medici Minores, Stephanus, Theophilus, Aetius, Joannes Zacharias Actuarius and Avicenna's Canon were read in order to find out if they contained any reference to urine specific gravity (s.g.) and its correlation with the natural history of renal diseases. The term "specific gravity" was of course never mentioned by ancient and medieval writers. Indirectly, they referred to it by discussing the different location of a semisolid formation in the matula (urine examination vial). If it lay on the bottom, it was cold "hypostasis" (sediment), if suspended in the middle "enaeorema" (suspension) and if floating on the top "nephelion" (nebulum). All above medical authors agreed that sediment usually testifies a healthy condition and a floating formation a very severe disease. The suspension could either be a sign of recovery if it followed a nebulum and was thus descending or of deterioration if it followed a sediment and was thus assenting. As its location depended on the difference in weight between the semisolid formation and the liquid part of the urine, in a sense, it measured its specific gravity. Very recently, urine specific gravity gained ground as an accurate renal function marker, equal to creatinine clearance.

Key words

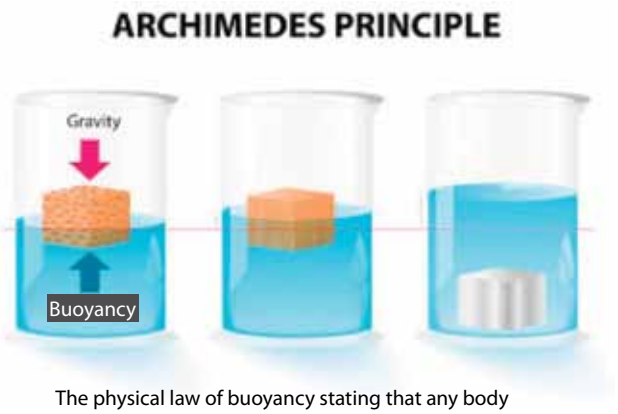
Byzantine medical authors
Classical medical authors
Proteinouria
Specific gravity
Urinometer

1. AIM

The aim of this paper was to try to find out if there was any reference to urine specific gravity in Ancient and Medieval Greek literature and its correlation with the natural history of renal diseases.

2. INTRODUCTION

Any discussion on specific gravity should start with Archimedes' fundamental principle, as presented in his treatise on Floating Bodies: *Any object, totally or partially immersed in a fluid or liquid, is buoyed up by a force equal to the weight of the fluid displaced by the object*[1] (fig. 1). The principle found a practical application as early as in Pliny's times. It was subsequently used for verifying the purity of precious stones and metals as described in the *Carmen de ponderibus et mensuris*, an anonymous Latin poem, dated between the late 4th and the early 6th cent. AD, and dedicated to a Symmachus, perhaps the father-in-law of Boethius; it is a skilfully formed and clearly structured didactic poem in 208 hexameters, concerning weights and measures.[2] It describes the function of a hydrometer in an embryonic form. An early description of this instrument appears in the 5th century AD fifteenth letter from Synesius of Cyrene to the Greek scholar Hypatia of Alexandria.[3] It has a glass shaft with numerical markings and a bulb ending, filled with ball bearings. When immersed in a fluid, it measures its specific gravity. The lower the density of the fluid, the deeper a hydrometer of a given weight sinks; and



The physical law of buoyancy stating that any body completely or partially submerged in a fluid (gas or liquid) at rest is acted upon by an upward, or buoyant, force the magnitude of which is equal to the weight of the fluid displaced by the body. **In an embryonic form it describes the use of a hydrometer and a urinometer.**

Figure 1.

conversely, the higher the density of the fluid, the higher the hydrometer floats. A urinometer is a medical hydrometer designed for urinalysis. As urine specific gravity is dictated by its ratio of solutes (wastes) to the loose portion of the urines, a urinometer allows a quick assessment of a patient's overall hydration level and or the amount of the solutes excreted in the urine and the kidneys' ability to respond appropriately, in order to dilute or concentrate urine over that of plasma. This instrument, in the simple form of a thermometer-shaped mercury-based floating urinometer, was introduced in 1849 by the Viennese scientist Johann Florian Heller (1813–1871).[4] As Ancient and Medieval medical writers lacked the knowledge of the urinometer or of the practical application of the specific gravity principle to body fluids, they never mentioned it in connection to urine examinations.

3. MATERIALS

We read the original relevant works by Hippocrates, Galen, Anonymi Medici Minores, and Stephanus, Theophilus, Aetius, Joannes Zacharias Actuarius and correlated them with Avicenna's Canon. Before proceeding to the presentation of particular authors' writings on the subject, it would be useful to define some of the terms they used (a) and their proposed equivalent in current medical knowledge (b).

3.1. Glossary

3.1.1. Digestion. In a broad sense, it denotes the metabolism. It was based on the theory of the Four Humors and was generally subdivided into three stages. (a) *The First Digestion happens in the gastrointestinal tract (GI) where food is bound with the pneuma and produces chyle; its waste product is the faeces.* (b) Digestion in the intestine requires oxygen. If the blood flow is compromised, the intestine opens more capillaries.[5] *The Second Digestion takes part in the liver where the chyle, or digested food, is brought from the GI and is worked up into an impure blood, imbued with the first form of pneuma innate to all things, the natural spirits. There, the Innate Heat is converted into the Metabolic Heat, or Ignis* (whence etymologically the word ignition as e.g. in cars). *Together with the Natural Force, the Metabolic Heat generates the Four Humors and cooks or concocts the humors in a process of pepsis* (whence etymologically the word Pepsi cola). (b) The hepatic circulation perfuses one of the largest organs and maintains the organic composition of the blood [...] It consists by 80% of venous blood from the GI and the rest from the hepatic artery. For this double perfusion, the liver requires the largest oxygen consumption.[6] (a) *The concocted humors enter the veins where the Third Digestion takes place. The waste products are eliminated via the bile, the urine and sweat. Any imperfect digestion there causes abnormal urine. From the veins, the blood returns to the heart whence it captures peuma from the lungs and little by little reaches all tissues where the Fourth Digestion occurs.* (b) The blood from the liver, full of processed nutrients, enters the heart via the hepatic vein where it is reoxygenated and returns to the general circulation.[7]

3.1.2. Pneuma. We propose that this corresponds to oxygen. This is backed by the fact that the ancients described as pneuma the content of the arteries, not meaning air but aerated blood; hence the arteries were naturally, but in fact wrongly, described by later commentators as empty.

3.1.3. Concoction. (a) Breaking down via metabolism the various nutrients and /or renal handling of the useless residue resulting in transparent urine. This idea was proposed in a rudimentary form by Aristotle.[8] (b) The kidneys are essential for homeostasis (maintaining a constant internal environment) of the body's extracellular fluids. Their basic functions include, between others, the filtration of a variety of water-soluble waste products and environmental toxins into the urine for excretion.

3.1.4. Hypostasis (sediment). This is the matter containing the insoluble components of urine, separated or aggregated with protein or mucus, and laying at the bottom of the uroscopy vial (matula/amis in Greek).

3.1.5. Enaeorema (suspension). This is the same matter, suspended somewhere in the middle of the matula.

3.1.6. Nepheloma (cloud). The same matter floating on the urine surface.

Although the presented comparison between the ancient and modern ideas of the body functions is exciting if just only based on extrapolation, the use of current medical knowledge, as well as logic and philosophy, to interpret ancient bio-medical texts makes them relevant to modern readers.[9]

4. METHOD

We put forward the hypothesis that the location of insoluble urine components depends on the weight difference between these components and the loose part of urine. As the urine examination is "the window to the kidney" any correlation between their location and the underlying renal pathology depends on the "eye of the beholder". Hence, we present some ancient Greek and Byzantine statements on the issue.

5. RESULTS

Hippocrates was the earlier writer correlating the location of the non-soluble particles of the urine with the course of a disease: *"The sediment or cloud is more favourable when it occupies the bottom, than when it floats towards the surface of the fluid".*[10]

"The bowels, in all diseases, were disordered, and in a bad state, but worst of all in these. The urine, in most of them, was either thin and crude, yellow, and after a time with slight symptoms of concoction in a critical form, or having the proper thickness, but muddy, and neither settling nor subsiding; or having small and bad, and crude sediments; these being the worst of all".[11] *"And one should consider respecting the kinds of urine, which have clouds, whether they tend upwards or downwards, and the colours which they have and such as fall downwards, with the colours as described, are to be reckoned good and commended; but such as are carried upwards, with the colours as described, are to be held as bad, and are to be distrusted".*[12] The 10th aphorism reports that when the ripeness is complete, sediments settle at the bottom of vessel, and when it is intermediate, these [the sediments] are suspended, and when it is at the beginning, these float. The 11th aphorism clarifies that bright white sediments are the best indicators of complete cooking: The bright white sediment is praiseworthy and indicative of complete ripeness because cooking power is complete.[13,14]

Because as the urine is coming from the blood and filtered through the kidneys and ends at the bladder, anything abnormal appearing in it originates from the circulation or from these two organs, […] thus the thin ones indicate a disease of the veins; While the no thin (thick) the bladder,[15] referred by Deros.[16]

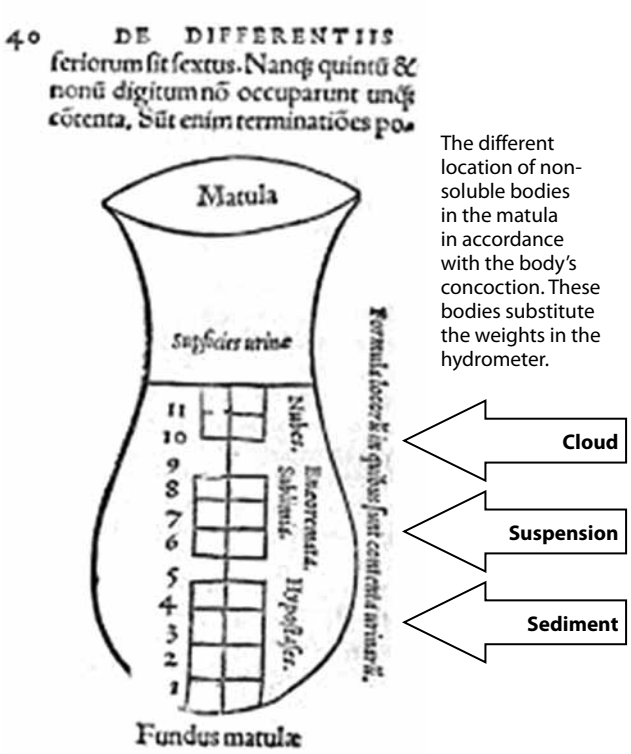
Another interesting reference is that of Stephanus of Athens (7th cent A.D.) in "De urinis". He wrote about bubbles in urine during the course of fever: *"...if bubbles show on the upper surface of urine, just like when a crystal is in fire, this means that urine consist of thick substance; if thick urine are observed during fever and after this they become thin and excess in volume, this means that the fever will subside...".*[17] Here, he probably talks about albuminous urine, as it is known today that during fever there is excess excretion of albumin in urine. *"Again, there is another complexity, having the sediment white colour but its location is in the middle and it is then called suspension […] because … the excess of a spread out wind made it lighter has lifted it in the middle. In addition, if in many cases the spread out wind is in abundance and pushes the sediment it lifts it from the middle in the surface and then it is called cloud.*[18]

The idea of this spread out wind, *pneuma* in the original language, requires a more detailed discussion. According to Ancient Greek writers, there are two kinds of pneuma; respiratory and digestive.[19] The second promotes digestion. Later, a third one was added, the *psychic*, involved in all neurological functions.[20]

When concoction is completed the pneuma is consumed; hence, no wind is left in the urines to push the sediment, which then floats to the bottom. The less the digestion is completed, the more pneuma is left and the higher the location of the particles in urine. Other medical writers of the era followed the same model of thought. Aetius Amidenus (6th cent) detailed the underlying cause of the upwards movement of urine sediment to enaeorema and then nepheloma, calling the "spread out wind" an "invisible force" pushing the formed particles from the bottom upwards.[22] Theophilus Protospatharious (7th cent?) explained the location of the nepheloma and enaeorema in a similar manner.[23] The close similarity between Aetius', Stephanus', Theophilus' Magnus Emesius' (an obscure author of contested date who is believed to be the proposer of the tripartite location of urine cellular components) treatises on uroscopy and their hypothesised connection with Pseudo-Galen's *De urinis Compendium* make it very difficult to be certain about the authentic authorship of any such document. The matter is complicated by the existence of manuscripts haphazardly put together. But generally, they all adhere to the described model.[24] Before proceeding to a medical writer of Late Byzantium, an overview is necessary for comparison of the Islamic views on the subject, mainly of its more prominent author, Avicenna (10th/11th cent). He defined "sediment" with foresight as regards its relation to specific gravity. "In the first place one must specify the meaning of the term "sediment". It is not "that which sinks to the bottom of the vessel". It is "that whole substance is denser in essence than wateriness, which separates out from the wateriness - regardless of whether it settles down. or not, floats or not".[25] Ten verses later, he continues in line with Greek writers: *"If a cloud appears floating in the upper portion of the vial, it indicates crudeness of the illness. If a certain maturity exists in the urine, wind is causing the sediment to renascent to the surface. If the sediment is half way up, be aware that the wind is in a small quantity […] The sediment remains suspended when air is captured in the organic matter, which nature doesn't ripen and digest".*[25]

Joannes Zacharias Actuarius (13th/14th cent) adhered to the tripartite location of urine cellular components. He correctly noted that the more severe the disease or the fever (causing presumably heavier proteinuria and a higher specific gravity), the higher these formed elements stand

in the amis (the examining bottle, which he was the first to insist that it should be made from an excellent quality of glass). When the disease subsides (and hence, proteinuria decreases) the sediment precipitates. However, Joannes goes a step further. He introduced a uroscopy vial with eleven horizontal lines numbered from the bottom upwards. When the cellular components occupy the second to fourth line, they are called Hypostasis, when the sixth to the eighth enaeorema, while the nepheloma lays in the 10th to 11th line. Using this vial, a more accurate description of the cells' location was possible. There are also intermittent zones (figures 2, 3). In his treatise on urines, he also expressed the overall parallelism in Byzantine thinking between the microcosm and macrocosm. Acturius e.g. writes: *"Because it has also been said that during obstructions the excreted urines may appear to be thin, it is worth mentioning the presumed causes. [...] Because whenever some people had a muddy and thick wine, they had passed it repeatedly through a straining cloth, and satisfactorily thinned it, having taken away the thickness through the passage, [...] similarly, it must be considered that the same may happen if during obstructions in any quarter the urine is seen thin, [hence] someone would rather blame the material obstructing the passages than a metabolic disorder".*[26] The notion that a renal obstruction may cause thinner urine has been recently verified when it was stated that the most sensitive test that obstruction and renal limitation is occurring is the urine's concentrated specific gravity.[27,28]



The different location of non-soluble bodies in the matula in accordance with the body's concoction. These bodies substitute the weights in the hydrometer.

Figure 2. Woodcut De Urinis by Joannes Actuarius, translated by Leo of Nola, published: 1529. Wellcome L0012935.

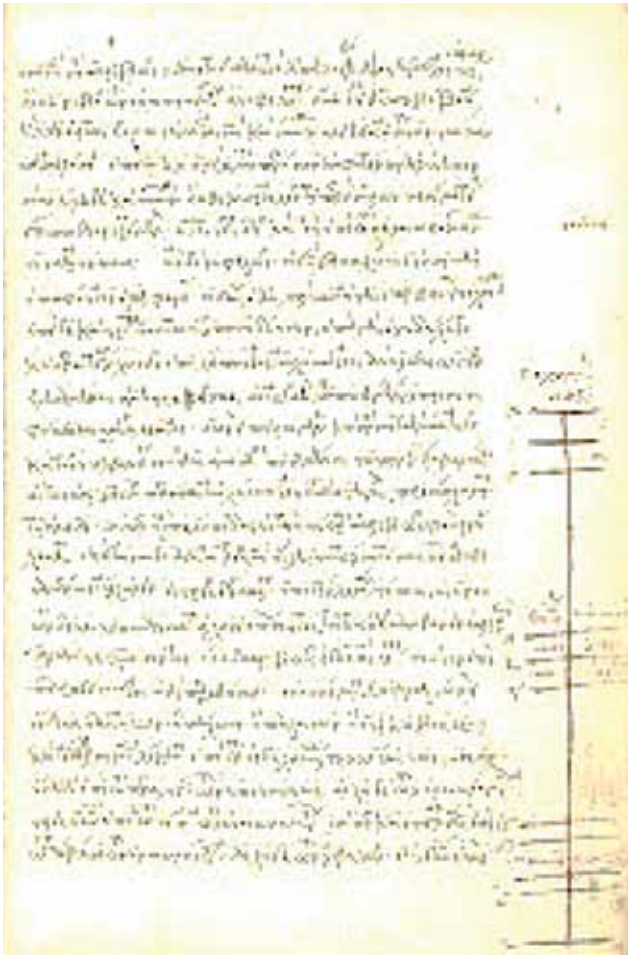


Figure 3. MS copy of Ioannes Actuarius' De Urinis. On the right hand margin a drawing of his vial with the various zones of the non-soluble mater (scribal addition?) MS.MSL.52 (f. 54r). Welcome Library), London.

6. DISCUSSION

With Zacharias, Byzantine uroscopy came to an end and about a century later so did the Byzantine Empire itself. Nevertheless, in its last days, a didactic poem, *"On urines",* was written by Nicephorus Vlemmydes (13th cent) about the same time with Zacharias' works. Both were cultural products of the Imperial Court in Nicea and later in Constantinople. The manuscript has been edited and revived in music by the author of this article in a small volume also containing a similar medical poem by Michael Psellus (11th cent).[29] In the same volume, the author discussed the importance of medical didactic poems in Antiquity and

the Middle Ages and beyond. There follow only few lines implying urine specific gravity.

Psellus verses 510–525:

"[the sediment's] is again triple and depends on its location and site.
[…] Well, since the urines' nature is three fold
All elements cannot be mixed at random.
Because the thin, white and undigested urine
Obviously cannot be mixed with the cloudy material body.
Because how could ever be possible to fuse digestion with indigestion"

Vlemymydes' Ode I:

"The milky urine when it is completely coagulated
Be aware that in all cases this implies imminent death for the patient"

With the presented extracts from Ancient and Byzantine medical texts, we reached the twilight of indirect references to urine specific gravity. A new dawn started in the West with a trend for a more scientific approach. Its prophet can be considered the renowned 15th century theologian and scientist Nicholas of Cusa who in *The Layman: Experiments with Weights* writes that, in creation, God ordered "all things in measure, number and weight."

In the background stands the saying from the *Book of Wisdom:* 11.21. This way number and mathematical ideas take on more than their usual employment for human ends and become a way to the Creator always present in human thought.[29] *"Orator: Do you think that in all cases the situation is as you indicated it to be in the case of water? Layman: Yes, I do. For identical sizes, of whatsoever different things, are not at all of the same weight. Accordingly, since the weight of blood or the weight of urine is different for a healthy man and for a sick man or for a youthful man and an elderly man or for a German and an African, wouldn't it be especially useful to a physician to have all these differences recorded? Orator: Most certainly. Indeed, through the recorded weights, the physician could render himself admirable. Layman: I think that a physician can make a truer judgment from the weight of urine together with its colour than from just its colour, which is misleading.*[30] Two centuries later this became a dictum: *"Neither the naked hand nor the understanding left to itself can effect much. It is by instruments and helps that the work is done"* – Francis Bacon, Novurn Organum (1620).[31] The path to a more scientific evaluation of specific gravity was thus opened.

7. CONCLUSIONS

7.1. General

Several ancient and medieval medical writers had suspected that the floating of the urine's non-soluble materials correlates with the course of a renal disease. As the positioning of these materials depends on the difference between their weight and that of the soluble material, we propose that, in essence, these writers measured urine specific gravity (although they ignored the term) and hence disease severity. They hypothesised that an invisible force was responsible for the upwards movement of non-soluble materials. We now know that such an invisible force exists; it is called buoyancy and its strength depends on the difference of the liquid and solid parts of urine, which in turns depends on proper kidney function and the kind of circulating blood in them. We could not trace any similar hypothesis in the current literature. This was our final remark when presenting this paper at the Larissa XIth IAHN Congress on 13 September 2019 and this was also published as the colophon of the corresponding abstract.[32]

7.2. A belated moral lesson

Surprisingly, while searching the literature for writing the full paper, a 200-year-old book was found, stating the same similarity! *"When a mucous cloud is present [in the urine] it ascends and descends in the fluid according to specific gravity, thus serving the purpose of a hydrometer".*[33] However, as a consolation, Osborne concludes the preface of his book by declaring "*Thus the following treatise may be regarded as an index of what has been hitherto discovered concerning the urinary secretion, and is an attempt to frame for any person interested in the subject, such a sketch as I should have been desirous to possess, when I commenced my inquiries".*[34]

Poetry may better, although crudely, highlight the different changes that the description of urine specific gravity underwent through the centuries:

[…] Later will our enemies the new sophists come
When we in our old age will lie wretchedly.
And some of us will have gone to Hades.
Our present words and works will appear strange
(and ridiculous perhaps) since the enemies will change sophistics' style and tendencies. Like me and them who some much transformed the past things.
What we portrayed as beautiful and proper The enemies will reveal to be foolish and useless, repeating the same things differently (without much effort).
Just as we spoke the old words in another manner.[35]

ΠΕΡΙΛΗΨΗ

Το ειδικό βάρος των ούρων σύμφωνα με αρχαίες και μεσαιωνικές ελληνικές πηγές

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Τα σχετικά πρωτότυπα κείμενα του Ιπποκράτους, Γαληνού, Ανωνύμων Ελασσόνων Ιατρών, του Στέφανου, Θεόφιλου, Αέτιου, Ιωάννη Ακτουάριου και Αβικένα μελετήθηκαν με σκοπό να εντοπισθούν αναφορές τους στο ειδικό βάρος των ούρων. Αν και ο όρος δεν χρησιμοποιήθηκε ποτέ, εν τούτοις ο σχολιασμός τους για τη θέση των αδιάλυτων συστατικών των ούρων μέσα στην ουροσκοπική φιάλη είναι απόλυτα ενδεικτικός της υποψίας που είχαν για το θέμα. Η χαμηλή θέση τους (υπόσταση), η μεσαία (εναιώρημα) και η ανωτέρα (νεφέλη) συσχετίζονταν με την ποιότητα του προσαγομένου στους νεφρούς αίματος και με τη λειτουργία των ιδίων των νεφρών. Επειδή η θέση τους εξηρτάτο από τη διαφορά βάρους του υδαρούς και του εμμόρφου στοιχείου των ούρων, έμμεσα δήλωνε το ειδικό βάρος τους.

Λέξεις ευρετηρίου: Βυζαντινοί ιατρικοί συγγραφείς, Ειδική βαρύτητα, Κλασικοί ιατρικοί συγγραφείς, Ουρινόμετρο, Πρωτεϊνουρία

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LABORATORY PROCEDURE
ΕΡΓΑΣΤΗΡΙΑΚΗ ΜΕΘΟΔΟΣ

Urine colour variation in internal diseases according to Enrico Cauchi

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ΑΡΧΕΙΑ ΕΛΛΗΝΙΚΗΣ ΙΑΤΡΙΚΗΣ 2020, 37(Συμπλ 2):104 – 107

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In ancient times, urine was considered an important element for both religious tradition and for diagnostic procedures. Over time, several researchers reported on how urine variation may help in diagnosing different diseases. In 1933, Enrico Cauchi, member of the Medical Council of Malta, collected all comprehensively organised information in his book "Fisiologia e Patologia dell' urina", edited by A. Wasserman, Milano, Italy. Following the suggestions of "Urological Curves" by Augusto Murri, Enrico Cauchi reported all different data at that time about urine colour variation.

Η αλλαγή στο χρώμα των ούρων στις παθολογικές ασθένειες σύμφωνα με τον Enrico Cauchi

Περίληψη στο τέλος του άρθρου

Key words

Augusto Murri
Enrico Cauchi
Tuberculosis
Urine colour variation
Urological curves

1. INTRODUCTION

Uroscopy was systematically used in Ancient Greek times, when philosophers and doctors focused their attention on urine and blood.[1–3] Hippocrates suggested that the colour of urine derived from the mixing of the colours of the four humours: the red of the blood, the white of the phlegm, the dark yellow of yellow bile, the greenish of black bile.[1] Moreover, he suggested human temperament as conditioning urine colour variation: citrine and tenuous in choleric, white and tenuous in phlegmatic, white and dense in melancholic, red and dense in bloody temperament.[1,3]

Over time, several researchers reported on how urine colour variation may help in diagnosing numerous diseases.[2] In 1933, Enrico Cauchi, member of the Medical Council of Malta collected all comprehensively organised information in his book "Fisiologia e Patologia dell' urina", edited by Wasserman, Milano, Italy. He followed the suggestions of Augusto Murri according the so called "Urological Curves".[4]

Augusto Murri always insisted on the urine test evaluation and recommended that doctors use the so-called "Urological Curves" in their practice. He stated that the urine test is important not only for the diagnosis but also for the prognosis of many generalised and local diseases.[4] The most frequent pathologies at the beginning of the twentieth century were tuberculosis, typhus, cancer and helminthiasis.

2. MATERIAL AND METHOD[4]

2.1. Urine colour variation tests for tuberculosis

Moritz and Weisz developed a urine test for diagnosing tuberculosis, using a 5 mL solution of fresh unfermented urine and 15 mL of distilled water. The solution was divided into two equal parts; 3 drops of potash permanganate were added to one part of the solution while the other was used as a control. The test was considered positive if the urine solution was gold or canary yellow or greenish yellow or orange yellow in colour. These colours where associated by some authors with other infectious diseases.[4]

Comas L. and Martinez A. developed a test for tuberculosis using in a 5 mL testing tube of albumin-free urine mixed with a 2% solution of potassium ferrocyanide. To the mixture, boiled ½ mL of 3.3% ammonium chloride

solution was added. The test was considered positive if at the bottom of the tube a blue precipitate appeared while the remaining solution was green: after few hours, another Prussian blue precipitate was formed.[4]

Russo M. developed a urine test for incipient miliary fevers using four drops of methylene blue added to 4–5 mL of albumin-free urine. The test was considered positive when a light green colour appeared.[4]

2.2. Urine colour test variation for typhus

Russo M. developed a urine test for abdominal typhus using a solution of methylene blue mixed with 1% distilled water; subsequently 4–5 drops of this solution were added to 5 mL of urine. The test was considered positive if the urine became intense green, mint green or emerald green. Some authors disagreed with the results of Russo and Wiener test, suggesting that the urine colour variation was not due to chemical reactions but to the reagent used.[4]

Wiener G. mixed 4 mL of urine with 4 mL of ether, adding 2 mL of distilled water, 3 drops of Jenner's liquor and 10 drops of 1% permanganate solution. The test was considered positive if the urine showed an intense green colour. In malaria, this urine colour test turned blue.[4]

Another urine test was developed by Petzetakis M. who used 15 mL of filtered urine added to a 5% iodine alcoholic solution. The test was considered positive if the urine became yellow gold.

Moretti E. showed the same yellow gold colour of the urine treating the urine with lead acetate added to ammonium sulfate.[4]

De Silvestri G. 4 performed a urine test mixing 3 mL of albumin-free urine in a testing tube containing 2 mL iron perchloride and 4–5 drops of pure sulfuric acid. A brown red ring appeared in positive tests.

2.3. Urine colour test variation for cancer

Davis A. mixed 50 mL of albumin-free urine with hydrochloric acid in a glass; after heating it up he added 15 mL of pure sulphuric ether. After 24 hours, the ether was extracted and the solution was placed in a porcelain capsule left in the air. A light yellow or brown-yellow precipitate appeared in positive tests.[4]

Salomon D. and Saxel F.[4] performed a colour variation test using a 100 mL albumin-free urine solution added to 10 mL of hydrochloric acid. This solution was boiled in a Becker container adding 200 mL of boiled water and 10 mL of barium chloride at 10% concentration if the urine specific weight was less than 1,020 while barium chloride if the urine specific weight was greater than 1,020. The Becker container was placed in boiling water for 6 hours and then left to rest for 24 hours. The solution was then filtered and placed in an Erlenmayer flask adding 3 mL of Merck perhydrol and boiled for 15 minutes. The test was considered positive when a brown precipitate of barium sulphate appeared.

2.4. Urine colour test variation for pancreas diseases

Cammidge PJ[4] reported that in pancreas diseases urine showed a so-called Cammidge reaction and recommended removing albumin and sugar from urine before performing the test.

Licini C. developed the urine colour variation according to Cammidge showing controversial results using the following method: Firstly, albumin and sugar were removed from the urine. Then, 20 mL of clear urine were mixed with 1 mL of hydrochloric acid and the solution was boiled in a sand bath for ten minutes. Subsequently, the urine was left to cool down and distilled water was added to bring the solution back to 20 mL. The solution was filtered: 4 g of powdered lead carbonate were added and it was then filtered again; 4 g of tribasic lead acetate were added and it was then filtered again; 2 g of sodium sulphate were added and it was then filtered again. The solution was boiled in a sand bath, filtered and let to cool. A 10 mL solution is taken and 8 mL of distilled water is added, plus 80 mL phenylhydrazine hydrochloride plus g 2 sodium acetate and 1 mL acetic acid at 50% concentration. Finally, the solution is boiled for 10 minutes in a sand bath and then fully filtered. Positive tests showed yellow gold rosettes and small needle-shaped crystals that dissolved in a 33% sulphuric acid solution.

2.5. Urine colour test variation for heart diseases

Ehrlich P. reacted a urine sample with dimethylaminobenzaldehyde in a hydrochloric solution, showing that in heart patients the urine colour test ranged from pink to red. The intensity of the urine colour adding formolus depended on the severity of the cardiac disease. The urine colour variation was considered to define the prognosis of heart diseases: the prognosis was considered favourable when the urine colour returned to normal colour, while in cardiac instability urine colour returned transiently to normal colour. Prognosis was considered serious when the urine did not return to normal.[4]

2.6. Urine colour test variation for peritoneal diseases

Sgampati P. used a two-phase test:[4]

- 8–10 mL of urine were placed in a test tube, adding 3 mL of pure nitric acid. A red yellow ring appeared at the contact point between the urine and nitric acid and after another dark ring appeared.
- This test phase aims to confirm test positivity; to this end, 3 mL of chloroform were added to the solution after 24 hours. The chloroform was first blue and then, if the urine test was positive, it turned ruby.

2.7. Urine colour test variation for flu

Aradas T. used two test tubes. Then 1 g methylene blue was placed dissolved in distilled water and alcohol to reach 100 mL of solution. In one test tube, 5 mL of filtered urine were added to 5 drops of the prepared solution and in another test tube 5 mL of distilled water were added to 5 drops of the same solution. The test was considered positive when the tube with the urine showed a green to bottle green solution colour.[4]

2.8. Urine colour variation test for helminthiasis

Jefinoso B. used a mixture of 10 mL albumin-free urine and a 10 mL solution of mercury nitrate. The test was considered positive for roundworms, tapeworms and pinworms if a grey sediment was observed. This sediment can become dark to black according to disease severity.[4]

2.9. Urine colour test variation for liver diseases

Roch M. suggested the following method: After breakfast in the morning and after taking 0.04 mg of sodium salicylate, the urine was collected between 9–11 am and 10–3 pm. A few drops of 1% iron perchloride solution were added to the urine. A violet cloud appeared when the test was positive.[4]

2.10. Urine colour test variation for kidney diseases

According to Becker H.J. a small amount of urine was mixed with kaolin to make a slurry fluid that was then filtered. The urine became yellow or brownish when the test was positive.[4]

Kronberger's urine test variation for distinction between normal and pathological urine. He mixed 10 mL urine with 1 mL of Lugol's solution, 1 mL of gentian solution (1:200) and 10 mL of absolute alcohol. Normal urine showed a blue-violet colour while pathological urine showed a red colour.[4]

3. CONCLUSIONS

The data reported in Enrico Cauchi's book allow the deduction of epidemiological data on the frequency of common diseases at the beginning of the twentieth century. The most common pathologies in that period were tuberculosis, typhus, cancer and helminthiasis. No efficient laboratory tests were developed in that period and the study of urine colour variation was considered a useful test for diagnosing various internal diseases. The data he reported serve to affirm that a simple urine examination today is very useful and a modern concept[5] considering that it is possible to examine urine using sophisticated technology. For us, the ancient interest in urine examination is akin to going back to the future. Thus the application of current technology, i.e. mass spectrometry, will allow avoiding delays in diagnosis, therapy and diagnosis, at a low cost.

ΠΕΡΙΛΗΨΗ

Η αλλαγή στο χρώμα των ούρων στις παθολογικές ασθένειες σύμφωνα με τον Enrico Cauchi

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Στην αρχαιότητα, τα ούρα θεωρούνταν σημαντικό στοιχείο τόσο για τη θρησκευτική παράδοση όσο και για διαγνωστικές διαδικασίες. Με την πάροδο του χρόνου, πολλοί ερευνητές ανέφεραν πως η αλλαγή των ούρων μπορεί να βοηθήσει στη διάγνωση διαφόρων ασθενειών. Το 1933, ο Enrico Cauchi, μέλος του Ιατρικού Συμβουλίου της Μάλτας, συνέλεξε όλες τις πληροφορίες, διεξοδικά οργανωμένες, στο βιβλίο του "Fisiologia e Patologia dell' urina", που εκδόθηκε από τον A. Wasserman στο Μιλάνο, Ιταλία. Σύμφωνα με τις προτάσεις των «Ουρολογικών Καμπυλών» του

Augusto Murri, ο Enrico Cauchi ανέφερε όλα τα στοιχεία που ήταν γνωστά εκείνη την εποχή σχετικά με την αλλαγή του χρώματος των ούρων.

Λέξεις ευρετηρίου: Αλλαγή χρώματος ούρων, Augusto Murri, Enrico Cauchi, Ουρολογικές καμπύλες, Φυματίωση

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LABORATORY PROCEDURE
ΕΡΓΑΣΤΗΡΙΑΚΗ ΜΕΘΟΔΟΣ

The role of the microscope in renal disease as described in Giulio Bizzozero's handbook of clinical microscopy

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ΑΡΧΕΙΑ ΕΛΛΗΝΙΚΗΣ ΙΑΤΡΙΚΗΣ 2020, 37(Συμπλ 2):108–113

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Giulio Bizzozero (20 March 1846–8 April 1901) was an eminent Italian pathologist, the first microscopist to describe the role of platelets as the third morphological element of the blood. He also made innovative discoveries about the haematopoietic function of the bone marrow, the histological structure of the epidermis, phagocytosis and many other original intuitions. Since the beginning, his career was extremely productive: for his valuable research work, at the age of 26 he was appointed full Professor of General Pathology at the University of Turin, Italy. Here he emphasised the use of microscopy against the outdated vision of old academics and promulgated experimental methods in opposition to the vitalistic philosophy of the time. Bizzozero's revolutionary vision of medicine aimed to allow every scientist to reach new discoveries in their field, which were previously the privilege of an elite, making him a model both as a doctor and as a humanist. The advancement of his studies and the development of the art of microscopy led to the publishing of his masterpiece "Manuale di Microscopia Clinica" (Handbook of Clinical Microscopy) in 1879. In that, he underlined how the microscopic examination of the urine gave physicians of the time indicative criteria of kidney alterations, often essential for diagnosis. The author makes a detailed analysis of the methods of his time, laying the foundations for modern microscopy and the diagnosis of renal diseases. During his career, he was elected president of many medical societies and was an active member of several public health commissions. The contribution of this esteemed scientist was significant both in expanding knowledge within the scientific community and in promoting the public understanding of the benefits of medicine.

Ο ρόλος του μικροσκοπίου στις νεφρικές παθήσεις, όπως περιγράφεται στο εγχειρίδιο κλινικής μικροσκοπίας του Giulio Bizzozero

Περίληψη στο τέλος του άρθρου

Key words

Giulio Bizzozero
Manuale di Microscopia Clinica
Platelets as the third morphological elements
University of Turin
Bizzozero's Biography

1. BIZZOZERO'S BIOGRAPHY

Giulio Bizzozero is considered the father of Italian histology. He was born in Varese, Italy, on 20 March 1846, to a middle-class family. He studied in Milan and Pavia, where, at the age of 16, he enrolled at the Medical Faculty. He graduated at the age of 20, and received the "Mateucci Prize", awarded to students who achieving the highest grade in all courses. He began to carry out histological and histopathological research under the direction of Paolo Mantegazza who, in 1861, founded the Laboratory of Experimental Pathology and was Bizzozero's most influential teacher.[1]

In this period, he engaged in research by conventional microscopy and published his first papers (at the age of 16), and visited scientific institutes abroad, Zurich (Heinrich Frey), Würzburg (Rudolf Albert von Kölliker), Wien (Ernst Wilhelm Brücke) and Berlin (Rudolf Virchow).[2]

In the period immediately after his graduation, Italy was at war with the Austro-Hungarian Empire, and Bizzozero volunteered as an army medical officer.[3] Shortly after, in 1868, he was appointed Supplementary Professor of Histology at the University of Pavia and continued to teach there until the end of 1872, when he was appointed Chair of General Pathology at the University of Turin.[4]

In 1873, he began his teaching and scientific activity at the Laboratory of Anatomy, in some rooms granted by the Dean Joseph Timmermans. With the death of the Dean, the concession was revised and Bizzozero had to set up a Laboratory in his home, on Nice Street, Turin.

In 1876, he obtained some rooms in the former Convent of St. Francis da Paola, where he developed great histopathological experience, making use of the microscope.

In 1878, he became a full Professor of Histology, a

position he kept until his death. Many of Italy's younger pathologists have been his pupils: among them Professor B. Golgi (Pavia), Tizzoni (Bologna), Canalis (Genoa), Foà (Turin), Salvioli (Padua), and Morpurgo (Siena).

Giulio Bizzozero was a member of the most influential Italian and foreign societies of his time. He was one of the most active members of the Superior Council of Public Instruction and the Superior Council of Public Health. For his great service to science and education, he was named a Senator of the Kingdom of Italy by King Humbert I.[5]

He remained active at the University of Turin until his death on 8 April 1901, aged 55 years, caused by pneumonia. On the occasion of his death, Virchow, who enjoyed ties of great mutual respect with Bizzozero, wrote to his family: "la perte de l'homme le plus célèbre dans notre science" ("the loss of the most famous man in our science").

2. GIULIO BIZZOZERO'S MAIN CONTRIBUTIONS TO MEDICINE

Over his lifetime, Bizzozero published nearly 80 papers, on various topics. In 1868, he discovered that red blood cells originate in the bone marrow from nucleated precursor cells and wrote "Sulla funzione ematopoetica del midollo delle ossa. Comunicazione preventiva"[6] (On the haematopoetic function of bone marrow. Prior communication). In his work, he also underlined the importance of haemotransfusion[7] in anaemic patients.

Bizzozero's name is linked with the discovery of platelets but actually he was not the first to identify these elements; instead, he coined the term and was the first to clearly demonstrate their role in promoting thrombosis *in vivo* and blood coagulation *in vitro*.[8] "The existence of a constant blood particle differing from red and white blood cells has been suspected by several authors", states Bizzozero in his introductory historical review of his masterpiece paper.[9] "It is astonishing" –he continues– "that none of the previous investigators made use of the observation of circulating blood in living animals". By his investigations, he reached "the surprising conclusion that indeed morphological elements of a third kind are circulating within the vessels, besides red and white blood corpuscles. The former corresponds to extremely thin platelets".[10]

He also commented that "An investigator who is not prepared in advance to look for other than the known elements will be attracted only by the red and white corpuscles".[11]

Another remarkable discovery attributed to Bizzozero are the desmosomes, intercellular junctions of epithelia and cardiac muscle that can resist mechanical stress due the adoption of a strongly adhesive state.[12] They are also called "connecting bodies", and they have also been named after him as Nodes of Bizzozero.[13]

Bizzozero also provided a detailed description of the phagocytosis process, in the anterior chamber of the eye, in two papers, published in 1871 and 1872 in the Italian medical journal *Gazzetta Medica Italiana – Lombardia*.[14,15]

In 1893, Giulio Bizzozero was also the first to observe and describe spiral organisms in the stomach of animal models,[16] depicting *Helicobacter pylori*.

He gave special attention to the process of cellular differentiation, classifying the tissues concerning their capacity to self-renew during the adult life in labile, stable and permanent tissues.[17]

3. THE "HANDBOOK OF CLINICAL MICROSCOPY"

The advancement of his studies and the development of the art of microscopy led to the publishing of his masterpiece "Manuale di Microscopia Clinica" (Handbook of Clinical Microscopy) in 1879. In that, he underlined how the microscopic examination of the urine gave physicians of the time indicative criteria of kidney alterations, often essential for diagnosis. The author makes a detailed analysis of the methods of his time, laying the foundations for modern microscopy and the diagnosis of renal diseases.

The first chapter of the book is dedicated to the description and use of the microscope.

Bizzozero details the techniques for using the microscope through an accurate list of existing types of machines, making a meticulous analysis of their main characteristics. An interesting detail is the reference to the name and address of the manufacturer, the cost of the microscope depending on the price of gold established during the sale, on the financial conditions of the owner. The following chapters are dedicated to the examination of blood, exudates, pus, skin, mouth contents, vomit, faeces, spit, nasal mucus, eye and annexed parts, secretions of the male and female genitals, breast secretions, pathogenic schizomycetes and urine. Interesting to note that Bizzozero personally designed most of the elements of the urinary sediment (fig. 1).

Bizzozero proposed a classification for pathological urine: (a) Sediment consisting of normal or altered cells (epithelial cells, red blood cells, leukocytes) or made by products collected in the kidneys or in their excretory ducts, (b) sediment consisting of chemical elements precipitated

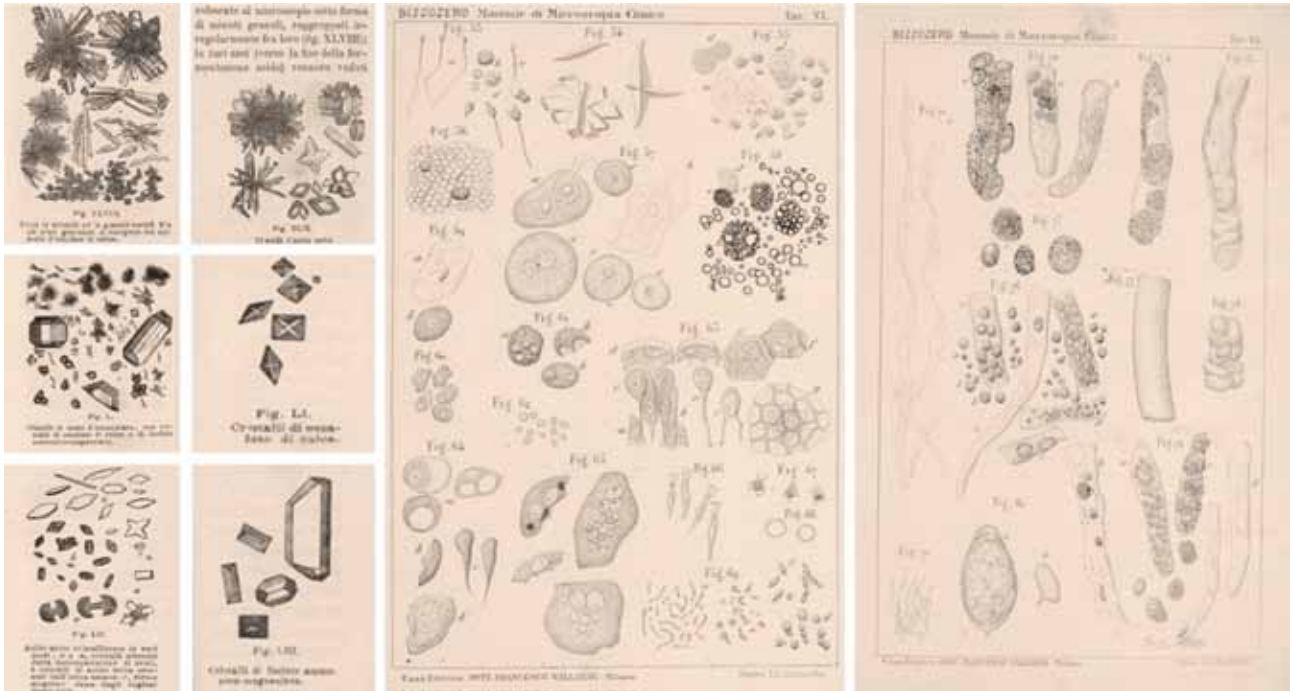

Figure 1. Tables representing different kind of urinary calculi and elements of urinary sediment, 1879 "Handbook of Clinical Microscopy", G. Bizzozero.

in the urine, (c) sediment formed by vegetable or urinary cylinders.

The presence of red blood cells represented a great diagnostic sign in urinary sediment. Bizzozero emphasises that red blood cells *"come from the kidneys when, by means of fibrin or exudation materials, they come together in cylinders that reproduce the shape and diameter of the renal canaliculi".*[18]

Red blood cells, on the other hand, did not have strictly renal origin but could be traced back to the urinary tract when:

- There is a significant presence of epithelia of the lower urinary tract
- The blood in the urine is well represented
- Urine at the beginning of excretion comes out lighter than urine at the end of urination
- Urine takes on a light red colour
- There is presence of clots.

In his treatise, Bizzozero also described the different types of cylinders visible with the microscope.

Urinary cylinders were identified for the first time in 1837 by Dottor Valentin and Dottor Vigla in urine.

The author, following Dottor Carlo Rovida's classification, divides urinary cylinders into three classes: (a) Cylinder hyaline or colourless; (b) cylindroid; (c) yellow or waxy cylinders.

- *Hyaline or colourless cylinder could be: straight, curved, variously folded, with regular margins.*
  The diameter is up to 12 micrometers, reaching up to 40–50. They have been mostly associated with acute nephritis.
- *Cylindroids: they are very thin (5–20) micrometers, often several cylindroids are grouped in a ball-shaped string. They are frequently found in normal urine sediments, although the author finds them abundantly associated with cystitis cases. They have the form of filaments or form of ribbons. They have an irregular outline, a very wavy or tortuous course.*
- *Yellow or waxy cylinders are formed by a slightly yellowish coloured substance, more refracting and with more distinct contours, more massive, harder and less elastic (reason why they get crushed under the coverslip sometimes). They are characterized by regular, smooth, wavy contours. Waxy cylinders are larger than hyaline cylinders, they have a length that varies from a few micromillimeters to two tenths of a millimeter.*

They were often associated with chronic processes and refer to more severe morbid processes. Of particular interest

is Bizzozero's classification concerning the examination of urine in the main kidney and urinary tract diseases:

- *Venous congestion*
- *Acute diffuse inflammation*
- *Chronic diffuse inflammation*
- *Interstitial chronic nephritis*
- *Kidney amyloid degeneration*

Venous congestion presents these urine characteristics: scarce amount, strongly coloured, high specific weight, little albuminous content, few hyaline cylinders, red blood cells, white blood cells.

Acute diffuse inflammation presents poor presence or total absence of urine, intensely coloured, turbid, due to precipitates of urates and red blood cells, high specific weight, white blood cells generally numerous, renal epithelia well preserved or browned by the colouring substance of the blood, cylinders often in large quantities.

Chronic diffuse inflammation presents a small amount of yellowish, turbid urine, a high specific weight, mostly above 1020, acidic with a lot of albumin, white blood cells in large quantities, red blood cells of low quantity, renal epithelia in fair quantities often in fatty degeneration, cylinders usually in large quantities, both hyaline and yellowish cylinders.

Interstitial Chronic Nephritis: more abundant urine than normal due to hypertrophy of the heart (could be less represented due to a decrease in the strength of the heart), light in colour, clear, low specific weight, acidic, little or no albumin. Urinary sediment is usually scarce with generally thin hyaline cylinders.

Kidney Amyloid Degeneration: associated with various forms of chronic nephritis and systemic diseases. The diagnosis in this case is contradictory and a confirmation with systemic symptoms is needed to identify the disease. The presence or absence of cardiac hypertrophy or amyloid degeneration in other organs must be assessed.

This masterpiece of medicine literature (his "scientific testament" according to Matoni[19]) saw, besides five Italian editions (from 1880 to 1901), also translations in German, French, Danish, Spanish, English and even in Russian and Japanese.[20]

Interestingly, probably influenced by the Manual of Frey,[21] it stands out for the autonomy of content development and a strongly clinical and completely original approach for those times.[22,23]

Bizzozero's masterpiece definitely represents a milestone in scientific literature, a witness of the radical evolution of modern medicine and experimental research.

4. CONCLUSIONS

During his career, Bizzozero emphasised the use of microscopy against the obsolete vision of old academics and promulgated experimental methods in opposition to the vitalistic philosophy of the time. Bizzozero underlined the idea of "teamwork" and his strong connection with his close collaborators, saying that in a laboratory "*a mind should give the idea and the direction of work while other minds join together dealing with particular executions*".[24]

Bizzozero's revolutionary vision of medicine aimed to allow every scientist to reach new discoveries in their field, which were previously the privilege of an elite, making him a model both as a doctor as a humanist.[25] In one of his memorable speeches he declared: *"We need to undress science of the cloak of mystery and authority: the professor in the school must not offer a series of dogmas supported by the prestige of his name, he must instead expose science in the real state in which it is found, with its doubts and its unresolved mysteries".*

Benedetto Morpurgo, Bizzozero's successor to the Turin Chair, said about him: *"He entered the difficult environment of a university aged and closed in dogmatic teachings, fearful of any innovation. The admirable instrument of Bizzozero's discoveries, the microscope, appeared to be an infernal weapon, destined to bring down the consecrated dogmas of the cathedratics.*

Bizzozero and the microscope were considered as one entity, as were Galileo and his glasses, dangerous threats to the solemn quiet of classical university teaching".

For the author, the microscope was an instrument of pivotal importance, to the point where it could definitely be claimed that no other scientific instrument of the time could offer such a broad range of characterisation techniques and strategic functions for the progress of medicine. The innovation brought by the use of the microscope represented a real revolution in the methods and approach to science, in which Bizzozero was a real guide and pioneer.

ΠΕΡΙΛΗΨΗ

Ο ρόλος του μικροσκοπίου στις νεφρικές παθήσεις, όπως περιγράφεται στο εγχειρίδιο κλινικής μικροσκοπίας του Giulio Bizzozero

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Ο Giulio Bizzozero (20 Μαρτίου 1846–8 Απριλίου 1901) ήταν ένας διάσημος Ιταλός παθολόγος, ο πρώτος μικροβιολόγος που περιέγραψε το ρόλο των αιμοπεταλίων ως το τρίτο μορφολογικό στοιχείο του αίματος. Έκανε επίσης καινοτόμες ανακαλύψεις σχετικά με την αιματοποιητική λειτουργία του μυελού των οστών, την ιστολογική δομή της επιδερμίδας, τη φαγοκυττάρωση και πολλές άλλες πρωτότυπες διαισθήσεις. Από την αρχή, η καριέρα του ήταν εξαιρετικά παραγωγική: χάρη στο πολύτιμο ερευνητικό του έργο, στην ηλικία των 26 ετών διορίστηκε τακτικός Καθηγητής Γενικής Παθολογίας στο Πανεπιστήμιο του Τορίνο της Ιταλίας. Εκεί, υποστήριξε τη χρήση μικροσκοπίας ενάντια στο ξεπερασμένο όραμα των παλαιών ακαδημαϊκών και υιοθέτησε πειραματικές μεθόδους που έρχονταν σε αντίθεση με τη βιταλιστική φιλοσοφία της εποχής. Το επαναστατικό όραμα του Bizzozero για την ιατρική είχε ως στόχο να επιτρέψει σε κάθε επιστήμονα να φτάσει σε νέες ανακαλύψεις στον τομέα του, οι οποίες ήταν προηγουμένως το προνόμιο μιας ελίτ, καθιστώντας τον πρότυπο τόσο ως ιατρό όσο και ως ανθρωπιστή. Η πρόοδος των σπουδών του και η ανάπτυξη της τέχνης της μικροσκοπίας οδήγησε στη δημοσίευση του αριστουργήματός του "Manuale di Microscopia Clinica" (Εγχειρίδιο Κλινικής Μικροσκοπίας) το 1879. Σε αυτό, υπογράμμισε πώς η μικροσκοπική εξέταση των ούρων παρείχε στους ιατρούς της εποχής ενδεικτικά κριτήρια νεφρικών αλλοιώσεων, που ήταν συχνά απαραίτητα για τη διάγνωση. Ο συγγραφέας κάνει μια λεπτομερή ανάλυση των μεθόδων της εποχής του, θέτοντας τα θεμέλια για τη σύγχρονη μικροσκοπία και τη διάγνωση των νεφρικών νόσων. Κατά τη διάρκεια της σταδιοδρομίας του, εξελέγη πρόεδρος πολλών ιατρικών συλλόγων και ήταν ενεργό μέλος πολλών επιτροπών δημόσιας υγείας. Η συνεισφορά αυτού του αξιότιμου επιστήμονα ήταν σημαντική τόσο στην επέκταση της γνώσης μέσα στην επιστημονική κοινότητα όσο και στην προώθηση της κατανόησης του οφέλους της ιατρικής από το κοινό.

Λέξεις ευρετηρίου: Giulio Bizzozero, Manuale di Microscopia Clinica, Πανεπιστήμιο του Τορίνο, Τα αιμοπετάλια ως το τρίτο έμμορφο στοιχείο

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LABORATORY PROCEDURE
ΕΡΓΑΣΤΗΡΙΑΚΗ ΜΕΘΟΔΟΣ

Erythropoietin, a first intuition of renal secretion by Giustiniano Nicolucci

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ΑΡΧΕΙΑ ΕΛΛΗΝΙΚΗΣ ΙΑΤΡΙΚΗΣ 2020, 37(Συμπλ 2):114–116

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In 1846, the medical journal *"Filatre Sebezio"* featured the paper "Sull'Intima struttura dei reni con alcune considerazioni sulla loro funzioni e malattie" by Giustiniano Nicolucci, a young doctor who had graduated just the previous year from the University of Naples. Nicolucci had already taken part as a major speaker at the "VII Congress of Italian Scientists", held in Naples in 1845. On that occasion as well in previous essays, he showcased his skills by using a microscope, at a time when Neapolitan physicians tended to combine medical observation with notions derived from comparative anatomy and physiology. On page 82 of this publication, Nicolucci refers to comparative anatomy, and in particular to Jacobson's 1821 research "De sistemate venoso peculiari in permultis animalibus observato", which showed that in fish, as well in birds and reptiles, there is a type of renal portal, which helps the lungs oxygenate the blood. On this basis, Nicolucci argued for a respiratory function of the kidneys, but, as he was not able to find Jacobson's renal vein in humans, he assumed that this respiratory function of the kidneys could be accomplished through the formation and multiplication of red blood cells, as was recently observed in the liver of a human embryo by Kölliker. According to Nicolucci, further research was needed to seek respiratory principles in urine. The intuition of the Neapolitan physician, unfortunately, did not receive due attention in subsequent studies: it was only in 1977 that Takaji Miyake was able to extract the erythropoietin molecule from the urine of a patient with aplastic anaemia.

Ερυθροποιητίνη, μια πρώτη διαίσθηση της νεφρικής απέκκρισης από τον Giustiniano Nicolucci

Περίληψη στο τέλος του άρθρου

Key words

Giustiniano Nicolucci
Kölliker A.
Renal secretion of erythropoietin

1. INTRODUCTION

In 1846, the Neapolitan medical journal *"Filatre Sebezio"* featured the paper "Sull'Intima struttura dei reni con alcune considerazioni sulle loro funzioni e malattie", by Giustiniano Nicolucci.[1] Nicolucci, who had graduated the previous year from the University of Naples, had already taken part as a major speaker at the "VII Congress of Italian Scientists", held in Naples in 1845. On that occasion, he effectively compared his observations with a microscope with that of the other present scientists. At that time, it was common among Neapolitan doctors to combine medical observation with notions taken from comparative anatomy and physiology.[8] His studies were supported by his thorough knowledge of the history of Greek and Latin medicine. He had an in-depth knowledge of Galen's works and he had extensively studied the "Tabulae Anatomicae" (1552) and "De renum structura, officio atque administratione" (1564) by Bartolomeo Eustachio, two studies in which blood circulation of urinary organs was clearly displayed for the first time, as well as the research by Morgagni and Malpighi. The individuality of his work lay in his ability to use the microscope; in fact, he could compare the results of his research with those of the most important English, French and German scientists.

On page 82 of the aforementioned publication, he writes:

"In the three inferior classes of vertebrates another task is performed by the kidneys, which are crossed by a particular venous system making the blood they transport lose its venosity, making it acquire the venous character which reaches fully the respiratory organs. Jacobson, discoverer of this venous system together with other physiologists, found that actually the kidneys in those animals assisted the lungs in their respiratory function. We do not have a complete analysis of the urine of birds, reptiles and fish to confirm that respiratory principles exist in this liquid; that is, if the respiratory function of the kidneys is involved in the formation and multiplication of the blood globules, as observed recently by Kölliker, like the liver in embryonic life. Further research is necessary in this regard and we will soon study it further".

2. MATERIAL AND METHOD

The research carried out previously by Jacobson and Kölliker's observations on an embryo liver will be analysed, starting from Nicolucci's considerations.

About Jacobson's identification of a renal portal vein:

"... But the veins of the stomach, spleen, pancreas, intestines, some small accentuated branches, usually form the "portal vein system".[2]

"According to Jacobson's 1821 "De sistemate venoso peculiari in permultis animalibus observato" in fish, as well as in birds and reptiles, there is a kind of renal portal system, formed by several branches, collecting the blood from a portion of the trunk muscles, which converge in a large vein that runs through the vertebral canal above the medulla, and distributes trunks transversely to the kidneys; but since the portion of this vein situated beyond the abdomen communicates through lateral branches with the vena cava, which flows under the spine, one can well believe that it therefore falls within the class of ordinary veins".[3]

"According to my knowledge, the blood bodies of a human embryo have been studied only by E.H. Weber (thesis at the University of Leipzig) and in a 12-week embryo described as flat globulets with a nucleus of 0.0042 microns in size; it is clear that this indication, although perfectly correct, does not fulfil all the conditions that intervene in the life of the embryo. In fact, when I dealt with investigating the blood bodies of mammals randomly stored in a human embryo for three months, I found such remarkable results that I could not help making them known, although I did not have any other opportunities to further study them.

The blood bodies of the above embryo are divided into three groups:

- Coloured and core-provided
- Coloured and without nucleus
- Not coloured.

The coloured bodies with a core can be seen in the portal vein, reaching approximately ¼ of the coloured bodies. In the remaining blood there are between 1/6 and 1/8 and most of them measure 0.004 microns. Only in the blood of the liver they are slightly larger –up to 0.006 microns– and in some smaller amounts up to 0.003 and even below 0.0025 microns. Most of the bodies are flat; a few are deep in the form of globules, a minor part, only in the blood of the liver, round and elliptical. In the same blood, the bodies are also distinguished by their colour, which goes from pale yellow to reddish-yellow and in the darker ones the phenomenon is really evident so that it is not possible to recognise the nucleus without reagents. In the rest of the blood, almost all the bodies with a nucleus behaved like the darker blood bodies of the liver.

Water and acetic acid have similar effects on these bodies as in those of adults, that is, they deprive them of colour more or less rapidly, make them swell to such an extent that the membrane rarely explodes and lets the core out, and even after a rather long application, they do not melt. The cores, with no exception, maintain the membrane and in the case of the flat ones, are found more on the margins.[6]

3. DISCUSSION

Nicolucci does not find in the human kidney the anatomical formation of the so-called "portal vein", found in fish, birds and reptiles: in fact, the circulating blood does not change in appearance and does not acquire the characteristics of oxygenated blood. Surely, however, Comparative Anatomy had affirmed the existence of a respiratory function in this organ. The evolution of the species to mammals suggested that this function had been preserved, no longer as an anatomical apparatus, but through another –perhaps humoral– mechanism, at the base of the formation and multiplication of red blood cells.

Therefore, Nicolucci refers to Weber's research, confirmed by Kölliker, that is, to the evidence of erythropoiesis in the human embryonic liver. The progenitor cells from which the "globules" derive would also be at the base of "neoangiogenesis".

Therefore, the anatomical and perhaps humoral research would only be a different aspect of the same function: in fact Nicolucci states that the analysis of urine carried out on birds, reptiles and fish had not yet highlighted the existence of substances with a respiratory function. In other words, the respiratory function should also have occurred through humoral action, which could not be limited to the multiplication and growth of red blood cells, but should also have affected the formation of new vessels.

4. CONCLUSIONS

Only about 50 years after the hypothesis made by Nicolucci, it was noticed that the bone marrow was capable of producing a greater quantity of red blood cells in subjects who lived in environments lacking oxygen (for example at higher altitudes).

The existence of a hormone able to regulate the production of erythrocytes by the bone marrow was hypothesised in 1906 by Paul Carnot, professor of the Hôtel-Dieu of Paris,

and his assistant Camille Deflandre. The substance was called haemopoietin.

In the 1940s, Finnish researchers,[4,5] Bonsdorff and Jalavisto, continuing their studies on red blood cells, named this substance erythropoietin. A few years later, Kurt Reismann showed that the kidney was the main production site of this substance, but only in 1977 was Takaji Miyake able to extract the molecule from the urine of a patient with aplastic anaemia.[7]

The young Neapolitan doctor could not continue his studies on this interesting theme because of his liberal ideas: the Bourbon police became hostile to him, and exiled him to his homeland. There, he started studies of Anthropology, becoming the first anthropologist in Italy.

ΠΕΡΙΛΗΨΗ

Ερυθροποιητίνη, μια πρώτη διαίσθηση της νεφρικής απέκκρισης από τον Giustiniano Nicolucci

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Το 1846, το ιατρικό περιοδικό *"Filatre Sebezio"* παρουσίασε το άρθρο "Sull'Intima struttura dei reni con alcune considerazioni sulla loro funzioni e malattie" του Giustiniano Nicolucci, ενός νεαρού γιατρού που είχε αποφοιτήσει μόλις το προηγούμενο έτος από το Πανεπιστήμιο της Νάπολης. Ο Nicolucci είχε ήδη συμμετάσχει ως κύριος ομιλητής στο «7ο Συνέδριο Ιταλών Επιστημόνων», που πραγματοποιήθηκε στη Νάπολη το 1845. Με την ευκαιρία αυτή καθώς και σε προηγούμενα δοκίμια, παρουσίασε τις δεξιότητές του χρησιμοποιώντας ένα μικροσκόπιο, σε μια εποχή που οι Ναπολιτάνοι ιατροί τείνουν να συνδυάζουν ιατρική παρατήρηση με έννοιες που προέρχονται από συγκριτική ανατομία και φυσιολογία. Στη σελίδα 82 αυτής της δημοσίευσης, ο Nicolucci αναφέρεται στη συγκριτική ανατομία και ειδικότερα στην έρευνα του Jacobson του 1821 "De sistemate venoso peculiari in permultis animalibus observato", η οποία έδειξε ότι σε ψάρια, καθώς και σε πτηνά και ερπετά, υπάρχει ένας τύπος νεφρικής πύλης, η οποία βοηθά τους πνεύμονες να οξυγονώνουν το αίμα. Σε αυτή τη βάση, ο Nicolucci υποστήριξε την αναπνευστική λειτουργία των νεφρών, αλλά επειδή δεν κατάφερε να βρει την νεφρική φλέβα του Jacobson στους ανθρώπους, υπέθεσε ότι αυτή η αναπνευστική λειτουργία των νεφρών θα μπορούσε να επιτευχθεί μέσω του σχηματισμού και του πολλαπλασιασμού των ερυθρών αιμοσφαιρίων, όπως παρατηρήθηκε πρόσφατα στο ήπαρ ενός ανθρώπινου εμβρύου από τον Kölliker. Σύμφωνα με τον Nicolucci, χρειάζονται περαιτέρω έρευνες για την αναζήτηση αναπνευστικών αρχών στα ούρα. Η διαίσθηση του Ναπολιτάνου ιατρού, δυστυχώς, δεν έλαβε τη δέουσα προσοχή στις μετέπειτα μελέτες: μόλις το 1977 το Takaji Miyake κατάφερε να απομακρύνει το μόριο της ερυθροποιητίνης από τα ούρα ενός ασθενούς με απλαστική αναιμία.

Λέξεις ευρετηρίου: Giustiniano Nicolucci, Kölliker A., Νεφρική απέκκριση ερυθροποιητίνης

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LABORATORY PROCEDURE
ΕΡΓΑΣΤΗΡΙΑΚΗ ΜΕΘΟΔΟΣ

Chloride anion and sodium sensitive hypertension
A historical review

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ΑΡΧΕΙΑ ΕΛΛΗΝΙΚΗΣ ΙΑΤΡΙΚΗΣ 2020, 37(Συμπλ 2):117–124

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Ανιόν χλωρίου
και νατριοευαισθησία
στην υπέρταση:
Μια ιστορική ανασκόπηση

Περίληψη στο τέλος του άρθρου

Arterial hypertension is one of the most devastating diseases in modern societies. As early as 1920, Frederick Allen showed that sodium restriction ameliorates hypertension. After that, in 1929, Robert Berghoff and Angelo Geraci showed in an observational study that administration of high sodium chloride increases blood pressure where as substitution of sodium chloride by an equimolar quantity of sodium bicarbonate has no effect on blood pressure. It was the first clinical study in humans showing that chloride anions may be responsible for the high blood pressure observed with increased salt consumption. During the '70s, it was experimentally proven that chloride anions play a crucial role in intracellular volume regulation and in signalling renin secretion via macula densa cells. In the mid '90s, the discovery of sodium chloride transporter mutations as candidates for Bartter and Gitelman syndromes pointed toward the possibility that chloride anions may play a crucial role in blood pressure regulation. In the beginning of second millennium, the discovery of a new class of protein kinases, named with-no-lysine kinases (WNKs), and shortly thereafter the discovery that two mutations in WNK1 and WNK4 are candidates for an inherited form of familial hypertension with hyperkalemia and acidosis known as pseudohypoaldosteronism type II or Gordon's syndrome raised the question of the possible pathogenic role of sodium-chloride co-transporters in the distal nephron in hypertension. Subsequent research supports that WNKs act as intracellular chloride sensors and regulate the activity of transepithelial sodium-chloride co-transporters in the distal nephron. Moreover, it was experimentally shown that the sodium-independent chloride-bicarbonate exchanger pendrin in the collecting tubule plays a crucial role in transepithelial sodium chloride transport in this nephron segment. In conclusion, after nearly a century of intense research, it has been shown that sodium transcellular transport in distal nephron epithelia is accomplished mainly via chloride co-transport. Furthermore, chloride anions play a crucial role in renin secretion and in cell volume regulation. WNKs are the housekeepers of intracellular chloride concentration. We suggest that it may be time to talk of "chloride-sensitive" and not of "sodium sensitive" hypertension.

Key words

Chloride anion
Pendrin
Sodium sensitive hypertension
With no-lysine-kinases

1. INTRODUCTION

Arterial hypertension is one of the most devastating diseases in modern societies. In the early 1900s, the use of the Riva-Rocci sphygmomanometer in clinical practice showed that hypertension was encountered almost exclusively in the USA and European population, being very rare or absent in the rest of the world, as in Africa, Asia, Oceania, Australia and South America, suggesting that environmental factors and especially dietary habits play a crucial role in the pathogenesis of the disease.

As early as 1920, Frederick Allen[1] showed that sodium restriction ameliorates hypertension. After that, in 1929, Robert Berghoff and Angelo Geraci[2] showed experimentally that high sodium chloride administration leads to increased blood pressure, where substitution by sodium bicarbonate failed to increase blood pressure. It was the first clinical observation that chloride anions may be responsible for the high blood pressure observed with increased salt consumption.

Berghoff's and Geraci's pioneering observation was

neglected for a long time, until the 1970s, when Floyd Kregenow[3] showed experimentally that chloride anions play a crucial role in cell volume regulation under hyperosmotic stress. After that, Theodore Kotchen[4] showed that chloride anions regulate renin secretion by signalling to the macula densa cells.

In the early 1980s, the discovery of Na-K-2Cl co-transporters in the thick ascending limp of Henle's loop and Na-Cl co-transporters in the distal convoluted tubule proved that sodium trans-cellular transport in distal renal tubular epithelia is accomplished via chloride co-transport.[5]

In the beginning of new millennium, it became evident that mutations of the newly-discovered "with-no-lysine" kinases are responsible for the pathogenesis of a familial form of inherited hypertension.[6] After that, it was shown experimentally that these kinases directly affect the function of NCC and NKCC2 and that their activity is modulated by intracellular chloride concentration, because they act as intracellular chloride sensors and are capable of modulating their own activation and deactivation according to intracellular chloride concentrations.[7]

Meanwhile, it was shown experimentally that β-intercalated cells in the collecting tubule can transport sodium and chloride via the coupled action of the sodium-driven chloride bicarbonate exchanger (NDCBE) and the chloride bicarbonate exchanger pendrin, both located on the luminal surface of the cell membrane.[8]

In this review article, we attempt to elucidate the early steps pointing to the importance of the anion, which accompanies sodium and mediates its capacity to increase blood pressure under circumstances of increased salt consumption until the new discoveries, which emphasise the importance of chloride anions in cell volume regulation and sodium transport in the distal nephron.

1.1. The importance of anions in hypertension

The first experimental evidence that chloride anions play a crucial role in increased salt consumption-induced hypertension came in 1929, from a primitive study performed by Berghoff and Geraci.[2] The study comprised 50 patients with various morbidities but without serious complications, seven of them were hypertensive. Patients were administered 6 drams (=10.6 g) of sodium chloride per day for one month. After a one-month washout period, salt was substituted by 6 drams (10.6 g) of sodium bicarbonate per day for another month. Although they did not perform a statistical analysis, they concluded that: (a) *"An excessive intake of sodium chloride (six drams) markedly elevates blood pressure in true nephritics and almost equally so in arteriosclerosis".* (b) *"An excessive intake of sodium chloride even in individuals with a normal and subnormal vascular tension elevates blood pressure".* (c) *"An equal amount of sodium bicarbonate does not cause similar results"*.

Authors performed a meta-analysis on the original data presented by Berghoff and Geraci and compared systolic blood pressure (SBPns) and diastolic blood pressure (DBPns) under normal salt consumption with systolic blood pressure (SBPhs) and diastolic blood pressure (DBPhs) under high salt consumption and we found that increased sodium chloride administration produced a statistically significant increase in systolic blood pressure (t=-2,049, p=0,043), (fig. 1) and a statistically marginally significant increase in diastolic blood pressure (t=-1,973, p=0,051), (fig. 2). When we compared systolic and diastolic blood pressure under normal salt consumption with systolic blood pressure (SBPbcn) and diastolic blood pressure (DBPbcn) after substitution with an equal amount of sodium bicarbonate, we found no statistically significant difference (SBPns vs SBPbcn: t=-0,075, p=0,940 NS and DBPns vs DBPbcn: t=0,359, p=0,719 NS).

After that, we compared systolic and diastolic blood pressure under high salt consumption with systolic and diastolic blood pressure after substitution of sodium chloride with an equal amount of sodium bicarbonate and we found a statistically significant reduction in systolic and diastolic blood pressure (SBPhs vs SBPbcn: t=2,062, p=0,041 and DBPhs vs DBPbcn: t=2,610, p=0,010), (figures 1, 2). These new data confirm Berghoff's and Geraci's original state-

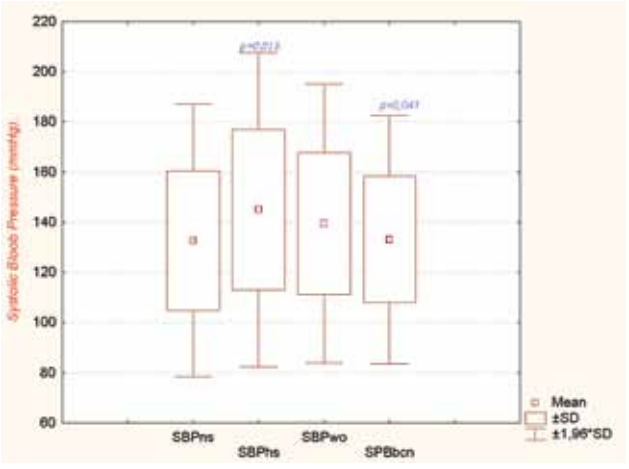

Figure 1. Systolic blood pressure shows a significant increase during high salt consumption (SBPhs) compared to basal conditions (SBPns). No alteration of SBP was observed after substitution of salt with an equal amount of sodium bicarbonate (SBPbcn). Conversely, systolic blood pressure exhibits a significant decrease during sodium bicarbonate administration compared to high salt consumption.

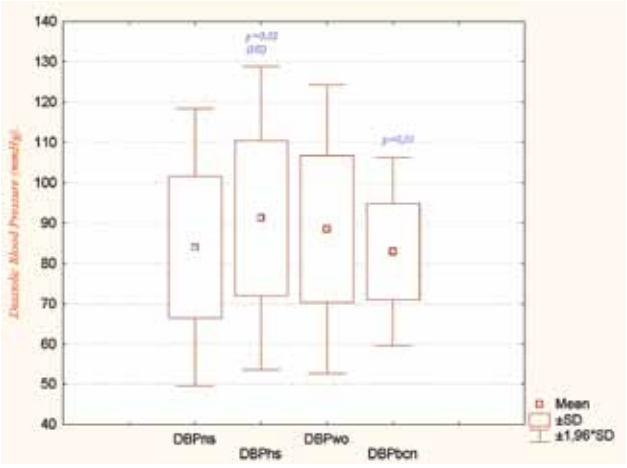

Figure 2. Diastolic blood pressure shows a significant increase during high salt consumption (DBPhs) compared to basal conditions (DBPns). No alteration of DBP was observed after substitution of salt with an equal amount of sodium bicarbonate (DBPbcn). Conversely, diastolic blood pressure exhibits a significant decrease during sodium bicarbonate administration compared to high salt consumption.

ments and concern all patients and not only hypertensives, as usually cited in the literature.

Berghoff's and Geraci's study was long neglected, mainly because investigators perceived the harmful effect of increased salt consumption on blood pressure as an exclusive effect of sodium, overlooking the obligatory presence of chloride.

Many years later, Theodore Kurtz et al in 1987 repeated Berghoff's and Geraci's experiment in five hypertensive patients and showed that administration of sodium chloride (240 mmoL Na^+/day for one week) increased blood pressure whereas administration of sodium citrate (240 mmoL Na^+/day) for one week had no effect. Furthermore, when blood pressure was increased by sodium chloride administration substitution for sodium citrate, in equal amounts, blood pressure returned to normal values.[9]

Studies in experimental animals such as stroke-prone spontaneous hypertensive (SHPSP) rats, Dahl salt-sensitive rats and DOCA-salt hypertensive rats showed that substitution of sodium chloride with equal amounts of sodium coupled with other anions such as bicarbonate, phosphate, aspartate, glutamate and glycinate failed to increase blood pressure.[10]

1.2. Physiological role of chloride anions

Chloride anion (Cl^-) is the most abundant anion in mammals because it counteracts the positive charge of sodium (Na^+) and potassium (K^+) cations, as well as other positively charged macromolecules, to ensure electroneutrality in biological fluids. Its distribution in the extracellular and intracellular space exhibits a wide variation. In mammals, extracellular chloride anion concentrations are about 120 mEq/L while intracellular concentrations vary between approximately 5–10 mEq/L among neuronal cells, reaching up to 40 mEq/L in epithelial cells.[11]

Although its physiological role was long neglected, it plays a crucial role in biological systems such as intracellular vesicle acidification through its transmembrane transport, osmoregulation and cell volume regulation acting as osmolyte, together with other positively charged osmolytes. It can also bind with certain proteins such as cathepsin C and with WNKs, modifying their function. Chloride transport through cell membranes generates electrical currents if its moving is not coupled with an equal amount of cations to ensure electroneutrality (co-transporters) or with exchangers in a 1:1 stoichiometry.[10]

As early as 1956, Otto Hutter and Padsha S. Mahmood showed experimentally that chloride anions contribute to skeletal muscle membrane conductance.[12] One year later, Allan Hodgkin and Paul Horowicz obtained the same results in isolated skeletal muscle fibres.[13] Hodgkin's publication overshadowed Hutter's because it concerned isolated muscle fibre and because of Hodgkin's careful presentation. After that, Hutter continued his experiments and in 1960, together with Denis Noble, showed, in frog skeletal muscle, that chloride anions contribute by about 68% to the muscle's resting membrane conductance and can pass the cell membrane, increasing its intracellular concentration in a very labile way, affected by pH and metallic cations.[12] It was shown experimentally for the first time that chloride anions can pass the cell membrane and stabilise the resting potential of the membrane, contributing in cell effective excitability.

In 1971, Floyd Kregenow[3] showed experimentally that duck erythrocytes, placed in a hyperosmolar environment after initial shrinkage, retain their normal volume via the moving of potassium and chloride ions in intracellular space. Subsequent investigations showed that cellular volume regulation is accomplished by discrete mechanisms in two phases. The first takes place after a few seconds and mainly triggers ions moving across the cell membrane. The second last a few hours and concerns the production and moving of organic osmolytes via the cell membrane.[14] Under hyperosmotic stress, the cell inwardly transfers sodium, potassium and chloride ions by activation of Na^+/H^+ exchangers, Cl^-/$HCO3^-$ exchangers and Na^+:K^+:$2Cl^-$ co-transporters (NKCC1). Under hypo-osmotic stress, the cell

outwardly transfers potassium and chloride ions via activation of K^+:Cl^- co-transporters (KCC) and separate potassium and chloride channels.[14] In hyperosmotic stress, chloride anions predominate amongst ions moving inwards in the cell and play a crucial role in acute cell volume regulation.

In 1978, Theodore Kotchen and colleagues experimentally showed, in sodium-deprived rats, that chloride anions and not sodium signals to macula densa cells and inhibit renin secretion from the juxtaglomerular apparatus.[4] Tianxin Yang and colleagues experimentally showed, in isolated mouse macula densa cell lines, that a low chloride content and not sodium, in perfusate medium, increases cyclooxygenase-2 (COX-2) expression and prostaglandin E2 (PGE2) production.[15] Macula densa cells sensing of chloride content is accomplished via the Na^+:K^+:$2Cl^-$ co-transporter (NKCC2), which is the main sodium chloride co-transporter in the luminal surface of macula densa cells membrane and is chloride-sensitive. COX-2 expression is mediated via phosphorylation of p38 and ERK1/2 kinases.[15] Downstream propagation of the signal is achieved via microsomal fraction of prostaglandin E synthase (mPGES), which increases the synthesis of prostaglandin E2 which in turn via the EP2 and EP4 receptors increase renin release from the juxtaglomerular cells.[16]

1.3. Sodium chloride transport in the distal nephron

In 1981, Rainer Greger and Eberhard Schlatter discovered the sodium potassium 2 chloride co-transporter (NKCC2) in the thick ascending limp (TAL) of Henle's loop in the rabbit kidney.[5] They showed that the presence of potassium ions in the luminal fluid was necessary for the proper function of the transporter and the stoichiometry of ion transport was $1Na^+$:$1K^+$:$2Cl^-$.

A few years later (1987), David Ellison and colleagues discovered the presence of the sodium chloride co-transporter (NCC) in the distal convoluted tubule of rats and they showed that NCC was the main sodium chloride transporter in the early tubule segment. Chloride was necessary for sodium reabsorption because removing chloride from perfusate solutions reduced sodium transport.[17]

In 1993 and 1994, Geraldo Gamba and colleagues cloned and purified the thiazide sensitive sodium chloride co-transporter (NCC) from the urinary bladder of the fish winder flounder and, soon after, the bumetanide sensitive sodium potassium 2 chloride co-transporter (NKCC2) from the rat kidney.[18,19]

A few years later, in 1996, David Simon and colleagues showed that mutations in the *SLC12A3* and *SLC12A1* genes, encoding NCC and NKCC2, respectively, are responsible for Gitelman and Bartter syndromes known as salt loosing tubulopathies and characterised by the presence of hypochloremic-hypokalemic alkalosis, low blood pressure and increased renin and aldosterone levels.[20,21] These discoveries raised the question of the possible role of chloride anions in the regulation of blood pressure because the mutated proteins are mainly chloride transporters and their activity is regulated by chloride concentrations in the luminal fluid.

In 2004, Nikola Jeck and colleagues discovered a mutation in the CLC-Kb chloride channel (T481S) among Ghana's native population, which increases the channel activity almost 7-fold compared to wild type.[22] They subsequently showed that carriers of the mutation exhibited higher plasma sodium concentrations and increased systolic and diastolic blood pressure compared to normal individuals.

In 2010, Leviel and colleagues discovered, in β-intercalated cells of mice cortical collecting ducts, a sodium-dependent chloride bicarbonate exchanger (NDCBE/SLC4A8), which is sensitive to thiazide diuretics, and drives 1 Na^+ and 2 $HCO3^-$ ions inside the cell, exchanging them by 1 Cl^-, ensuring cell membrane electroneutrality.[8] In the same study, they showed that the parallel action of the sodium independent Cl^-/$HCO3^-$ exchanger pendrin (SLC26A4) recycles chloride anions inside the cell and extrudes bicarbonate anions to the tubular lumen. Chloride anions exit the basolateral cell membrane to the extracellular space via the chloride channel CLC-Kb and couples with the sodium cation extruded by the Na^+/K^+-ATPase and contributes significantly to NaCl reabsorption by this nephron segment.

1.4. WNKs and sodium-chloride co-transporters

Our knowledge of the crucial role of chloride anions in regulating blood pressure expanded greatly in the beginning of the new millennium, when Bing-e Xu and colleagues, in 2000, discovered a new protein kinase, from mouse brain extractions, which they termed "with-no-lysine kinase-1" (WNK-1). The name is derived from the fact that the new kinase lacks the characteristic catalytic lysine (Lys-72) in β3-helix of subdomain II, which characterises almost all other known protein kinases. Instead, the new kinase's catalytic lysine (Lys-233) is in an atypical position in β2-helix of subdomain I and it is a serine/threonine kinase.[23] Three more members of this kinase subfamily were subsequently discovered, termed WNK 1, 2, 3 and 4, respectively.

In 2001, Frederic Wilson and colleagues discovered that two mutations in the genes encoding WNK-1 and WNK-4 are responsible for a familial form of hypertension with

hyperkalemia and acidosis.[6] This form of hypertension is transmitted via an autosomal dominant hereditary pattern and it is known as Pseudohypoaldosteronism type II or Gordon's syndrome. Gordon's syndrome is expressed phenotypically as the mirror of Bartter's and Gitelman's syndromes and is manipulated easily with low doses of thiazide diuretics, suggesting that the underlying abnormality represents NCC gain of function in the distal convoluted tubule.

After that, some key questions emerged such as: (a) What are the substrates of WNKs and what is their biological role? (b) How do these kinases regulate the activity of NCC and possibly of other ion transporters in the distal nephron? (c) What is the role of chloride anions in this process?

Subsequent investigations by Alberto Vitari and colleagues, of downstream substrates activation by WNKs, showed that the cellular substrates of WNKs are two serine threonine kinases known as oxidative stress responsive element-1 (OSR-1 kinase) and ste-20 related proline alanine rich kinase (SPAK kinase), which are conserved in many species and distributed in multiple organ systems.[24]

Accumulated evidence suggests that WNKs phosphorylate and activate OSR-1 and SPAK kinases which in turn phosphorylate and activate NCC, NKCC1 and NKCC2 and also phosphorylate and deactivate the KCC co-transporter.[25] Moreover, WNKs inhibit epithelial sodium channel (ENaC) via inactivation of Sgk1 and also inhibit the renal outer medullary potassium channel (ROMK) by promoting clathrin mediated endocytosis (fig. 3). Thus, the coordinated cellular action of WNKs and their substrates points toward increasing the intracellular chloride anion concentration in an attempt to conserve intracellular volume.

Bing-e Xu and colleagues also showed that the WNK-1 molecule has the capacity of autophosphorylation of certain serine residues such as Ser-382 and Ser-378. Phosphorylation of Ser-382 increases enzyme activity by 100% whereas Ser-378 phosphorylation increases enzyme activity by only 50%. Thus, these two serine residues and especially Ser-382 act as the main modulators of enzyme activity.[26]

Alexander Piala and colleagues[7] showed that the WNK1 molecule contains in its kinase domain a specialised structure known as DLG motif, which can interact with a

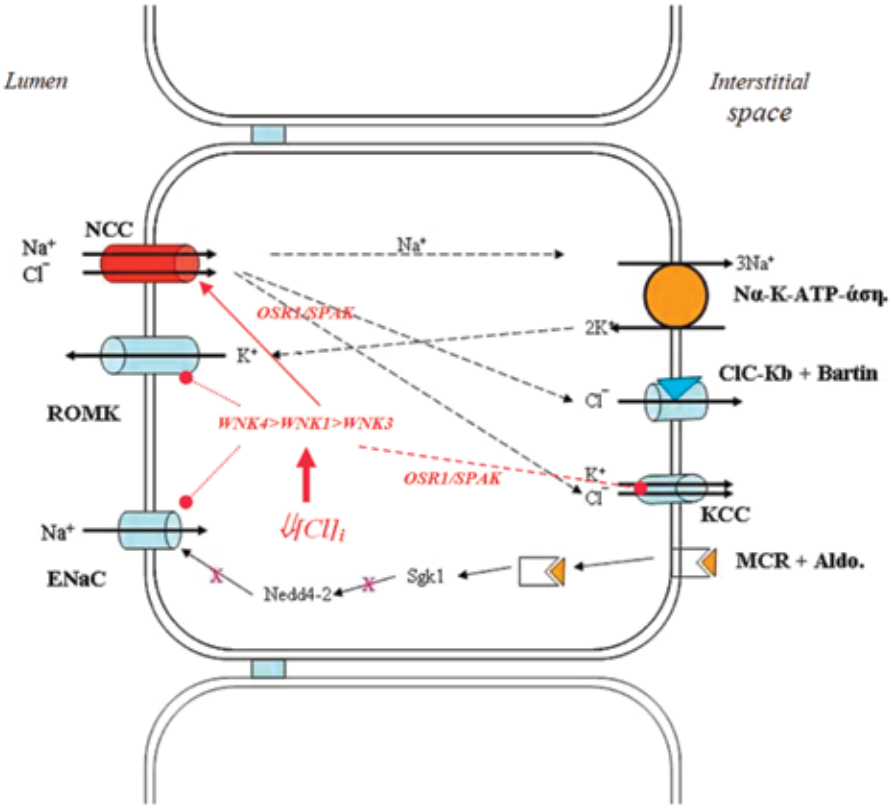

Figure 3. Schematic representation of a distal convoluted tubule epithelial cell. Note that decrease in intracellular chloride concentration leads to WNK activation in a sensitivity manner WNK4>WNK1>WNK3. Downstream activation of OSR1/SPAK kinases leads to phosphorylation and activation of NCC and phosphorylation and inactivation of KCC. WNKs also inhibit the function of ENaC and ROMK via different mechanisms.

chloride anion by making hydrophobic chloride hydrogen bonds between chloride and certain amino acid residues such as Phe-283, Leu-299, Leu-369 and Leu-371. The trapping of chloride anions in the DLG motif produces conformational changes in the WNK1 molecule, which inhibit Ser-382 phosphorylation and hence induce kinase inactivation. These findings suggest that WNK1 acts as an intracellular chloride sensor and modulate its own activation and deactivation according to intracellular chloride concentration changes.

In parallel to the above work, in 2010, Leviel and colleagues showed, on the luminal surface of intercalated mice cells, the presence of a sodium-dependent chloride bicarbonate exchanger (NDCBE), which promotes the electroneutral exchange of 1 intracellular chloride anion with 1 sodium cation and 2 bicarbonate anions from the luminal fluid.[8] NDCBE is sensitive to thiazide diuretics. The exchanger operates in parallel with the sodium-independent chloride/bicarbonate exchanger pendrin, which is also located on the luminal surface of intercalated cells, and drives chloride anions inside the cell by exchanging each with one bicarbonate anion. Chloride anions exit to the extracellular space via the chloride channel CLC-Kb, located on the basolateral cell membrane. In parallel, sodium is driven to the extracellular space via NaK-ATP-ase. The net result of the coupled function of NDCBE/pendrin is the absorption of sodium chloride, in this nephron segment, resulting in increases in extracellular volume and blood pressure.

They further produced a line of transgenic mice with human pendrin gene (*TgB1-hPDS*) overexpression in intercalated cells of the collecting duct and showed experimentally that transgenic mice exhibited increased chloride absorption with a concomitant increase of sodium absorption via the epithelial sodium channel (ENaC) and NDCBE.[27] When animals were fed with an increased sodium chloride diet, they developed hypertension but when an equal amount of sodium bicarbonate was administered, their blood pressure was not altered significantly. These findings indicate that pendrin overexpression in intercalated cells produces a form of chloride-sensitive hypertension.

2. CONCLUSIONS

After almost one century of vigorous research efforts we now know that although sodium is the principal extracellular cation determining extracellular volume and hence blood pressure control, its reabsorption by the kidney and movement to the extracellular space is principally dependent on chloride anion. WNKs are the housekeepers of intracellular chloride concentration, striving to preserve intracellular volume. Pendrin plays a crucial role in sodium chloride reabsorption in the distal nephron. Given this, it may be time to talk of "chloride-sensitive" and not of "sodium-sensitive" hypertension.

ΠΕΡΙΛΗΨΗ

Ανιόν χλωρίου και νατριοευαισθησία στην υπέρταση: Μια ιστορική ανασκόπηση

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Η αρτηριακή υπέρταση είναι μία από τις πλέον καταστροφικές ασθένειες των σύγχρονων κοινωνιών. Ήδη από το 1920 ο Frederick Allen έδειξε ότι ο περιορισμός της πρόσληψης νατρίου βελτιώνει την υπέρταση. Στη συνέχεια, το 1929, οι Robert Berghoff και Angelo Geraci δημοσίευσαν μία κλινική μελέτη στην οποία έδειξαν ότι η χορήγηση αυξημένης ποσότητας χλωριούχου νατρίου σε 50 ασθενείς οδηγούσε σε αύξηση της αρτηριακής πίεσης ενώ η ίδια ποσότητα διττανθρακικού νατρίου δεν είχε καμία επίδραση στην πίεση. Αυτή ήταν η πρώτη κλινική μελέτη σε ανθρώπους η οποία έδειξε ότι πιθανώς η αύξηση της αρτηριακής πίεσης που παρατηρείται σε καταστάσεις αυξημένης πρόσληψης αλατιού οφείλεται στο ανιόν χλωρίου και όχι στο νάτριο. Στην δεκαετία του '70 διαπιστώθηκε πειραματικά ότι το ανιόν χλωρίου έχει ουσιαστικό ρόλο στη ρύθμιση του ενδοκυτταρίου όγκου και στη σηματοδότηση έκκρισης ρενίνης μέσω των κυττάρων της πυκνής θηλής. Στα μέσα της δεκαετίας του '90 η ανακάλυψη ότι μεταλλάξεις των γονιδίων που εφορεύουν τη σύνθεση των συνμεταφορέων νατρίου-χλωρίου, στο παχύ ανιόν σκέλος της αγκύλης του Henle και στο άπω εσπειραμένο νεφρικό σωληνάριο, ευθύνονται για την εμφάνιση των συνδρόμων Bartter και Gitelman, αντίστοιχα, δημιούργησε βάσιμες υπόνοιες ότι πιθανώς το ανιόν χλωρίου παίζει πρωτεύοντα ρόλο στην ρύθμιση της

αρτηριακής πίεσης. Στην χαραυγή της νέας χιλιετίας ανακαλύφθηκε μια νέα ομάδα πρωτεϊνικών κινασών στις οποίες δόθηκε η ονομασία "With no-lysine-kinases" (WNKs) εξ αιτίας της άτυπης θέσης της καταλυτικής λυσίνης στο μόριό τους. Ένα χρόνο μετά ανακαλύφθηκε ότι μεταλλάξεις των γονιδίων των WNK1 και WNK4 ευθύνονται για την εμφάνιση μιας μορφής οικογενούς υπέρτασης που συνοδεύεται από υπερκαλιαιμία και οξέωση γνωστής και ως ψευδής υποαλδοστερονισμός τύπου ΙΙ ή σύνδρομο Gordon. Οι ως άνω ανακαλύψεις έθεσαν επί τάπητος το ερώτημα για τον πιθανό παθογενετικό ρόλο των συνμεταφορέων νατρίου-χλωρίου στον άπω νεφρώνα στην υπέρταση. Η έρευνα που ακολούθησε έδειξε ότι οι WNK κινάσες λειτουργούν ως ενδοκυττάριοι αισθητήρες χλωρίου και ρυθμίζουν αντίστοιχα την δραστηριότητα των συνμεταφορέων νατρίου-χλωρίου στον άπω νεφρώνα. Επί πλέον αποδείχθηκε ότι ο ανταλλάκτης χλωρίου/διττανθρακικών, γνωστός ως Πεντρίνη (pendrin), που εκφράζεται στα β-εμβόλιμα κύτταρα του αθροιστικού σωληναρίου, παίζει σημαντικό ρόλο στην επαναρρόφηση χλωριούχου νατρίου από το συγκεκριμένο τμήμα του νεφρώνα. Συμπερασματικά μετά από σχεδόν έναν αιώνα επισταμένης έρευνας καταδείχθηκε ότι η διακυτταρική μεταφορά νατρίου στον άπω νεφρώνα επιτελείται κυρίως μέσω συμμεταφοράς με χλώριο. Το ανιόν χλωρίου παίζει πρωτεύοντα ρόλο στην έκκριση ρενίνης και την ρύθμιση του ενδοκυτταρίου όγκου. Οι WNK κινάσες παίζουν το ρόλο ρυθμιστή της ενδοκυττάριας συγκέντρωσης χλωρίου και μέσω αυτού του ενδοκυταρίου όγκου. Μετά από αυτά ίσως είναι καιρός να μιλάμε για «χλωριοευαίσθητη» και όχι «νατριοευαίσθητη» υπέρταση.

Λέξεις ευρετηρίου: Ανιόν χλωρίου, Νατριοευαισθησία στην υπέρταση, Πεντρίνη, With no-lysine-kinases

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The hard way from bench to bedside
History lessons from the pathogenesis of idiopathic membranous nephropathy (MN)

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Membranous nephropathy (MN) is one of the most common causes of adult nephrotic syndrome. Histopathology involves typical subepithelial immuncomplexes, with an obvious pathogenetic role. Today, the study of pathogenesis, which began in 1959, has proven that MN is an organ-specific autoimmune disease. Our aim was to follow and draw some historical lessons from this 60-year long course of studies on MN. Heymann nephritis (HN; 1959) is the classical animal model, in which the pathogenetic role of immuncomplexes in MN was first established. HN is induced by injection in rats of tubules brush border (BB) antigens (active HN) or the corresponding antibodies (anti-BB; passive HN). In 1978, lesions of HN forming ex vivo after anti-BB injection in an isolated perfused rat kidney model, i.e. in the absence of circulating BB antigens, proved that immune-complex formation occurs in situ. In 1982, megalin was identified as the epithelial auto-antigen in HN. However, as megalin could not be detected in human podocytes, pathogenesis of human MN still remained unresolved. In 2002, neutral endopeptidase was identified as the podocyte antigen in cases of antenatal allo-immune human MN, clearly implicating the pathogenetic role of podocyte membrane proteins and in situ immune-complex formation. In the next years, phospholipase A2-receptor and Thrombospondin type-1 domain containing 7A were identified as organ-specific auto-antigens associated with MN. The maxim "sciencia facit altus" could precisely describe the evolution of 60 years of research on the pathogenesis of MN, which was decisively promoted with the breakthroughs made in the last 20 years. This pattern may change as we reach the exciting new scientific era.

Ο δύσκολος δρόμος από τον πάγκο του εργαστηρίου στην κλίνη του ασθενούς. Ιστορικά μαθήματα από τον παθογενετικό μηχανισμό της ιδιοπαθούς μεμβρανώδους σπειραματονεφρίτιδας

Περίληψη στο τέλος του άρθρου

Key words

Heymann nephritis
History of medical research procedures
Megalin
Membranous nephropathy

1. INTRODUCTION

Membranous Nephropathy (MN) is one of the most common causes of adult nephrotic syndrome.[1] It was first described and defined clinically and histopathologically in 1959.[2] Its histopathology involves typical sub-epithelial immune complex deposits and gradual thickening of the basement membrane. These immune complexes activate C5b-9, the complement membrane attack complex, which is the major mediator of proteinuria.

The majority of cases with MN (about 80%) are idiopathic and 20% are associated with autoimmune disease, infection, malignancy or drugs. The clinical course of idiopathic MN is varying and 30% of cases have a spontaneous remission of nephrotic syndrome, while 30% show a progression towards end-stage renal disease within 5–15 years from diagnosis.[3]

Research on the pathogenesis of MN began from the first clinicopathological description[2] and the development of the experimental animal model of Heymann Nepritis (HN) in 1959.[4] From this beginning, the research –still ongoing– formulated three possible mechanisms for the formation of the sup-epithelial immune complexes (fig. 1).

- Preformed circulating immune complexes are entrapped in the sup-epithelial basement membrane
- Circulating pathogenic antigens are planted in the sup-epithelial space, where they bind with autoantibodies to form immune complexes *in situ*

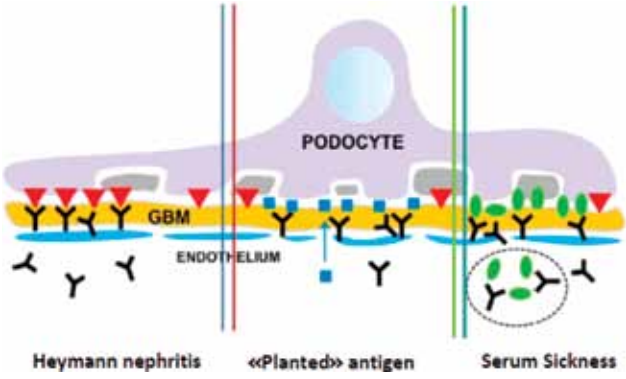

Figure 1. The three possible mechanisms of the sup-epithelial immune complex formation in membranous nephropathy *(see text for details)*.

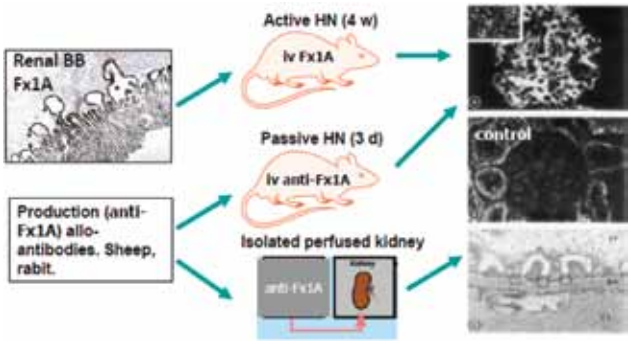

Figure 2. Active Heymann Nephritis (HN), 3–4 weeks after immunisation of Lewis rats by renal brush border (BB) antigen (Fx1A). Passive HN 3 days after injection in Lewis rats of (sheep or rabit) antibodies against rat renal BB antigen (anti-Fx1A). Formation of sup-epithelial immune deposits in an isolated perfused rat kidney after addition in the perfusate of antibodies against rat renal BB (anti-Fx1A).

- Autoantibodies bind to pathogenic antigens inert to the podocyte cell membrane with subsequent in situ sup-epithelial immune complex formation.

Today, research has proven that MN is an organ-specific autoimmune disease.[1] The aim of the present study was to draw some historical lessons from this 60-year long course of studies on MN.

2. HEYMANN NEPHRITIS

Heymann nephritis (HN; 1959) is the classical animal model of MN, in which the pathogenetic role of immune complexes was first established.[4] In the initial experiments by Heymann, a paediatrician from Cleveland (OH, USA), nephritis was induced by immunisation of Lewis rats by whole kidney extracts. From the crude kidney extract only the fractions from the tubules brush border (BB, Fx1A) induced HN (active HN). In addition, passive immunisation with injection of Lewis rats with the corresponding antibodies (anti-BB; anti-Fx1A) induced passive HN. Because HN was not induced by glomerular but rather by tubular BB extracts, the model of active HN indicated that the deposits came from circulating immune complexes. However, the model of passive HN in rats argued against this scenario and supported the possible pathogenetic role of antigens inert to the podocyte's membrane (fig. 1).[5]

This question was answered with certainty only 20 years later (in 1978), when two groups independently showed in an isolated perfused rat kidney model, that HN lesions form *ex vivo* after anti-BB (Anti-Fx1A) injection (fig. 2). The formation of sup-epithelial immune complexes in the absence of circulating BB antigens finally proved that immune-complex formation in HN occurs *in situ*.[6,7] For this reason, research efforts intensified to assess the auto-antigen responsible for HN in rat podocytes.

These efforts finally bore results in 1982. Megalin was identified as the epithelial auto-antigen in HN. These findings, 33 years after Heymann's first description, allowed a significant clarification in the pathogenesis of Heymann nephritis.[8,9] Furthermore, it seemed absolutely justified to hypothesise that human membranous nephropathy would follow a similar pathogenetic pattern with HN, also involving megalin.[9] However, really unexpectedly megalin could not be detected in human podocytes.[1,5]

3. ANTIGENS IN MEMBRANOUS NEPHROPATHY

Megalin is localised in tubular epithelial cells but not in human podocytes.[5] For this reason, the pathogenesis of human MN still remained unclear. For many years, all efforts to assess an auto-antigen in human podocytes with a role in human MN similar to the role of megalin in HN were unsuccessful.[5] This failure was most probably due to the reduced sensitivity of the applied methodology, especially of mass spectrometry, and the use of cultured podocytes as the main source of antigens.

In 2002, neutral endopeptidase was identified as the podocyte antigen in cases of antenatal allo-immune human MN,[10] clearly implicating the pathogenetic role of podocyte membrane proteins and in situ immune-complex formation. This impressive proof that the formation of immune complexes in MN occurs in situ led to the intensification of all research efforts to assess the auto-antigen responsible for MN on human podocytes.

Finally, in 2009 and 2014, two human podocyte proteins were identified as pathogenetic antigens of idiopathic MN. Specifically, phospholipase A2-receptor (PLA2R) and thrombospondin type-1 domain containing 7A (THSD7A) were identified as organ-specific auto-antigens associated with MN.[11,12] A long-standing problem was solved.

The methodological approach was similar to the studies on HN 25 years earlier. It was also based on microdissection of human glomeruli, proteomic technology and mass spectrometry. However, the technological precision of the implemented methods was better in these recent studies and represented a central contributing factor for success. However, the main reason for this success is that non-reducing conditions were applied during the detection procedure. This is based on a simple idea, namely that under non-reducing conditions the disulfide bonds remain intact and protein conformation does not change. Indeed, the antibody reactive epitopes of both antigens involved in idiopathic MN were reduction-sensitive (i.e. conformation-dependent epitopes) and the serum samples from patients with MN did not recognise the antigens under reducing conditions.

4. CONCLUSIONS

Research on the pathogenesis of MN began in 1959 with the description of HN the experimental animal model for MN. Thereafter, the first step forward was to prove the in situ formation of immune complexes in HN. This was achieved by an ex vivo model, applied simultaneously by two scientific groups (1978). The second decisive step was to show that the same principle also applies in human idiopathic MN. Progress came from a rare case of neonatal MN analysed with scrutiny by a specialised group in 2002. The final step was then to identify the specific podocyte auto-antigens in MN, as was already done for HN in 1982. This was achieved thanks to technology and to a very simple idea, namely that the antigen epitopes might be conformation-specific and thus reduction-sensitive (in 2009 and 2014).

The maxim "sciencia facit saltus" could precisely describe the above-described evolution of 60 years of research on the pathogenesis of MN, which was decisively promoted with the breakthroughs made in the last 20 years. This pattern may change, or simply become faster, as we reach the exciting new scientific era.

ΠΕΡΙΛΗΨΗ

Ο δύσκολος δρόμος από τον πάγκο του εργαστηρίου στην κλίνη του ασθενούς. Ιστορικά μαθήματα από τον παθογενετικό μηχανισμό της ιδιοπαθούς μεμβρανώδους σπειραματονεφρίτιδας

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Η μεμβρανώδης νεφροπάθεια (ΜΝ) είναι η πιο συχνή αιτία νεφρωσικού συνδρόμου στους ενήλικες. Η ιστοπαθολογία εμπλέκει τυπικά υποεπιθηλιακά ανοσοσυμπλέγματα, με εμφανή παθογενετικό ρόλο. Σήμερα, η μελέτη της παθογένεσής της, η οποία άρχισε το 1959, έχει αποδείξει ότι η Μεμβρανώδης Νεφροπάθεια αποτελεί μια αυτοάνοση ασθένεια συγκεκριμένων οργάνων. Στόχος μας ήταν να παρακολουθήσουμε και να αντλήσουμε μερικά ιστορικά μαθήματα από την εξηκονταετή πορεία των μελετών πάνω στη Μεμβρανώδη νεφροπάθεια. Η νεφρίτιδα Heymann (ΗΝ, 1959) αποτελεί το κλασικό ζωικό μοντέλο στο οποίο καθιερώθηκε για πρώτη φορά ο παθογενετικός ρόλος των ανοσοσυμπλεγμάτων στη ΜΝ. Η νεφρίτιδα Heymann επάγεται με ένεση σε αρουραίους αντιγόνων (ενεργούς ΗΝ) ψηκτροειδούς παρυφής (ΒΒ) ή των αντίστοιχων αντισωμάτων (αντιγόνα ψηκτροειδούς παρυφής, παθητική νεφρίτιδα Heymann). Το 1978, οι αλλοιώσεις σχηματισμών ex νίνο της νεφρίτιδας Heymann μετά από ένεση αντιγόνων ψηκτροειδούς παρυφής σε ένα απομονωμένο μοντέλο εμποτισμένου νεφρού αρουραίου, δηλ. απουσία κυκλοφορούντων αντιγόνων ψηκτροειδούς παρυφής, απέδειξαν ότι ο σχηματισμός ανοσοσυμπλόκου προκύπτει *in situ*. Το 1982, η μεγαλίνη (megalin) αναγνωρίστηκε ως το επιθηλιακό αυτοαντιγόνο στη νεφρίτιδα Heymann. Ωστόσο, καθώς δεν είναι δυνατή η ανίχνευση της μεγαλίνης στα ανθρώπινα ποδοκύτταρα, η παθογένεση της ΜΝ στον άνθρωπο παρέμενε ανεξήγητη. Το 2002, η ουδέτερη ενδοπεπτιδάση αναγνωρίστηκε ως το αντιγόνο ποδοκυττάρων σε περιπτώσεις προγεννητικής αλλοάνωσης ανθρώπινης ΜΝ, που συνεπάγεται σαφώς τον παθογενετικό ρόλο των πρωτεϊνών

της μεμβράνης ποδοκυττάρων και τον *in situ* σχηματισμό ανοσοσυμπλόκου. Τα επόμενα έτη, ο υποδοχέας Α2 φωσφολιπάσης και η θρομβοσπονδίνη τύπου-1 που περιέχει 7Α ταυτοποιήθηκαν ως αυτοαντιγόνα συγκεκριμένων οργάνων που σχετίζονται με τη ΜΝ. Το αξίωμα *«η επιστήμη κάνει άλματα»* θα μπορούσε να περιγράψει με ακρίβεια την εξέλιξη της εξηκονταετούς έρευνας πάνω στην παθογένεση της ΜΝ, η οποία προχώρησε αποφασιστικά με τις ανακαλύψεις που έγιναν τα τελευταία 20 χρόνια. Αυτό το μοτίβο ενδέχεται να αλλάξει καθώς φτάνουμε στη συναρπαστική νέα επιστημονική εποχή.

Λέξεις ευρετηρίου: Ιστορία της ιατρικής έρευνας, Μεγαλίνη, Μεμβρανώδης νεφροπάθεια, Νεφρίτις Heymann

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ΒΟΤΑΝΟΛΟΓΙΚΗ ΘΕΡΑΠΕΙΑ

Nephrology in an Alexandrian manuscript of late antiquity

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ΑΡΧΕΙΑ ΕΛΛΗΝΙΚΗΣ ΙΑΤΡΙΚΗΣ 2020, 37(Συμπλ 2):129–138

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Οι νεφρολογικές παθήσεις σε ένα αλεξανδρινό κείμενο της ύστερης αρχαιότητας

Περίληψη στο τέλος του άρθρου

A medical manuscript with the title *Dynameron* is kept in the Marciana National Library of Venice (Cod. gr. Z. 295) and originates from a text initially written in Greek by a physician named Aelius Promotus, who lived and worked in Alexandria (1st to 2nd century AD). This manuscript should not be confused with the enormous *Mega Dynameron* of Nicolaos Myrepsos, with 2667 recipes, which was written in the 13th century. *Dynameron* of Aelius Promotus contains 130 chapters dealing with different diseases and their treatment, described in 870 recipes. In the cited 41 recipes related to ailments of the kidneys and the urinary bladder, are included almost 80 different herbs, 6 ingredients of animal origin, and also 1 mineral. The large number of ingredients used in each recipe implies that Aelius Promotus was a follower of the so called "Empiric school" of medicine, although in his work are easily recognizable also influences from other theoretical sects. Many of the herbal ingredients proposed by the author are known for their diuretic, spasmolytic, analgesic and antiseptic properties. Hence, they are suitable for treating nephrolithiasis, strangury, dysuria, hematuria, as well as inflammations of the kidneys and the urinary bladder. Some of the recipes refer to ingredients that cannot be granted any apparent therapeutic reasoning. Additionally, some treatments seem more like superstitious rituals. However, when *Dynameron* is evaluated as a whole, the conclusion is that Aelius Promotus was a competent practicing physician with great experience, typical of the famous medical tradition of Alexandria during the late Roman era. There is evidence that *Dynameron* was highly estimated and was copied several times thereafter, in order to serve as a therapeutic manual for the common ailments a physician might encounter in his everyday practice.

Key words

Aelius Promotus
Alexandria
Dynameron
Nephrology
Urolithiasis

1. INTRODUCTION

In Hellenistic and Roman Alexandria, there was a remarkable progress in medicine and surgery, partly due to the pre-existing local healing practices and the anatomical knowledge gathered along time as a result of the embalmment of the dead.[1,2] Many archaeological findings show the existence of a variety of elaborate surgical instruments, made mainly of bronze.[3]

A physician who lived and worked in Alexandria is Aelius Promotus (second half of the 1st and first half of the 2nd century AD), who wrote a large treatise with the title *Dynameron,*[4] containing detailed recipes for the treatment of numerous diseases. A copy of this work, made in Sicily in the 15th century, is currently kept in the Marciana National Library of Venice (Cod. gr. Z. 295).[5] This manuscript has been made upon order of Basilios Bessarion (1403–1472), who at that time acted as a Cardinal of the Catholic Church in Rome.[6]

The present article describes and discusses for the first time the parts of *Dynameron* referring to remedies and diseases related to the kidneys and the urinary bladder.

2. THE AUTHOR AND THE MANUSCRIPT

Little is known about Aelius Promotus and his life. The manuscript has the title *Dynameron by Aelius Promotus of Alexandria*, indicating that he lived in Alexandria and may have been also born in this city. Based on chronological clues, one can conclude that Aelius Promotus practiced medicine in the first half of the second century AD. In *Dynameron*, he acknowledges three other physicians, as his sources: Soranus (recipe 6, Chapter 3), Menemachus (recipe 1, Chapter 19) and Hermogenes (recipe 4, Chapter

63). At least Soranus of Ephessus, had lived and worked in Alexandria during the turn of the first to the second century.[7] The author mentions that one recipe for the treatment of respiratory diseases had been used by the troops of Emperor Trajan (recipe 8 in Chapter 35). We know that Trajan (Marcus Ulpius Traianus) died the year 117 AD, while still in charge of a military expedition against Parthians in northern Mesopotamia.[8,9] So, at least this piece of information must have been added to the text after the year 117 AD. On the other hand, Galen, in his book on *Synthetic remedies*, describes a collyrium for trachoma referring to it as a "recipe of Aelius".[10] Indeed, in *Dynameron* there are several ophthalmological preparations with a composition similar to the one described by Galen. Knowing that Galen had lived for a while in Alexandria, he was very likely to have known the work of Aelius Promotus. These associations suggest that his reference to "Aelius" concerns indeed Aelius Promotus of Alexandria. Therefore, *Dynameron* should have been written before 160 AD, when it is estimated that Galen started writing his own books.

Aelius has used the Greek language of late antiquity, known as "Biblical Greek" or "Koine Helliniki", the *lingua franca* of much of the Mediterranean region and the Middle East, following the expedition of Alexander the Great.[11] The word *Dynameron* is relevant to the word *dynameis* (actions of medicinal products), where also the modern term *Pharmacodynamics* originates from.

Dynameron, has the form of a "vade mecum", a practical manual of therapeutics, with 870 different recipes for the treatment of 130 pathological contitions.

3. RECIPES IN DYNAMERON RELATED WITH NEPHROLOGY

Aelius Promotus describes in *Dynameron* 36 different recipes of nephrological interest, which are allocated in the following 4 chapters: Chapter 15: "Patients with kidney diseases". Chapter 16: "Urolithiasis and diuretics". Chapter 17: "Diuretics". Chapter 18: "Ailments of the bladder and urination of blood".

The recipes of each chapter are presented with ascending enumeration. A standard recipe includes: (a) The diseases for which it is indicated; (b) all required ingredients and excipients, with their respective weight or volume units; (c) instructions for the proper mixing and preparing the ingredients; and (d) dosage and also directions for administration. For reasons of simplicity, in the recipes cited here only the names of the ingredients are mentioned, without the respective weight and volume units. All ingredients used in these recipes are presented in table 1, with comments on their identity, as well as a short description on their therapeutic use in antiquity, whenever possible.

3.1. Chapter 15. Patients with kidney diseases (Πρός νεφριτικούς)

3.1.1. Patients with kidney diseases, suffering from empyemas, gastric ailments, and recent or chronic catarrh.

Ladies' seal, Crocus, Torchwood, Myrrh, Spikenard, Dog rose, Storax, Camel's hay, Frankincense, Costmary, Apple, Raisin, Wild carrot, Honey, Sweet wine. Give with honey diluted with water, or with sweet wine, a quantity equal to an Aegyptian bean or to a haze lnut.

3.1.2. Patients with kidney diseases and difficulty in micturition (strangury).

Costmary, Parseley, Black pepper, Sweet wine. Smash and dilute in sweet wine and give the half with a probe.

3.1.3. Kidney diseases.

Wild carrot, Anise, Cucumber, Celery, Alexandrian senna, Bay laurel, Giant fennel, Alpine valerian, Water. Dilute with water and make lozenges having the size of the seed of lupin. Give with empty stomach, at bedtime, with up to three cups of water.

3.2. Chapter 16. Patients with urolithiasis and diuretics (Πρός λιθιῶντας καί διουρητικά)

3.2.1. Patients with urolithiasis, from my own experience.

Bay laurel, Black pepper. Give a large spoonful, with honey diluted in warm water.

3.2.2. Diuretic, and for patients with urolithiasis, or difficulty in micturition.

Henbane, Hemlock, Opium poppy, Celery, Cucumber, Pine cones, Mallow, Almonds, Walnuts. Give for improvement.

3.2.3. Diuretic, and for patients with urolithiasis.

Myrrh, Wild carrot, Crocus, Bitter almonds. Give to drink with water.

3.2.4. Suitable for dissolving kidney stones.

Bay laurel. Boil pieces of bark of bay laurel in water, until it evaporates to one third. Give to drink. Very effective.

3.2.5. Patients urinating blood.

Myrrh, Cabbage, Opium poppy. Dilute with sweet wine. Make pills and give the patient.

3.2.6. Breaking down the stones of the kidney and expelling them.

Baldmoney, Purple betony, Parseley, Rock foil, Gromwell, Flax, Wild carrot, Skirret, Jews' stone, Black pepper, Wine, Honey.

Table 1. Ingredients in the recipes of *Dynameron* referring to diseases of the kidneys and the urinary bladder.

Name	Description	Comments
Alexandrian senna – Κασία	*Senna alexandrina* (*Fabaceae*)	Laxative and fungicide
Almonds – Κάρυα Θάσια	*Prunus dulcis* (*Rosaceae*)	Source of minerals and other useful nutrients
Alpine valerian* – Νάρδος [Κελτική]	*Valeriana celtica* (*Caprifoliaceae*)	Strong diuretic
Alumen – Στυπτηρία	The hydrated double sulfate salt of aluminium	Astringent (reducing mucosal secretions)
Anise* – Ἄννησον	*Pimpinella anisum* (*Apiaceae*)	Carminative (reducing flatulence), diuretic and expectorant
Apple – Μῆλον	*Pyrus malus* (the fruit) (*Rosaceae*)	Digestive
Arabic gum* – Ἀραβικόν κόμμι	The dried exudate of *Vachellia seyal (Fabaceae),* known as "Red acacia"	A mixture of glycoproteins, used as an excipient. As emollient in urolithiasis
Asarabacca* – Ἄσαρον	*Asarum europaeum* (*Aristolochiaceae*) (the root)	Diuretic and emmenagogue
Baldmoney* – Μῆον	*Meum athamanticum* (*Apiaceae*) (the root)	Antiseptic and against cough. Used as a diuretic
Bay laurel* – Δάφνη	*Laurus nobilis (Lauraceae)* (decoction of the dried fruit or the bark)	Digestive (the essential oil of the fruit and the leaves). Used in strangury
Bitter almonds – Κάρυα [πικρά]	*Amygdalus communis var. Amara* (*Rosaceae*) The nuts (bitter almonds)	They contain amygdalin, which eventually yields glucose, benzaldehyde and traces of hydrocyanic acid
Black pepper – Πέπερι μέλαν	*Piper nigrum* (*Piperaceae*) (the fruit)	Digestive, stimulating, antibacterial, antipyretic
Butchers's broom* – Κοράλλιον	*Ruscus aculeatus* (*Asparagaceae*) (the root)	Diuretic
Cabbage* – Κράμβη [σπέρμα]	*Brassica* spp (*Brassicaceae*) (the seeds)	Mild laxative and diuretic
Camel's hay – Σχοινανθός	*Andropogon schoenanthus* (*Graminaceae*) (the essential oil)	A native plant of Near East, with diuretic and antiseptic properties
Caper bush* – Κάππαρις [ῥίζα]	*Capparis spinosa* (*Capparaceae*) (the root)	Diuretic, emmenagogue and carminative
Cardamom* (green) – Καρδάμωμον	*Elettaria cardamomum* (*Zingiberaceae*).	Expectorant and gastroprotective
Castoreum – Καστόριον	Secretion of the perineal sacs of European beaver (*Castor fiber, Castoridae*)	Antiinflammatory
Celery* – Σέλινον [κηπαίον]	*Apium graveolens* (*Apiaceae*)	Diuretic, especially the seeds
Chicken egg – Ὠόν [ῥοφητόν]	The raw egg of *Galus galus* (*Phasianidae*)	A source of protein
Cicadas – Τέττιγες	Dried cicadas (*Tibicen plebejus*, *Cicadidae*), collected during summer	No information available
Costmary* – Κόστος	*Tamasetum balsamita* (*Asteraceae*), or *Saussurea lappa* (*Asteraceae*)	Digestive, astringent, antiseptic and diuretic
Crocus* – Κρόκος	*Crocus sativus var. graecus* (*Iridaceae*) (the stigmas of the flower)	Diuretic, not only the stigmas but also the root, when is taken with wine
Cucumber* – Σίκυς [ἥμερος]	*Cucumis sativus* (*Cucurbitaceae*) (the seeds)	Diuretic, laxative and vermifuge Suitable for ulcerations of the bladder
Cyclamen* – Κάσσαμος	*Cyclamen hederifolium* (*Primulaceae*) (the bulb)	Purgative and diuretic
Dog rose* – Ῥόδα [φύλλα]	Cynorrhodom (*Rosa canina, Rosaceae*) (the leaves)	Antiinflammatory, antimicrobial, astringent
Fennel* – Μάραθρον	*Foeniculum vulgare* (*Apiaceae*) (the seeds, the decoction of the plant)	Carminative, digestive, lactogogue and diuretic. Suitable for kidney diseases and dropsy
Field mushroom* – Ἀγαρικόν	*Agaricus campestris* (*Agaricaceae*)	Suitable for kidney diseases with dysuria
Figs (dried)* – Ἰσχάδες	*Ficus carica* (*Moraceae*) (the dried fruit, dried figs)	Laxative and diuretic
Flax seed* – Λινόσπερμον	*Linum spp*. (*Linaceae*) (the seeds)	Diuretic and digestive
Frankincense – Λίβανος	*Boswellia sacra* (*Burseraceae*) (the resin)	A native plant of Near East with aromatic resin and presumed sedative and diuretic properties
Giant fennel* (oleoresin) – Ἀμμωνιακόν [θυμίαμα]	*Ferula communis var. brevifolia* (*Apiaceae*) (the resin)	Digestive and against dysentery. According to Dioscoridis, it may provoke hematuria

Brackets contain additional specific information in the original text of *Dynameron*. The asterisk (*) denotes that the plant is included also in the work Materia Medica of Dioscoridis.[12,13] Other sources were: Theophrastus,[21] Langkavel,[22] Schauenberg and Paris,[23] Riddle,[24,25] and an internet database on "Greek flora[26]".

Table 1. (continued) Ingredients in the recipes of *Dynameron* referring to diseases of the kidneys and the urinary bladder.

Name	Description	Comments
Giant Tangier fennel* – Κυρηναϊκός ὀπός (Σίλφιον)	*Ferula tingitana* (*Apiaceae*) (propably the dried oleoresin of the sap: *Assa foetida in lacrymis* (silphium)	A foul-smelling resin with applications against gastric and respiratory ailments
Ginger – Ζιγγίβερι	*Zingiber officinale* (*Zingiberaceae*)	Digestive, antiemetic, spasmolytic, antiinflammatory, antibacterial
Grass* – Ἄγρωστις βοτάνη	*Cynodon dactylon* (*Poaceae*) (decoction of the plant)	A potent diuretic, also effective against urolithiasis, with antiviral and antimicrobial properties
Grecian bladderseed – Φυσαλλίς βοτάνη	*Vesicaria graeca* (*Brassicaceae*) (the seeds)	No data available
Gromwell* (common) – Λιθόσπερμον	*Lithospermum officinale* (*Boraginaceae*)	Diuretic with stone dissolving properties, sedative and antipyretic
Hazelnuts – Κάρυα [Ποντικά, λεπισθέντα]	*Corylus colurna* (*Betulaceae*) (the nuts)	A rich dietary source of proteins and minerals
Hemlock* – Κώνειον	*Conium maculatum* (*Apiaceae*)	At very low doses, for urinary bladder infections
Henbane* – Ὑοσκύαμος	*Hyoscyamus niger* (*Solanaceae*)	At very low doses, as a spasmolytic
Hogweed – Σφονδύλιον	*Heracleum sphondylium* (*Apiaceae*)	Antiseptic, analgesic, digestive, antidiarrheal and antiepileptic
Honey* – Μέλι	Honey, often referred as "honey of Attica", was usually diluted with water	As an excipient, for improving the taste of the active ingredients
Hyssop* – Ὕσσωπος [Κρητικός]	*Hyssopus officinalis* (*Labiatae*) (Cretan)	For sore throat and as an expectorant. It has also beneficial effects in urinary tract infections
Iris* (bearded) – Ἶρις	*Iris germanica* (*Iridaceae*) (the rhizome)	Suitable as an excipient, because it contains aromatic viscous substances
Jews' stone* – Τηκόλιθος ἄρρην και θῆλυς ("male" and "female")[12]	*Lapis Judaicus*, *Lapis Syriacus*, *Phaenicites*, or *Tecolithos* ("solvent stone")	Fossil spines of the sea urchin *Balanocidaris* (now extict). Powder or shaves were used with the belief that they dissolve urinary stones
Laceflower* – Ἄμμι	*Ammi majus* (*Apiaceae*)	For dysuria
Ladies' seal* (or Red bryony, or Cretan bryony) – Φύλλον	*Bryonia dioica* (*Cucurbitaceae*). The curcubit *ampelos leuké* of Dioscoridis	A strong purgative, which has been used for gastro-intestinal disorders, lung and liver diseases, as well as a diuretic
Linseed* – Λινόσπερμα	*Linum usitatissimum* (*Linaceae*) (the seeds)	A laxative mucus preparation, in gastritis and enteritis
Liquorice* – Γλυκύρριζα	*Glycyrrhiza glabra* (*Fabaceae*) (the root)	Beneficial in gastritis and gastric ulcers. Also, as an expectorant. Proposed for the inflammations of the kidneys and the urinary bladder
Mallow* (common) – Μολόχη [ἀγρία, σπέρμα]	*Malva silvestris* (*Malvaceae*) (the seeds)	Diuretic and astringent. The seeds have soothing properties in ailments of the urinary bladder
Mullein* – Φλόμος [φλοιός ῥίζας]	*Verbascum thapsus* (*Scrophulariaceae*) (the bark of the root)	Astrigent, suitable to treat diarrhea. Also as an expectorant
Myrrh* – Σμύρνα (Smyrna, Balsam of Mecca) (the resin)	*Balsamodendron myrrha* (*Burseraceae*). A native plant of Near East	"Balsamon", a resin with antiseptic and diuretic properties
Nut grass* – Κύπερος [σπέρμα]	*Cyperus rotundus* (*Cyperaceae*) (seeds and the stem of the flower)	As a diuretic, in nephrolithiasis and dropsy
Opium poppy* – Μήκων	*Papaver somniferum* (*Papaveraceae*) (the sap of the fruit)	A sedative with strong analgesic and anticough properties
Oreganon* – Ὀρίγανον	*Origanum vulgare* (*Labiatae*) (boil to reduce to one third)	Smasmolytic, digestive, carminative, expectorant, with anticough properties. Used in dropsy
Panax* – Πάνακες (το) [ῥίζα]	*Opopanax hispidum* (*Apiaceae*) (the root)	Diuretic. It is mentioned by Theophrastus and also by Dioscorides who suggests its use in strangury
Parseley* – Πετροσέλινον [Μακεδονήσιον]	*Apium petroselinum* (*Apiaceae*)	Diuretic for patients with pain in the kidneys or the bladder

Brackets contain additional specific information in the original text of *Dynameron*. The asterisk (*) denotes that the plant is included also in the work Materia Medica of Dioscoridis.[12,13] Other sources were: Theophrastus,[21] Langkavel,[22] Schauenberg and Paris,[23] Riddle,[24,25] and an internet database on "Greek flora[26]".

Table 1. (continued) Ingredients in the recipes of *Dynameron* referring to diseases of the kidneys and the urinary bladder.

Name	Description	Comments
Pepper – Πέπερι	*Piper nigrum (Piperaceae)*	Orexigenic. Irritant for the mucosa in the alimentary and the urogenital system
Pine cones* – Στροβίλια [πεφωσμένα]	*Pinus halepensis* (*Pinaceae*) (the small cones, roasted)	Diuretic (the seeds), for patients with ailments of the bladder
Purple betony* – Βεττονίκη	*Stachys officinalis* (*Lamiaceae*)	Astringent with many uses in traditional medicine, diuretic
Raisins – Σταφίς [εκγιγαρτισμένη]	*Vitis vinifera* (*Vitaceae*) (the raisins, without the seeds)	Raisins are a precious source of sugars and minerals
Rhubarb* – Ῥῆον [Ποντικόν]	*Rheum Rhaponticum* (*Polygonaceae*)	Astringent, digestive, cholagogue, laxative and diuretic
Rocket* – Εὔζωμον [σπέρμα]	*Eruca longirostra* (*Cruciferae*) (the seeds)	Digestive, diuretic, antiseptic, antiinflammatory
Rock foil* – Σαρξιφάγον (σαξίφραγος)	*Saxifraga* spp (*Saxifragaceae*)	Digestive, sooths respiratory complaints, treats strangury and dissolves stones in the urinary bladder
Rue* – Πήγανος	*Ruta graveolens* (*Rutaceae*)	Diuretic, emmenagogue and abortifacient
Safflower – Κνῆκος	*Carthamus tinctorius* (*Asteraceae*)	No data available
Scorpion (mottled) – Σκορπίος [τέφρα]	*Mesobuthus europeus* (*Buthidae*) (the ashes)	No data available
Sheep sorrel* – Λάπαθον	*Rumex acetosella* (*Polygonaceae*)	A strong diuretic suitable for urolithiasis
Skirret* – Σίνων	*Sium sisarum* (*Apiaceae*).	A diuretic suitable for urolithiasis
Soapwort* – Στρουθίον	*Saponaria officinalis* (*Caryophyllaceae*).	A diuretic suitable for urolithiasis
Spikenard* – Ναρδοστάχυς	*Valeriana Dioscoridis* (*Nardaceae*) (the essential oil of the root)	An essential oil with pleasant odour and diuretic properties
Starch – Ἄμυλον	*Amylum* (a polysaccharide of glucose, isolated from plants)	As an excipient (mainly the wheat starch)
Storax – Στύραξ	*Styrax officinalis* (*Styracaceae*) (the oleoresin)	As an antiseptic together with frankincense and galbanum
Sweet flag* – Ἄκορον	*Acorus calamus* (*Acoraceae*) (the rhizome)	Digestive, carminative, antibacterial and diuretic
Thyme* – Θύμος	*Thymus vulgaris* (*Labiatae*) (the essential oil)	Contains thymol, which has been proposed for antiseptic, emmenagogue and diuretic properties
Torchwood* – Ξηροβάλσαμον	*Amyris elemifera* (*Rutaceae*) (the resin)	The essential oil of the resin has antiseptic and diuretic properties
Tragacanth*, Astragale de Marseille – Τραγάκανθα	*Astragalus tragacantha* (*Fabaceae*) (the gum-resin)	Diuretic
Turtle dove – Τρυγών [ὄρνεον, κόπρος]	*Streptopelia turtur* (*Columbidae*) (droppings)	No data available
Vetch* – Ὄροβος [άλευρον]	*Vicia sativa* (*Fabaceae*) (flour)	The flour of vetch is diuretic and may provoke hematuria
Wall germander* – Χαμαίδρυς	*Teucrium chamaedrys* (*Lamiaceae*)	Diuretic, suitable for patients with dysuria and dropsy.
Walnuts – Κάρυα [βασιλικά]	*Juglans regia* (*Juglandaceae*) (fruit)	A source of important nutrients
Water – Ὕδωρ	Usually collected rain water	As an excipient, for dissolving ingredients. Also, for enforcing diuresis
White Opium poppy* – Μήκων [λευκή]	*Papaver somniferum, var. album* (*Papaveraceae*)	A sedative with strong analgesic and anticough properties
White pepper – Πέπερι [λευκόν]	*Piper album* (*Piperaceae*). The exfoliated seeds of *Piper nigrum*	Orexigenic. Irritant for the mucosa in the alimentary and the urogenital system
Wild carrot* – Δαῦκος	*Daucus carota* (*Apiaceae*) (the root)	Digestive and diuretic
Wine [aromatic] – Κόνδιτος Wine [sweet] – Γλυκύς οἶνος Wine [white] – Οἶνος λευκός Wine [with honey] – Μελίκρατος (οἶνος)	Various types of wine and wine admixtures. The so-called "aromatic wine" (κόνδιτος) contained pepper and honey	Wines have been used as excipients for dissolving the ingredients of a recipe and also for improving the taste. Ethanol (usually 12-15%, per volume) is known for its diuretic properties
Wormwood* – Ἀρτεμισία [χυλός]	*Artemisia absinthium* (*Asteraceae*) (the sap). Most propably the plant described by Dioscoridis as «αψίνθιον»	Digestive, appetizer and anthelmintic. Diuretic, suitable for dropsy

Brackets contain additional specific information in the original text of *Dynameron*. The asterisk (*) denotes that the plant is included also in the work Materia Medica of Dioscoridis.[12,13] Other sources were: Theophrastus,[21] Langkavel,[22] Schauenberg and Paris,[23] Riddle,[24,25] and an internet database on "Greek flora[26]".

3.2.7. Suitable for urolithiasis, in order to urinate the stone.

Soapwort, Rhubarb, Caper bush, White wine. This remedy dissolves completely the kidney stones in eight days.

3.2.8. Provokes the urination of the kidney stones.

Turtle dove, Wine with honey.

3.2.9. Other similar.

Alexandrian senna, Myrrh, Frankincense, Wild carrot, Anise, White opium poppy, Nut grass, Jews' stone, Parseley, Crocus, Bitter almonds, Asarabacca, Storax, Black pepper, Honey, Wine, Water. Dilute with warm water and honey. Give a dose the size of an Aegyptian bean with wine to feverless patients, and with water to those with fever.

3.2.10. Other similar.

Mullein. A handful of bark from the root of verbascum should be smashed with a wooden mortar and pestle. Then treat with hot water and filter. Give the patient to drink for nine days, then stop for one or two days and then give to drink again for eleven days. After drinking the patient must take a long walk and have something to eat from time to time. It is very important to note that the patient and the physician should not have on them any iron item, nor in the fingers neither in the shoes or elsewhere. In addition, take care that the root of verbascum is taken off the earth without any iron instrument, and also that once taken off it should not touch the earth again. This remedy I have used successfully many times.

3.2.11. Another remedy for urolithiasis, tested with success by me.

Cicadas, Parseley, Ladies' seal, Wine (aromatic). Give a spoonful of aromatic wine (containing pepper and honey), together with smashed cicadas, which should be collected when the vines are ripe and should be dried up in the shadow. Collect and dry many cicadas, so you may have whenever you need them.

3.2.12. Patients who urinate sand.

Alpine valerian, Parseley, Black pepper, Rhubarb, Iris, Cabbage, Wine (aromatic). Give a small spoonful with aromatic wine or wine with honey.

3.2.13. Other remedy, for expelling stones, for nephropathies and for urination.

Alexandrian senna, Celery, Myrrh, White pepper, Frankincense, Jews' stone, Wild carrot, Anise, Storax, Opium poppy, Nut grass, Spikenard, Bitter almonds, Sweet flag, Asarabacca, Cucumber, Honey, Sweet wine. A dose the size of fava bean is given with honey diluted in water. To feverless patients can be given together with a cup of sweet wine.

3.2.14. Other. It breaks and expels stones.

Scorpion (mottled), Wine (aromatic). Burn down scorpions and mix up the ashes with diluted sweet wine. Give a small spoonful and you will be amazed with the results.

3.2.15. Other.

Oreganon. Boil oreganon in water, until it condenses to one third. Give a cup of the decoction, and the patient will urinate the stones.

3.3. Chapter 17. Diuretics (Διουρητικά)

3.3.1. Cucumber, Celery, Liquorice. Boil equal parts in water and give to the patient. You may observe the colour of blood in the urine.

3.3.2. Other. Patients with difficulty to urinate.

Celery, Anise. Boil together and give the patient to drink.

3.3.3. Other. Patients with difficulty to urinate.

Thyme, Bay laurel, Hyssop, Oreganon, Parseley, Black pepper, Chicken egg (raw). Trim, mix up and give together with a raw egg.

3.3.4. Other. A good diuretic for patients with difficulty to urinate.

Thyme, Fennel, Bay laurel, Wine, Chicken egg. Trim, mix up and give with egg, or diluted wine.

3.3.5. Other. Patients with painful urination (dysuria).

Parseley, Black pepper, Wine (sweet). Give a small spoonful with sweet wine, in the morning and the evening.

3.3.6. Other. For those seriously ill, men and women, who suffer from difficult and painful urination.

Costmary, Honey, Water. Give the patient to drink a cup with a mixture of these. Ask your payment beforehand.

3.3.7. Diuretic with the name "diabetes" (διαβήτης).

Alexandrian senna, Cyclamen.

3.3.8. Other.

Crocus, Liquorice, Wine. Dissolve in wine and make lozenges. Give one at a time, with wine.

3.3.9. Other. Patients with painful urination (dysuria). It is also digestive.

Myrrh, Black pepper, Castoreum. Give a mixture of equal parts, on demand.

3.3.10. Other. Patients with strangury. *Celery, Alexandrian senna, Thyme, Iris, Anise, Black pepper, Oreganon, Water.* Give as a warm water solution.

3.3.11. Other. Patients with strangury. Also effective in expelling stones.*Black pepper, Jews' stone, Spikenard, Parseley, Cardamom (green), Grass*. Give a decoction, together with wild grass (agrostis).

3.3.12. Other. Patients with dysuria.

Parseley, Figs, Water, Honey. Boil in water and give with wine and some honey.

3.3.13. Other.

Nut grass, Wine diluted in water. Give a small spoonful, together with diluted wine. The patient will urinate immediately.

3.3.14. Other. Patients with dysuria. *Fennel, Asarabacca*. Boil together and give the patient to drink.

3.4. Chapter 18: Ailments of the urinary bladder and for those who urinate blood (Πρός τά τῆς κύστεως πάθη καί αἷμα ἀπουροῦντας)

3.4.1. Opium poppy, Cucumber, Hemlock, Celery, Sheep sorrel, Pine cones, Crocus, Almonds, Hazelnuts, Grecian bladderseed, Cretan sweet wine. Mix and dissolve everything in Cretan wine. Those with urinary bladder ulcerations should be treated with instillation through the urethra.

3.4.2. Other. In patients with dysuria, it breaks down the stones and expels them with the urine. Moreover, it cures many ailments of the urinary bladder, such as inflammations, ulcerations and blood clots. *Parseley, Rue, Wild carrot, Wall germander, Safflower, Black pepper, Myrrh, Rocket, Laceflower, Ginger, Ladies' seal, Wormwood, Sweet wine. Give to drink with* sweet wine, before bathing.

3.4.3. Patients with ureteral pain, urinary retention, dysuria, blood urination and nephrolithiasis. It is called "Hippocrates's" (Ἱπποκράτους) or "herbal" (διά τών φυτῶν).

Asarabacca, Baldmoney, Alpine valerian, Honey of Attica. Mix with honey of Attica and give a dose equal to a hazelnut to healthy individuals. For children and old people, give less. Keep the ingredients dry, so they retain their efficacy.

3.4.4. Any kind of pain in the urinary bladder.

Mallow, Wine with honey. Dissolve in wine and honey, and give a cup. Stops the pain of the bladder and stops even the inflammation.

3.4.5. Other. Patients with blood in urine, urinary bladder inflammation and ulceration.

Linseed, Cucumber, White opium poppy, Tragacanth, Starch, Sweet wine. Dissolve first tragacanth in sweet wine, and then dissolve the other ingredients. To patients with blood in urine, give three cups with water and sweet wine. To others, according to their needs.

3.4.6. Other. Acute pain and ulcerations of the urinary bladder.

Wild carrot, Parseley, Myrrh, Field mushroom, Cardamom (green), Alexandrian senna, Panax, Crocus, Giant Tanagier fennel, Hogweed, Butchers's broom, Black pepper, Vetch, Wine with honey, Water. Dissolve in wine with honey. Give with water a dose equal to a fava bean.

3.4.7. Blood in urine.

Dog rose, Opium poppy, Pine cones, Sweet wine, Water. Give a dose equal to a hazelnut, with two cups of sweet wine and one cup of water.

3.4.8. Other. Patients with urinary bladder bleeding.

Alumen, Tragacanth, Arabic gum, Sweet wine, Water. Dissolve in wine and water.

3.4.9. Other. Blood in urine.

Myrrh, Opium poppy, Sweet wine. Dissolve in sweet wine and make pills to give the patient, according to the instructions.

4. DISCUSSION AND CONCLUSIONS

In the cited 41 recipes related to ailments of the kidneys and the urinary bladder, Aelius Promotus describes the use of about 80 different herbs, 6 ingredients of animal origin, as well as 1 mineral. As excipients, he uses water, wine or honey. A large number of active ingredients are applied in each recipe, a typical characteristic of the Empiric school of medicine. In most instances, they represent well-established remedies suitable for diuresis and for treating the causes and symptoms of specific ailments, such as strangury, dysuria, nephrolithiasis, hematuria, and the inflammation of the kidneys or the urinary bladder. Quite often, the author adds personal comments on the efficacy of a recipe, referring to his previous experience. This indicates that *Dynameron* is an account of treatments proposed by an experienced practicing physician, and not a mere compilation of earlier recipes.

Many of the recommended herbal ingredients are intended for diuresis in case of difficulty in micturition (strangury), mostly related to urolithiasis. Several other pathological conditions are not specified (as e.g. nephritis, cystitis or bladder cancer), although they are implied indirectly, by the terms "urination of blood", "urinary bladder inflammation" and "urinary bladder ulceration".

In general, Aelius Promotus proposes the use of several herbal remedies, in order to increase urination, as shown in table 1. Of these plants, some possess genuine diuretic properties, according to our current knowledge of Pharmacognosy.[17,20] On the other hand, there are also plants facilitating diuresis due to their high water content. So, increased urine output is mainly the consequence of an augmented fluid intake, a rather common practice by Greek

physicians in antiquity.[12] On the other hand, the use of a strong spasmolytic like henbane (*Hyoscyamus niger*) or a strong analgesic like opium poppy (*Papaver somniferum*) is fully justified for kidney diseases and especially in cases of nephrolithiasis. As a matter of fact the active ingredients of these plants (scopolamine and morphine, respectively) continue to be unreplaceable agents in the armamentarium of modern medicine.

With a few exceptions, most remedies proposed in *Dynameron* for the ailments of the kidneys and the urinary bladder can be encountered in *Materia Medica* of Dioscoridis, where they are granted similar clinical uses.[13,14] However, nowhere in *Dynameron* is mentioned the name of Dioskoridis, despite the fact that Aelius Promotus is usually very eager to acknowledge the origin of a recipe. It is true, that the time gap between these two authors is rather narrow, leaving space for a speculation that Aelius might have ignored the work of Dioscoridis. The fact that both writers advocate the same plants as remedies for the same clinical indications may simply show that all these therapies represented a well-established common knowledge of their time.

It is worth commenting the method proposed for the therapy of the "ailments of the urinary bladder and urination of blood" (Chapter 18), where it is suggested that patients with urinary bladder ulcerations should be treated with instillations through the urethra. This is a proof that Alexandrian physicians were aware of the anatomical details of the human body. Moreover, it reminds us the high level of expertise reached by surgery at that time, as well as the existence of elaborate instruments, such as catheters.[3]

Although Aelius Promotus was apparently a knowledgeable physician, some of his remedies are obscure and questionable. Perhaps the most typical example is *Jews' stone*, as an agent that contributes to the dissolution of renal stones. This very specific product was included in the official British Pharmacopoeia until the middle of the 19th century,[15] but the scientific community has not come yet to a conclusion on its possible therapeutic value.[16–18]

On the other hand, the detailed description of how mullein is harvested (Chapter 16, recipe 10) is definitely a supestitious ritual. In other chapters of *Dynameron*, not presented here, there are several examples of superstitions, usually referring to the moon phase, or to the need to invoke a divine power while preparing or administering a recipe. Magic remedies and superstitious beliefs, not uncommon among medical writers of that time including Dioscoridis, are gradually eliminated with the progress of time and they are virtually absent in medical texts of the late Byzantine period.[19,20]

Aelius Promotus describes the treatment of many ailments of the kidneys, by using about one hundred different ingredients, several of them easily recognizable for their efficacy in the light of modern science. By adding various comments to his recipes, he enriches the medical information with hints of the everyday clinical practice. In most instances, he is very confident and he does not hesitate to praise the efficacy of a recipe. However, there is one exception. In the 6th recipe of Chapter 17 ("For those seriously ill, men and women, who suffer from difficult and painful urination") he seems almost cynical in his final advice: "Give the patient to drink a cup with a mixture of these. *Ask your payment before hand*".

Overall, in the second century AD, Aelius Promotus left to the younger physicians an account of his personal medical experience on 130 ailments. *Dynameron* is an almost complete therapeutic manual written at a time when Alexandria was still a city with a glorious medical tradition. The historical value of this text has not been given yet the attention it deserves.

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ΠΕΡΙΛΗΨΗ

Οι νεφρολογικές παθήσεις σε ένα αλεξανδρινό κείμενο της ύστερης αρχαιότητας

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Ένα ελληνικό ιατρικό χειρόγραφο με τον τίτλο *Δυναμερόν* φυλάσσεται στην Εθνική Μαρκιανή Βιβλιοθήκη της Βενετίας (Cod. gr. 295) και αποτελεί αντίγραφο ενός έργου που αποδίδεται στον Αίλιο Προμώτο, έναν ιατρό ο οποίος έζη-

σε και εργάστηκε στην Αλεξάνδρεια τον 2ο αιώνα μΧ. Αυτό το χειρόγραφο δεν πρέπει να συγχέεται με το ογκώδες *Μέγα Δυναμερόν* που γράφηκε τον 13ο αιώνα από τον Νικόλαο Μυρεψό και περιέχει 2667 συνταγές. Το *Δυναμερόν* του Αίλιου Προμώτου περιέχει 130 κεφάλαια που περιγράφουν 870 συνταγές για διάφορες ασθένειες. Για τις νεφρολογικές παθήσεις, υπάρχουν 41 συνταγές, με μείγματα από περίπου 80 βότανα. Επιπλέον, υπάρχουν έξι προϊόντα ζωικής προέλευσης και ένα ορυκτό. Ο μεγάλος αριθμός συστατικών που χρησιμοποιούνται σε κάθε συνταγή υποδηλώνει ότι ο Αίλιος Προμώτος ήταν οπαδός της επονομαζόμενης «Εμπειρικής σχολής», παρόλο που στο έργο του είναι εύκολα αναγνωρίσιμες και επιρροές από άλλες ιατρικές θεωρίες. Πολλά από τα φυτικά συστατικά που προτείνει ο συγγραφέας είναι γνωστά για τις διουρητικές, σπασμολυτικές, αναλγητικές και αντισηπτικές τους ιδιότητες. Ως εκ τούτου, είναι κατάλληλα για τη θεραπεία της νεφρολιθίασης, της στραγγουρίας, της δυσουρίας, της αιματουρίας, καθώς και των φλεγμονών των νεφρών και της ουροδόχου κύστης. Ορισμένες από τις συνταγές περιέχουν συστατικά με ασαφείς ιδιότητες, για τα οποία δεν είναι δυνατή η συσχέτιση με κάποια λογική θεραπευτική δράση. Υπάρχουν, μάλιστα, και παραδείγματα συνταγών με χαρακτηριστικά δεισιδαιμονίας, που παραπέμπουν σε πρακτικές μαγικών ιεροτελεστιών. Ωστόσο, όταν αξιολογείται το *Δυναμερόν* στο σύνολό του, το συμπέρασμα είναι ότι ο Αίλιος Προμώτος ήταν ένας πεπειραμένος και πολυμαθής ιατρός, ιδιότητες που αντανακλούν την περίφημη ιατρική παράδοση της Αλεξάνδρειας κατά την ύστερη ρωμαϊκή περίοδο. Φαίνεται ότι το *Δυναμερόν* αντιγράφηκε αρκετές φορές κατά τους επόμενους αιώνες, προκειμένου να χρησιμεύσει ως εγχειρίδιο θεραπευτικής, για τις κοινές ασθένειες που μπορεί να αντιμετωπίσει ένας ιατρός στην καθημερινή του πρακτική.

Λέξεις ευρετηρίου: Αίλιος Προμώτος, Αλεξάνδρεια, *Δυναμερόν*, Νεφρολογία, Ουρολιθίαση

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HERBAL MEDICINE
ΒΟΤΑΝΟΛΟΓΙΚΗ ΘΕΡΑΠΕΙΑ

Herbal prescriptions for the treatment of kidney diseases in the Byzantine era

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ΑΡΧΕΙΑ ΕΛΛΗΝΙΚΗΣ ΙΑΤΡΙΚΗΣ 2020, 37(Συμπλ 2):139–142

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Φυτικά φάρμακα για τη θεραπεία ασθενειών των νεφρών κατά τη βυζαντινή εποχή

Περίληψη στο τέλος του άρθρου

This article focuses on nephrology diseases and illnesses as well as on their treatment with herbal formulations, as used in the Byzantine era and recorded in medical texts. The medical texts investigated concern the Byzantine period from the 4th to the 15th century. Various texts written in this period contributed to the evolution of medical science in both the West and East. These texts are divided in two categories: those focusing on the observation of urine (Uroscopy) with a diagnosis of kidney diseases, and those on the treatment of kidneys diseases. Our primary source material was the medical collections of Oribasius, Aetius of Amida, Alexander of Tralles, Paul of Aegina, Symeon Seth, Nikolaos Myrepsos and Ioannis Actuarios, who report nephrological diseases and herbs to manage them. In these texts, we searched for those medical prescriptions related to kidney disease and we notice the plants containing them. These studies confirmed the ongoing research and methodological approach to urine testing. Combination of herbs is also recommended for the treatment of dysuria, strangury, lithiasis and nephropathy. This research leads us to the conclusion that the content of these texts provides a detailed view of the properties of the herbs that were able to effectively manage kidney diseases and also of the level of knowledge that existed during the Byzantine era.

Key words

Byzantine era
Herbal prescriptions
Kidney diseases
Medical texts
Nephrology

1. INTRODUCTION

Many medical and pharmaceutical text collections written during the Byzantine era contributed to the evolution of medical science. These are divided in two categories: those focusing on the observation of the Urine (Uroscopy) with a diagnosis of kidney diseases, and those on the treatment of kidneys diseases. This paper discusses the latter category.

2. MATERIAL AND METHOD

The texts are attributed to well-known writers such as Oribasius, Aetius of Amida, Alexander of Tralles, Symeon Seth, Nikolaos Myrespos and Ioannis Actuarios. Others are considered fake, and in reality anonymous, such as Pseudo-Galen, Pseudo-Oribasius. Other anonymous texts have not yet been published and are awaiting researchers to publish them.

3. RESULTS

3.1. Oribasius

During the early Byzantine years, Oribasius, physician to Emperor Julian,[1] wrote two collections of works based on the work of earlier physicians. First, a collection of fragments by Galen which, however, is missing; second, a large medical collection, consisting of 72 texts (Medical Collections, Iatrike Syntage), based on expert medical writers of the ancient world of which only 25 survive.[2] In this collection, Oribasius references, among others, medications that treat kidney diseases[3] such as dysuria, stranguria and lithiasis. Kidney disease is recorded 30 times. These recommend the ingestion of purslane and bent decoction and preparations containing, among other ingredients, parsley, nardostachys and pepper. For lithiasis, he recommends the following recipes: the first consists of crocus, myrrh, camel-hay, cassia, nardostachys, costus; the second of cucumber, celery, carrot, or water parsnip, as well as balsam-tree fruit, stones from sponges, pennyroyal, marshmallow, and in another one only Paul's betony. Oribasius always refers in his text collection to dysuria and stranguria jointly, and although he discerns one condition from the other, he recommends the same treatment for both. There is only one case of dysuria, that due to bladder infection, for which he specifically recommends oxymel (=vinegar with honey) or olive oil. Similarly, in only one case, where Oribasius provides a detailed medical analysis of stranguria, he proposes an aro-

matic concoction consisting of theriacs and cicada, adding a little nardus. In another chapter of his text, he proposes ingesting sainfoins leaves with wine to cure stranguria, while elsewhere he recommends a complex drug obtained from saxifragus, Pauls betony, parsley, nardostachys, dog mercury, rhubarb, hedge-mustard, pepper, honey and wine. In another section of the same text, he opts for curing stranguria by a fennel decoction.[4]

3.2. Aetius of Amida

Aetius of Amida lived in the mid-5th to mid-6th century AD. He was a Byzantine Greek physician and medical writer. In his work *Biblia iatrika ekkedeka,*[5] meaning "16 Medical books", he includes not only his own medical viewpoints, but also the viewpoints and theories of other physicians. He deals with the diagnosis, prognosis, aetiology and treatment of diseases as well as with simple herbs, mineral waters, sediments, urine, bleeding, brain diseases, ear nerves and much more. For the treatment of kidney disease, Aetius refers to several of Oribasius' recipes, but also of other earlier physicians' such as Asklepiad, Philagrios, Archigenes and many others, and urges patients to use these recipes for healing. In these, for the treatment of kidney disease he recommends mostly purslane and bentgrass. He additionally reports recipes of patches or beverages or conditum, a type of spiced Byzantine wine; in some, the basic ingredient is wax, in others oxymel and in others various herbs including: *Centaurium*, globularia, rue, leek, agaric, cassia, iris, hyssop, pennyroyal and squill. For lithotripsy, he mostly uses saxifrages, betony, parsley, matgrass, hedge mustard and pepper. According to Aetius, the above ingredients are most appropriate for kidney disease and lithotripsy. For lithiasis, Aetius recommends ingesting safflower, while in another recipe he recommends a decoction of fenugreek, mallow, flax or of artemisia, or of rosemary, parsley and matgrass.

Aetius also describes stranguria and he notes its symptoms as well as its treatment during pregnancy.[6] He recommends ingesting theriacs with vinehoney, diuretic foods, or aromatic decoctions. In one recipe, he recommends ingesting dried hedgehogs' offal with wine. In another, he recommends taking psomogaros, a yet unknown ingredient, with rue leaves together with some wine, while the field eryngo is said to be most suitable for stranguria. He also notes a conditum from Oribasius and the troche of Heras,[7] an ancient physician. He also recommends the use of a decoction made of marjoram or rue and in another recipe[8] a medicament consisting of garlic, oil, nitrum, terebinth, cedar or olibanum and sorrel. Aetius describes dysuria along with stranguria. For their treatment, he recommends taking parsley with rue oil or simply drinking amber, summer squash, bamboos, liquorice, a mixture of opium poppy accompanied with pepper trees or lentisk, or another mixture of opium poppy, starch, egg and purslane. We have found only a few prescriptions for the treatment of dysuria. Interestingly, Aetius is the only physician to report a dysuria prescription from the ancient physician Andromachos.[5]

3.3. Alexander of Tralles

Alexander of Tralles, another distinguished Byzantine physician, lived in the 6th century AD.[9] In his 12th volume of *Therapeutics,*[10] there are few but extensive reports, describing recipes to manage kidney disease, how kidney stones are created, and the medicinal herbs recommended to treat kidney diseases, such as fennel, anise, nardus, celery, toothpick-plant, casia and others. Referring to kidney disease, he defines how the physician distinguishes colics from kidney pain. Alexander diagnoses stranguria and he recommends houndstooth. He also recommends wine and absinthe for stranguria in case of frigidity. In case of dysuria, Alexander describes the disease, and recommends taking althaea, linum, nettles, in another recipe ingesting artemisia with garlic; while in another taking stone pine, figs and starch.

3.4. Paul of Aegina

Paul of Aegina lived in the 7th century AD. He wrote a 7-volume medical encyclopaedia entitled *Epitome of Medicine.*[11] Thanks to its accuracy and completeness, this work, containing all medical knowledge up to his time was considered a leading reference work.[12] Paul makes a few references to kidney disease, all of which in the seventh book. He recommends the use of pennyroyal, or alkanet which although containing bitterroot, has the greatest benefit for the kidneys. He also recommends a conditum formulation. In the most extensive prescription, Paul adds 19 different herbs, including lithosperm, anise, ammi, cucumber, althaea, spignel, white pepper and others. The addition of animal ingredients such as cicada, blood sing and fish rack should not surprise us. These, blended with honey, are optimal medicine. In another report on kidney disease, he recommends taking ingredient from various plants, such as tribulum, saxiphragus, sinon, Asparagus, Pentaphyllum. In another recipe, he recommends the use of swill of Barley grains and fishes and oak followed by nutrition necessary to treat stranguria. Elsewhere, in the same book, he mentions that oenanth remedies stranguria, while purslane is equally effective. When a patient suffers from stranguria, he benefits from taking purslane root with

asparagus. Other herbs and plants that cure stranguria are sainfoins and pseudobunion. Like Alexander, Paul of Aegina describes the kidneys and cystic disorders. Paulus, however, is the first author to quote, explain and interpret lithiasis. For lithiasis, he recommends taking carpesium or a mixture of oxymel to which saxifragus, betony, bentgrass, maidenhair fern, nardostachys, etc. have been added. In his work, dysuria is reported in parallel with stranguria. Halvana and helichrysum can be ingested with wine, as can cumin, vitex and garlic. Finally, there is a recipe from Archigenes, according to which the sufferer should take medication consisting of opium poppy together with a decoction made of lentisk or sugarcane, or glycyrrhiza. He also notes that ingesting smoked caelifera benefits dysuria.

3.5. Symeon Seth

Symeon Seth,[13] was an 11th-century Byzantine doctor. He used various medicinal herbs to create the right composition for the treatment of lithiasis. Among these, he preferred semidalis, namely semolina, as the most appropriate treatment. He mentions that according to the Indian people, garlic is used to treat stranguria, as is goose tongue. He recommends taking a potion of oil from rue, while in another recipe he reports that celery is equally effective in healing dysuria.

3.6. Nikolaos Myrepsos

Nikolaos Myrepsos wrote the extensive Dynameron, a collection of medical prescriptions, in the mid-13th century AD. In this, he reports over 155 recipes for kidney disease, 110 recipes for dysuria and stranguria, and 58 recipes for bladder stones. In total, he reports over 320 medical prescriptions for kidney diseases. This book, containing approximately 3,000 recipes, was published for the first time in April 2019 in a commented edition.[14] This edition makes Dynameron a unique source, with countless references waiting for researchers to read and investigate. The 320 recipes on kidney diseases[15] are scattered throughout the text and include patches, kidney tracheas and antidotes for kidney clearance, lithiasis, stranguria and dysuria, ointments for dysuria and stranguria and beverages for bladder stones. Many different herbs are recommended for the treatment of kidney disease.[16] However, the most common ones are pumpkin seed, sweed and bitter fennel, Juniper berry, lovage root, olive leaf, knotgrass herb, blackcurrant, nettle and agnus castus fruit.[17]

3.7. Ioannis Actuarios

As mentioned in one of his works, Ioannis Actuarios lived in the late thirteenth century AD1. His work on Diagnosis[18] presents findings of dysuria and provides conclusions that provide physicians with unique information for better understanding the condition and guiding its management and treatment. He makes only one reference to stranguria as an observation of women's uterine diseases.

4. DISCUSSION AND CONCLUSIONS

The above show that Byzantine authors had a plethora of recipes of plant origin for kidney diseases; constantly focusing on these and based mainly on their empirical knowledge. By attempting to cross-link that information with current knowledge and research results, we find that the plants mentioned by the Byzantines are the most effective for kidney disease. This is also confirmed by the European Medicines Agency,[19] which considers these plants the most effective in treating kidney disease. We can thus conclude that Byzantine medical knowledge can still be useful and should continue to be thoroughly studied and used anew, as happened during the Renaissance.

ΠΕΡΙΛΗΨΗ

Φυτικά φάρμακα για τη θεραπεία ασθενειών των νεφρών κατά τη βυζαντινή εποχή

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Το άρθρο εστιάζει στις νεφρολογικές παθήσεις και ασθένειες καθώς και στη θεραπεία φυτικών σκευασμάτων που χρησιμοποιήθηκαν στην ύστερη βυζαντινή εποχή και καταγράφονται σε ιατρικά κείμενα. Τα ιατρικά κείμενα που έχουν ερευνηθεί αναφέρονται στη βυζαντινή περίοδο από τον 4ο έως τον 15ο αιώνα. Σ΄ αυτή την περίοδο γράφτηκαν κείμενα που συνέβαλαν στην εξέλιξη της ιατρικής επιστήμης. Από αυτά ξεχώρισαν ιδιαίτερα τα κείμενα για τα ούρα, που μελετήθηκαν επισταμένα από τους γιατρούς. Αυτά τα βιβλία χωρίζονται σε δύο κατηγορίες: τα βιβλία που

επικεντρώνονται στην παρατήρηση των ούρων (την ουροσκοπία) με σκοπό τη διάγνωση των νεφρικών νόσων και τα βιβλία που αναφέρονται στη θεραπεία των ασθενειών των νεφρών. Το πρωταρχικό μας υλικό ήταν οι ιατρικές συλλογές του Ορειβάσιου, του Αετίου, του Αλέξανδρου από τις Τράλλεις, του Παύλου του Αιγινήτη, του Συμεών Σηθ, του Νικολάου Μυρεψού και του Ιωάννη Ακτουάριου, οι οποίοι αναφέρουν νεφρολογικές ασθένειες και βότανα που τις αντιμετωπίζουν. Στα κείμενα αυτά αναζητήθηκαν εκείνες οι ιατροφαρμακευτικές συνταγές οι οποίες σχετίζονται με τις νεφρολογικές παθήσεις και καταγράφηκαν τα φυτά που αυτές περιέχουν. Από τις συνταγές αυτές επιβεβαιώθηκε η σημερινή έρευνα και μεθοδολογική προσέγγιση της εξέτασης των ούρων. Στις συνταγές της βυζαντινής εποχής υπάρχουν συνδυασμοί βοτάνων για τη θεραπεία της δυσουρίας, της στραγγουρίας, της λιθίασης και της νεφροπάθειας. Η έρευνα αυτή, μας οδηγεί στο συμπέρασμα ότι το περιεχόμενο αυτών των βιβλίων προσφέρει μια λεπτομερή εικόνα της νεφρολογίας και των ιδιοτήτων των βοτάνων που ήταν σε θέση να αντιμετωπίσουν αποτελεσματικά τις νεφροπάθειες και το επίπεδο της γνώσης που υπήρχε κατά τη βυζαντινή εποχή.

Λέξεις ευρετηρίου: Βυζαντινή εποχή, Ιατρικά κείμενα, Νεφρολογικές παθήσεις, Φυτικά φάρμακα

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HERBAL MEDICINE
ΒΟΤΑΝΟΛΟΓΙΚΗ ΘΕΡΑΠΕΙΑ

Urinary bladder lithiasis treatment in the "Mega *Dynameron*"

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ΑΡΧΕΙΑ ΕΛΛΗΝΙΚΗΣ ΙΑΤΡΙΚΗΣ 2020, 37(Συμπλ 2):143–147

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Θεραπεία λιθίασης ουροδόχου κύστης στο «Μέγα Δυναμερόν»

Περίληψη στο τέλος του άρθρου

Key words

Bladder lithiasis
Dynameron
Nikolaos Myrepsos

OBJECTIVE: **The Mega *Dynameron*, probably written in the 13th century by Nikolaos Myrepsos, included all up-to-then knowledge of Pharmacology. It consists of 24 sections, following the 24 letters of the Greek alphabet, and includes more than 2,600 pharmaceutical recipes. The Mega *Dynameron* was used as the reference book on drugs in Europe for about three centuries after its publication. Our study aimed to focus on recipes for nephrolithiasis, especially urinary bladder lithiasis.** METHOD: **For the purpose of this study, we read the Latin translation of "Mega *Dynameron*", published by Leonhart Fuchs in Basel in 1549, available online at the Biblioteca Digital Dioscórides of Universidad Complutense of Madrid, as well as the Greek publication by Elias Valiakos (2014 and 2019), based on Paris code gr.2243.** RESULTS: **Myrepsos refers to renal diseases in many recipes in his work. Most of them are intended for use in non-renal pathologies as well, and only a part of them is specifically for renal and urinary bladder lithiasis. "Antidotarium" in section "alpha" includes eight recipes referring specifically to dissolving bladder stones. Two of them concern exclusively urinary bladder lithiasis (ν'/LI and νβ'/LIII), while μα'/XLII and ρ$_{\text{ϟ}}$α'/CXCIII are used for both renal and bladder stones. The other four (β'/II, λθ'/XL, πη'/XC and τιδ'/CCCXX) are indicated for other diseases as well. Recipes include a rich variety of herbs, plants, vegetables and fruits, insects (e.g. cicada) and animal products (e.g. goat's blood), with detailed preparation instructions. Ingredients are mixed with honey, sugar, water, wine or chamomile, and administered with specific doses and duration of treatment. More recipes for renal inflammation, lithiasis and colics in *Dynameron* are found in the sections on ointments, patches, enemas, cathartics and others, while a couple of specific recipes for urinary bladder stones are referred in Index Salium/«Περί Αλάτων» (η'/VIII) and Index Lexopyretorum/«περὶ Ληξοπυρέτων» (κγ'/XXIII).** CONCLUSIONS: **With his reference book on drugs "Mega *Dynameron*", Nikolaos Myrepsos disseminated invaluable knowledge on the treatment of urolithiasis throughout the centuries, highlighting the importance of kidney function and uropathies.**

1. INTRODUCTION

The Mega *Dynameron* («Μέγα Δυναμερόν ή Περί συνθέσεως φαρμάκων»), originally written in Greek, includes over 2,600 pharmaceutical recipes. It is divided in 24 sections, following the 24 letters of the Greek alphabet. Its author was probably Nikolaos Myrepsos ["Myrepsos" meaning a person making myrrh or perfumes] who lived during the 13th century AD and was personal doctor to the Emperor Ioannis Vatatzis of Nicaea.[1–5] However, according to recent research (Valiakos 2019),[6] the initial core text of *Dynameron* might have been the work of a medical doctor named Nikolaos who lived during the early 12th century (or even earlier), which was enhanced in the following decades by different writers adding more recipes to the initial text, until the second half of the 13th century, when *Dynameron* was published as presently known in the text of Paris code gr.2243 (fig. 1).

Paris code gr.2243 is located in the National Library of France in Paris (BnF).[5] Its writing was completed in August 1339 in Athens, as noted in page 664r, by Kosmas Kamilos, priest and exarch of the Patriarchate in Athens, on behalf of Dr Dimitrios Chlomos. It includes a copy of Nikolaos Myrepsos' *"Dynameron"* between pages 002v and 550v, as well as more medical literature. In page 1v of the code, it

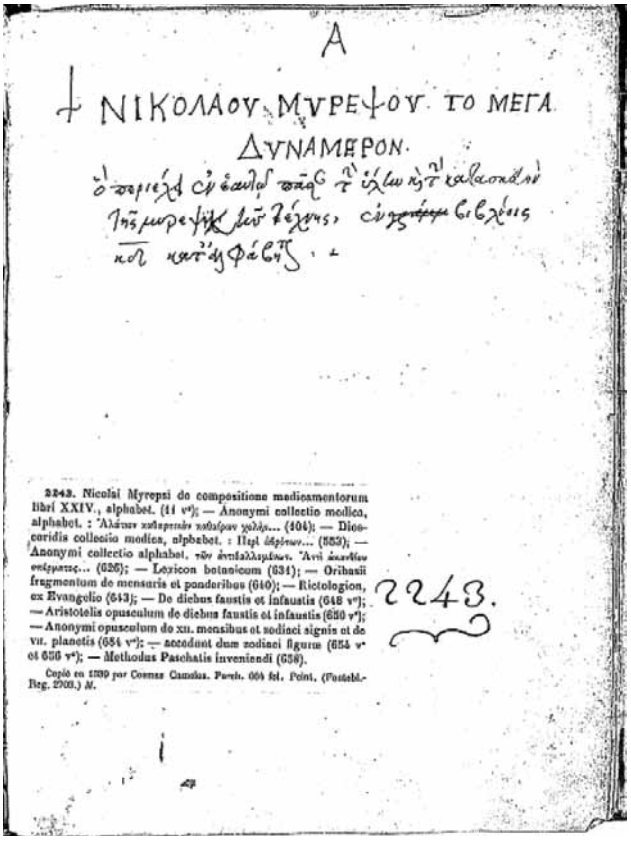

Figure 1. Paris code gr.2243, Nikolaos Myrepsos' *Mega Dynameron*.

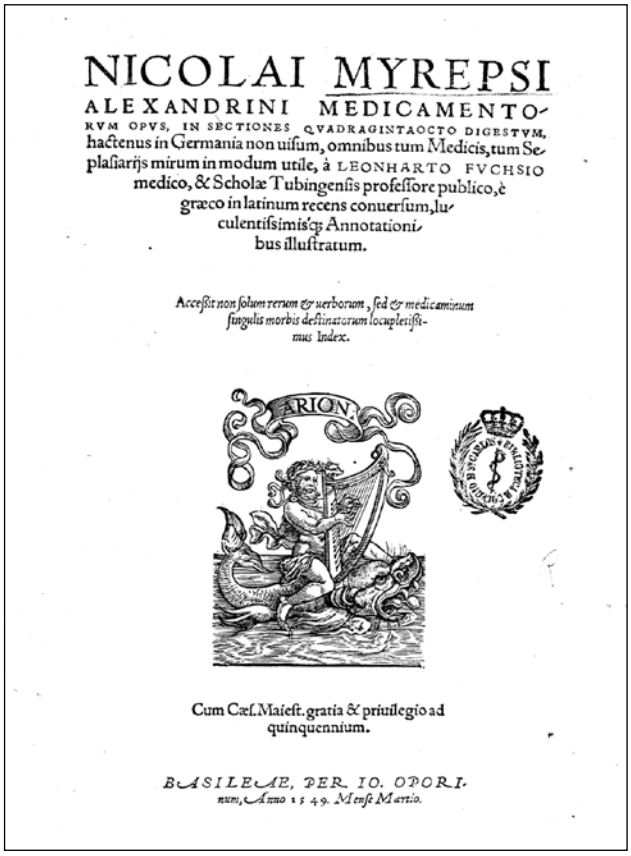

Figure 2. Nicolai Myrepsi Alexandrini Medicamentorum opus, by Fuchs Leonarht, Basileae, 1549.

is noted that Antonios Eparchos obtained this code, and, circa 1540, he sold it or donated it to the king of France Francis I, who in turn, donated it to the National Library of France in Paris, where it is still found.

The *Dynameron* became very well-known from its Latin translation, published by Leonhard Fuchs, professor of Medicine and Botanologist at the University of Tübingen, in 1549, and was titled "Medicamentorum Opus, Nicolai Myrepsi Alexandrini"[7] (fig. 2). The source text that Fuchs used seems to have been very close to the Paris Greek code gr.2243.5 The available codices clearly show that *Dynameron* was used as a reference book on drugs for a very long time.[5,6] From its Latin translation, we see that this text was of great importance and influenced later western pharmaceutical textbooks (Cordo (1546), Enchiridion (1564), Dispensatorium (1565).[6,10] It has been the reference book on drugs in Europe for two to three centuries after its publication.

In the *Dynameron*, Nikolaos Myrepsos recorded all up-to-then pharmaceutical knowledge. Based on older Greek, Latin and Arabic pharmaceutical textbooks and collections, he was influenced by his predecessor doctors or pharmacists, like Oribasius and Alexander of Tralles, as well as by the Antidotarium (magnus) of Nicholas from the Salerno Medical School.[6] The recipes include a great variety of ingredients, like plants, stones, animal or insect products. They are intended to treat all kind of diseases of the body.[8]

Many recipes in the *Mega Dynameron* concern renal and urinary bladder diseases in general. Some of these concern nephrolithiasis, urolithiasis and urinary bladder lithiasis. For the present study, we focused on recipes that clearly referred to the treatment of urinary bladder stones. This of course does not mean that other recipes concerning renal pathologies and nephrolithiasis or bladder inflammation in general could not have been effective for bladder lithiasis as well.

2. MATERIAL AND METHODS

We read the Latin translation of "Mega *Dynameron*" published by Leonhart Fuchs in Basel in 1549, available online at the Biblioteca Digital Dioscórides of Universidad Complutense of Madrid.[7] We also read the Greek publication of Paris code gr.2243, written in the 14th century and only recently edited and published for the first time in the original Greek language (Valiakos 2019).[6]

Through our study, we found that Nikolaos Myrepsos refers to

renal diseases in a substantial number of recipes in his work. From these, we separated recipes concerning urinary bladder stones (λίθοι κύστεως, vesica lapides/calculos). The recipes are intended for use in non-renal pathologies as well, and only a part of them are specifically for renal and urinary bladder lithiasis. In the following text, the recipe numbers are stated with Greek letters for the Paris code gr.2243, and with Latin numbers for the Fuchs (1549) edition.

3. RESULTS

"Antidotarium" or "About the Antidotes", in section alpha, includes about 90 recipes concerning renal diseases. From these, fewer than 40 recipes refer to urolithiasis (tab. 1) and only eight of them specifically to urine bladder stone treatment (tab. 2). Two of them are exclusively used for bladder lithiasis treatment (ν′/LI and νβ′/LIII), while recipes μα′/XLII and ρϟα′/CXCIII are used both for renal and bladder stones. The other four recipes (β′/II, λθ′/XL, πη′/XC and τιδ′/CCCXX) concern bladder stones, but they are also indicated for other diseases, like pulmonary, cardiac and gastrointestinal. The plants referred in the recipes were widespread in the Byzantine territory and were found throughout the eastern Mediterranean.

Interestingly, recipe number ν′/LI from Antidontarium is noted to have been used for the treatment of emperor Vespasianos, who lived in the 1st century AD. It includes nardos syriaci, hyssop and petroselini and is administered with water. «Νάρδος» or «ναρδοστάχην» or spikenard, is a flower plant of the Valerian family.[3,9] Its oil has been used since ancient times in medicine. It has diuretic and spasmolytic properties and many other therapeutic effects, such as antifungal, antimicrobial and antioxidant. «Ὑσσωπος» or hyssop, considered a gentle stimulant, is used in medicines, tonics, and alcoholic liqueurs. It is used as a spice due to its distinctive minty flavour. It is effective in urinary problems and in pulmonary, digestive and uterine diseases. It has antimicrobial, antioxidant and expectorant properties. «Πετροσέλινο» or "petroselini", commonly known as parsley («μαϊντανός» in Greek), is used as a diuretic, but it is said to also be useful for kidney stones, dysuria, cystitis and renal diseases. It is thought to have many pharmacological effects, including antioxidant, antibacterial, antifungal, anti-inflammatory, antidiabetic and spasmolytic properties.[3,9–11]

Table 1. Recipes referring to urolithiasis (kidney and or bladder stones) in Antidotarium.

α/I	ν/LI	ξα/LXII	σκθ/CCXXXIII
β/II	να/LII	πη/XC	σμ/CCXLIV
στ/VI	νβ/LIII	ροθ/CLXXXI	τ/CCCVI
λθ/XL	νγ/LIV	ρπε/CLXXXVII	τιδ/CCCXX
μ/XLI	νδ/LV	ρπη/CXC	τλζ/CCCXLIV
μα/XLII	νε/LVI	ρπθ/CXCI	τμθ/CCCLVI
μδ/XLV	νστ/LVII	ρϟα/CXCIII	τοα/CCCLXXVII
με/XLVI	νζ/LVIII	σκδ/CCXXVIII	τοζ/CCCLXXXIII
μστ/XLVII	νη/LIX	σκη/CCXXXII	υε/CDXI
μθ/L	ξ/LXI		

Table 2. Recipes referring to bladder stones in Antidotarium.

ν/LI	β/II
νβ/LIII	λθ/XL
μα/XLII	πη/XC
ρϟα/CXCIII	τιδ/CCCXX

Recipe νβ′/LIII is described as another remarkable cure for bladder stones. Amongst other ingredients, it includes «κασία»/"casiaea", «εύζωμο»/"eruca" and «σμύρνη»/"myrrhe" and is administered with honey. Casiaea [scientific name: *Cinnamomum aromaticum* or *Cassia Cinnamomum*] is an aromatic bark, similar to cinnamon, but differing in aromatic strength and quality. It has diuretic, analgesic, antipyretic, antiseptic and anti-allergic properties. «Εύζωμος» or "eruca" is the commonly known wild rocket («ρόκα» in Greek). Eruca sativa seed extract is considered to have anti-inflammatory and diuretic effects. «Σμύρνη» or "myrrhe" refers to Commiphora molmol or Commiphora myrrha and it has antiseptic, anti-inflammatory, antispasmodic and analgesic effects.[3,9–11]

Recipe μα′/XLII interestingly features the use of goat's blood and cicada, including detailed instructions for obtaining and processing them. It is suggested for renal diseases and people who suffer from stones and stranguria. It is also reported to be useful in dissolving bladder stones when used in hot baths («εν βαλανείω»). It is administered with honey and sugar. This recipe also refers to «άκορον» that is Acorus calamus or Calamus aromaticus, which has diuretic, spasmolytic, anti-inflammatory and analgesic properties. It also includes «Δαύκο κρητικό»/"daucus creticus", which is the commonly known carrot. It seems that carrots were very often used in kidney recipes and have an anti-oxidant effect.[9–11]

Recipe ρϟα′/CXCIII was used with sugar, honey or a combination of honey and wine and includes amongst else iris and pepper. «Ίριδα ιλλυρική» [scientific name: Iris illyrica] has antimicrobial, spasmolytic and anti-cancer properties. Pepper [«Πιπέρι λευκό, κοινό ή μακρύ» or «Piper nigrum, Piper album, Piper longum»] seems to have a diuretic and also a mild stimulant, antioxidant and anticancer effect.[3,9–11]

More recipes in Antidotarium refer to bladder lithiasis, but are indicated for other diseases as well. Of note, a couple of them refer to historical persons, such as recipe number 2 (β'/II), which is titled "antidote of Hadrian" and refers to the Roman Emperor who lived in the second century AD. Amongst other ingredients, it includes white pepper, cinnamomum, crocus, carrot and amomum. Moreover, recipe πη'/XC says that it was written by Peter the Apostole of the Lord for the health of all people and uses hyssop, iris, cinnamon and other ingredients.

Recipe λθ'/XL is indicated for bladder lithotripsy and as a laxative. It includes parsley, black pepper, cinnamomum, nard, white pepper and others. Interestingly, recipe τιδ'/CCCXX, indicated for kidney and bladder stone lithotripsy[6,7] and for pulmonary and abdominal diseases, includes ingredients from deer and elephant, as well as gold, pearl and silk in addition to plant ingredients.

More recipes for renal and bladder inflammation, lithiasis and colics are found in the *Dynameron* in the sections on salts (περί Αλατίων, index Salium), ointments (περὶ Ἀλειμμάτων, index unguentorum), patches (περὶ Ἐμπλάστρων, index emplastrorum), enemas (περὶ Ἐνεμάτων, index enematum), cathartics (περὶ Καθαρτικῶν ὑδραγώγων, index purgatoriorum), pills (περὶ Κοκκίων σκευασιῶν, index pilularum), pessaries (περὶ Πεσσῶν, index pessorum), pastilles (περὶ Τροχίσκων, index pastillorum) and others.

Amongst these, a couple of recipes refer more specifically to urinary bladder stones. Recipe number 23 (κγ'/XXIII) in Index Iexopyretorum («περί Ληξοπυρέτων») is indicated only for bladder stone treatment and includes pepper (common and long) and parsley, which we found in other recipes for bladder stones as well. Another one, in Index Salium («Περί Αλάτων» – About Salts), number 8 (η'/VIII), which is indicated for other diseases as well, includes parsley, hyssop, and celtic nard.

4. CONCLUSIONS

The *Dynameron* was likely written in the 13th century by Nikolaos Myrepsos and was later extensively copied and translated, influencing western medicine and pharmacology for centuries.

A substantial number of recipes in the *Dynameron* refer to renal diseases and some of them are specific to bladder lithiasis. Recipes include a rich variety of herbs, plants, vegetables and fruits, insects and animal products, as well as non-organic ingredients, like salts and stones. They are enhanced with detailed preparation instructions. Ingredients are mixed with the appropriate excipients, like honey, sugar, water, wine or chamomile, and are administered with specific doses and durations of treatment.

With his reference book on drugs "Mega *Dynameron*", Nikolaos Myrepsos disseminated invaluable knowledge on the treatment of lithiasis throughout the centuries, highlighting the importance of kidney function and uropathies. His book is a treasure trove for studying the different medicinal plants and their possible uses for the treatment of renal and other diseases nowadays.

It is a plentiful source of exploration that could highlight new pathways in disease treatment. We should remember that these recipes represent a pharmaceutical compendium of an entire era, used for centuries before modern pharmacology was established. Thus, there is much to learn from this documented experience of previous, medieval, scientists.

ΠΕΡΙΛΗΨΗ

Θεραπεία λιθίασης ουροδόχου κύστης στο «Μέγα *Δυναμερόν*»

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ΣΚΟΠΟΣ: Το Μέγα Δυναμερόν γράφτηκε πιθανότατα κατά τη διάρκεια του 13ου αιώνα από τον Νικόλαο Μυρεψό. Αποτελείται από 24 ενότητες που ακολουθούν τα 24 γράμματα του Ελληνικού αλφαβήτου και περιλαμβάνει περισσότερες από 2.600 φαρμακευτικές συνταγές. Το Δυναμερόν περιέχει κωδικοποιημένη τη γνώση στη Φαρμακολογία μέχρι την εποχή του. Αποτέλεσε το φαρμακευτικό βιβλίο αναφοράς στην Ευρώπη για περίπου τρεις αιώνες μετά τη δημοσίευσή του. Η παρούσα μελέτη είχε ως σκοπό να εστιάσει σε συνταγές για νεφρολιθιάσεις, και ειδικότερα για λιθιάσεις της ουροδόχου κύστης. **ΥΛΙΚΟ-ΜΕΘΟΔΟΣ:** Για τη μελέτη αυτή χρησιμοποιήθηκε η λατινική μετάφραση του

«Μέγα Δυναμερού», όπως εκδόθηκε από τον Leonhart Fuchs το 1549 στη Βασιλεία, η οποία είναι διαθέσιμη ηλεκτρονικά στην Ψηφιακή Βιβλιοθήκη Dioscórides του Πανεπιστημίου Complutense της Μαδρίτης, καθώς και την ελληνική έκδοση από τον Ηλία Βαλιάκο (2014 και 2019), που έχει βασιστεί στον κώδικα του Παρισιού gr.2243. **ΑΠΟΤΕΛΕΣΜΑΤΑ:** Το Δυναμερόν αναφέρεται σε νεφρικές παθήσεις σε ένα σημαντικό αριθμό συνταγών. Οι περισσότερες από αυτές προορίζονται για χρήση και σε μη νεφρολογικές παθήσεις, και μόνο ένα μέρος από αυτές είναι ειδικές για λιθιάσεις των νεφρών και της ουροδόχου κύστης. Το «Αντιδοτάριο» στην ενότητα «άλφα» περιλαμβάνει οκτώ συνταγές που αναφέρονται συγκεκριμένα στη διάλυση των κυστικών λίθων. Δύο από αυτές αφορούν αποκλειστικά τις κυστικές λιθιάσεις (ν'/LI and νβ'/LIII), ενώ η μα'/XLII και η ρϟα'/CXCIII χρησιμοποιούνται τόσο για λίθους νεφρών όσο και για λίθους ουροδόχου κύστης. Οι υπόλοιπες τέσσερις (β'/II, λθ'/XL, πη'/XC και τιδ'/CCCXX) ενδείκνυνται και για άλλες ασθένειες. Οι συνταγές περιλαμβάνουν μία πλούσια ποικιλία από βότανα, φυτά, λαχανικά και φρούτα, έντομα (π.χ. τζιτζίκια) και ζωικά προϊόντα (π.χ. αίμα τράγου), με αναλυτικές οδηγίες για την παρασκευή τους. Τα συστατικά αναμειγνύονταν με μέλι, ζάχαρη, νερό και κρασί ή χαμομήλι, και χορηγούνταν σε συγκεκριμένες δόσεις και διάρκεια θεραπείας. Περισσότερες συνταγές στο Δυναμερόν για τη φλεγμονή των νεφρών, τις λιθιάσεις και τους κωλικούς βρίσκουμε στις ενότητες για αλοιφές, επιθέματα, ενέματα, καθαρτικά, και άλλα, με ορισμένες πιο συγκεκριμένες συνταγές για τις κυστικές λιθιάσεις στο κεφάλαιο «περὶ Αλάτων»/"index Salium" (η'/VIII) και το «περὶ Ληξοπυρέτων»/"index Lexopyretorum" (κγ'/XXIII). **ΣΥΜΠΕΡΑΣΜΑΤΑ:** Ο Νικόλαος Μυρεψός με το φαρμακευτικό βιβλίο του «Μέγα Δυναμερόν» μεταλαμπάδευσε ανά τους αιώνες ανεκτίμητη γνώση για τη θεραπεία των ουρολιθιάσεων, τονίζοντας τη σημασία της νεφρικής λειτουργίας και των ουροπαθειών.

Λέξεις ευρετηρίου: Δυναμερόν, Λιθίαση ουροδόχου κύστης, Νικόλαος Μυρεψός

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ΒΟΤΑΝΟΛΟΓΙΚΗ ΘΕΡΑΠΕΙΑ

Ibn Al-Baitar
A 13th-century botanical scientist and his suggestions on urinary tract problems

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ΑΡΧΕΙΑ ΕΛΛΗΝΙΚΗΣ ΙΑΤΡΙΚΗΣ 2020, 37(Συμπλ 2):148–155

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Ibn Al-Baitar: Ένας επιστήμονας Βοτανολογίας του 13ου αιώνα και οι προτάσεις του για τα προβλήματα του ουροποιητικού συστήματος

Περίληψη στο τέλος του άρθρου

OBJECTIVE: **Ibn Al-Baitar was born in Malaga, Andalusia in the last quarter of the 12th century. He took botanical training in Andalusia and conducted extensive research in botanics, collected many drugs, vegetables, animal products, and introduced them to the medical world. He was recognised as the greatest botanical scientist and pharmacist of his time. 'Kitab Al-Jami Li-Mufradat Al-Adwiya Wa Al-Aghdhiya' is Ibn Al-Baitar's best-known work, acknowledged as the largest plant and drug book of the Middle Ages. It was published in Arabic in 1875, and translated into Latin, German, and French. To the best of our knowledge, so far drugs for urinary tract (UT) problems in Ibn Al-Baitar's work have not been reported in the literature. In this study, we summarised Ibn Al Baitar's suggestions for UT problems.** METHOD: **For this study, we examined one of the copies of Ibn Al Baitar's manuscript in the records of Turkey. This copy was published in Turkish by the Medical History and Ethics Department of the University of Health Sciences in 2017, and its original copy (written in 1573) is protected in the Hagia Sophia Collection in the İstanbul Süleymaniye Manuscripts Library (Library no: 3745). We identified the drugs that have an effect on the urinary system.** RESULTS: **In this book, the names of plants, animals and minerals used as medicines are classified alphabetically, and the manner of their preparation and use is described in detail. It has been found that almost 175 drugs were effective for UT, of which 150 were herbals. Their main effects were diuresis, treatment of UT infection, dissolving of urinary stones and analgesia.** CONCLUSIONS: **The majority of drugs reported in 'Kitab Al-Jami Li-Mufradat Al-Adwiya Wa Al-Aghdhiya' for UT are mixed-acting, and the product of vast experience and observations. Although modern medicine studies have demonstrated that they contain many active substances, it is hard to determine exactly which substance had a specific effect on the urinary system.**

Key words

Ibn Al Baitar
Kitab Al Cami
Urinary tract diseases in Andalusian medicine

1. INTRODUCTION

Ibn Al-Baitar was born in the city of Malaga, Andalusia in the last quarter of the 12th century. Ibn Baitar was his father's nickname; his original name was "*Ziyaeddin Abu Muhammad Abdullah bin Ahmed al-Andalus al-Maliki*". Since his father was a baitar (veterinary), he was interested in botany from an early age and hence called an "al-ashshab" (botanist). He was trained by Ibnur-Rumiyye on medicinal plants, their names and where they grew. He conducted extensive research together with his teacher in Seville. He travelled to different regions of Andalusia in his twenties, collected plant samples, was taught by famous pharmacists and did research on plants.[1–4]

In order to increase his knowledge and experience, he travelled across North Africa between the years 1220–1223, to Morocco, Tunisia, Algeria, and Tripoli. He came to Anatolia in 1223; he travelled to the northern Mediterranean coast and the Greek islands and then went to Alexandria. He became the chief botanist of the Egyptian Ayyubid sultanate. He conducted extensive research in botanics in the Middle East and trained many students in Cairo and Damascus. He died in Damascus in 1248. During his lifetime, he travelled to three continents and collected many vegetable, animal and mineral drugs and wrote an important book, "Kitab Al-Jami Li-Mufradat Al-Adwiya Wa Al-Aghdhiya". He was recognised as the greatest botanist of his time.[4,5]

Ibn Al-Baitar read the books of famous medical scholars

such as Dioscorides, Galen, Hippocrates, Ibn-i Sina, Ebubekir er-Razi, Gafiki and wrote commentaries on some of them. He also checked information about plants with observations and experiments and introduced many plants and medicines to medical literature. He also conducted research on animals and minerals.[4–6]

He produced seven works, the most famous being 'Kitab Al-Jami Li-Mufradat Al-Adwiya Wa Al-Aghdhiya'. In this, the names of plants, animals and minerals used as medicines are classified alphabetically, together with the methods used. This book is acknowledged as the largest plant and drug book of the Middle Ages, because it contains detailed descriptions of several medicinal plants, foods, and drugs together with their therapeutic values. It was written between 1242 and 1248 and presented to the Egyptian Ayyubid Sultan Melik Salih Necmeddin Eyyub.[4–6] This book was used in Europe until the 19th century. It was published in Arabic in 1875 and translated into Latin, German, and French.[1–6]

There are many publications in the literature explaining his works. To the best of our knowledge, so far drugs effective on UT mentioned in this book have not been reported.

2. MATERIAL AND METHOD

'Kitab Al-Jami Li-Mufradat Al-Adwiya Wa Al-Aghdhiya' was introduced into Ottoman Turkish in the 14th-15th centuries. The name of the translated book is 'Tercüme-i Müfredat-ı İbn-i Baytar'. This work was first translated from Arabic to Ottoman Turkish for "Gazi Umur Bey of Aydinogullari" (1334–1348), and called the "Tire" copy (Tire is an old town of İzmir, Turkey). After presenting this book to Umur Bey, 17 copies were produced by different copyists in the following years.[5] One of these 17 copies in records of Turkey is the copy in the Hagia Sophia Collection (Library No: 3745) that has not been translated into Turkish to date.[1,6] This copy was translated into Turkish by the University of Health Sciences (UHS) in 2017 (fig. 1). The translation team contributed to this book[1] by comparing the other five Ottoman Turkish copies and two Arabic copies especially based on the original book printing in Arabic in Beirut in 1992.[1,7]

Although its original Arabic form includes more than 1,400 drugs (animal products, vegetables, several minerals or stones), 200 herbal medicines have been identified for the first time in this book.[3–7] Since each of the translators made some selections and abbreviations in the number of drugs, there was a difference in numbers in the copies translated into Ottoman Turkish. There were 958 drugs numbered in the Arabic alphabet in the book translated by the UHS. We selected and introduced the drugs effective for UT.[1]

Figure 1. The first page of 'Tercüme-i Müfredat-ı İbn-i Baytar'.[1]

2. RESULTS

There were almost 175 drugs effective for UT, of which 150 were herbals. Their preparation and use are described in detail. The main effects of those drugs for UT were diuresis, dissolution of kidney and bladder stones, relieving kidney and bladder pain, prevention of urinary incontinence/retention, excretion of harmful substances, strengthening the kidneys/bladder, removing of bile damage from the kidneys and bladder, and treating oliguria-anuria.

We classified the effects of those drugs on the urinary system into four categories (tables 1–4).[1] Since the same drug may be placed in different tables because of its mixed effect, the total number of drugs seems to be increased (n: 215).

3.1. Diuretic drugs

We found that 125 drugs were possibly effective on diuresis; while 25 substances had single, the others had mixed effects on UT. Some of these drugs are shown in table 1.

3.2. Drugs effective for UT infections

In total, 23 substances had an anti-inflammatory effect, of which 9 had a single effect on UT (tab. 2).

Table 1. Diuretic drugs in the Ibn Al-Baitar's manuscript.[1]

Page	Drug name	Latin name/ingredients	Turkish name	Effect on urinary tract
22	ارمينين Arminun	Salvia horminum	Deve tabanı	Relief of urinary retention
23	Erak ارا ک	Salvadora persica	Misvak ağacı	Diuretic, clearance of bladder
29	Esel اسل	Juncus acutus	Kogalık	Diuretic
30	Istıragalis, اسطراغاليس	Astragalus L.	Tavşancıl toynağı-tırnağı	Diuretic
37	Aşhıs اشخيص	Atractylis gummifera	Sakız dikeni	Relief of urinary retention
37	Uşnan اشنان	Arthrocnemum glaucum	Çoğan, çöven otu	Relief of urinary retention
41	Agires, agirus اغيرس-agiros	Populus nigra	Kara kavak	Stimulates kidney, relieves urinary dripping
44	Afsentin افسنتين	A. absinthium	Pelin otu- acı pelin	Diuretic
46	Şarab-ı afsentin	Wormwood wine	Pelin otu şarabı	Diuretic, excretion of harmful substances
49	Akhuvan اقحوان	Anthemis cotula	Köpek Papatyası	Diuretic
56	اماريطن amaritun	H. stoechas	Altın çiçeği	Diuretic
59	incidan انجدان	Ferula assafoetida	Şeytan tersi	Stimulates kidney
59	Anisun انيسون	Pimpinella anisum	Anason	Diuretic, effective on kidneys
66	Unuberuhiş اونوبروخيش	O. viciefolia,	Yonca otu	Relieves urinary retention and dripping
67	Unumali انومالى	Honey and wine	Bal ve şarap	Diuretic
78	Badıncan باطنجان	S. melongena	Patlıcan	Diuretic
100	Balasan بلسان	C. opobalsamum	Belesan ağacı, balsam ağacı, Mekke pelesengi	Diuretic
102	Bellutu'l Arz	Teucrium chamaedrys	Yer peliti	Diuretic
119	Türmüs ترمس	Lupin	Termiye-ibn baytar Acı bakla-bedevian	Diuretic
123	Tilfaf تفاق	Sonchus oleraceus	Eşek marulu	Diuretic
143	Centayana جنطايانا	G. lutea	Centiyana	Diuretic
145	Cevz-i bevva (Cevz-i buva) جوز بوا	Myristica fragrans	Bayağı ceviz (ibn baytar) Küçük hindistan cevizi Besbase muskat	Diuretic

Table 1. (continued) Diuretic drugs in the Ibn Al-Baitar's manuscript.[1]

Page	Drug name	Latin name/ingredients	Turkish name	Effect on urinary tract
146	Haşa حاشا	Thymus capitatus	Kekik (koni başlı)	Diuretic
155	Harmel حرمل	Peganum harmala	Uzerlik	Diuretic
158	Harşef حرشف	Cynara scolymus	Kenger dibi	Diuretic
158	Hazazü's sahr حزاز الصخر	Usnea barbata	Taş kınası Çiçekli yosun	Diuretic
166	Hımmas حمص	Cicer arietinum	Nohut	Diuretic
175	Havr حور	P. pyramidalis	Kavak ağacı	Diuretic

Table 2. Drugs for urinary tract infections in the Ibn Al-Baitar's manuscript.[1]

Page	Drug name	Latin name	Turkish name	Effect on urinary tract
30	As آس	M. communis	Mersin	Improves bladder inflammation, diuretic Removes urine foam
134	Sil ثيل	A. repens	Ayruk otu	Recovery of bladder abscess Dissolving of urinary stones Relief of urinary retention, diuretic
162	Hulbe حلبه	Triganella foenum-graecum	Boy, çemen otu	Improves bladder cold Relief of urinary dripping
176	Hubbazi خبازى	Malva sylvestris	Ebegümeci	Improves bladder and kidney inflammation
193	Hulincan (havlıncan) خولنجان	Galanga officinarum	Havlıcan	Improves kidney cold
228	Rasan راسن	Inula helenium	Anduz, andız otu	Improves cold-related bladder malady diuretic, strengthens the bladder, removes harmful substances in blood via urine
254	Su'd سعد	Cyperus longus	Topalak	Improves cold-related bladder malady, diuretic, dissolving of bladder stones, stimulation of kidneys, prevention of urinary dripping
367	Nebiz نبيذ	Wine made from grapes, barley, wheat, honey and dates	Üzüm, arpa, buğday, bal ve hurmadan yapılan şarap	Relieves dysuria, diuretic, stimulates kidney and bladder, dissolves urinary stones, useful for kidney pains
388	Yeneste, yenestele ينيستاله	Equisetum arvense	Umsuh At kuyruğu	Improves kidney and bladder malady

3.3. Drugs effective for UT stones

In total, 40 substances were possibly effective for dissolving urinary tract stones, of which 15 had a single effect. Some of them are shown in table 3.

3.4. Analgesic drugs for the UT

In total, 27 analgesics were possibly effective for the UT; 13 were only analgesics while the others had mixed actions. Some of these are shown in table 4.

Table 3. Drugs effective on urinary tract stones in the Ibn Al-Baitar's manuscript.[1]

Page	Drug name	Latin name	Turkish name	Effect on urinary tract
6	İksar (aksar)	C. bulbocastanum conopodium denudatum	Hilal otu خلال	Dissolves kidney and bladder stones
9	Abanus آبنوس	L. ebenus-	Abanoz	Dissolves kidney stones
32	Şarabü'l as:	A kind of wine	Mersin şarabı	Diuretic Dissolves urinary stones
36	Uşne اشنه	Muscus arboreus	Yosun	Dissolves kidney and bladder stones
60	Encüre انجره	U. pillulifera	Isırgan	Dissolves kidney and bladder stones
70	Eyyil (üyyel, iyyel)	Alces alces	Sığın geyiği	Diuretic Dissolves bladder stones
72	Babunec بابونج	Chamomilla officinalis	Papatya	Diuretic, Dissolves urinary stones
92	Bıttih بطيخ	Citrillus vulgaris	Kavun kavun çekirdeği	Diuretic Dissolves bladder stones
94	Baklatü'l hamka بقله الحمقا	Portulaca oleracea	Tohmekan Semiz otu	Dissolves kidney and bladder stones Diuretic
139	Ceradü'l bahr	Cryfish	Kerevit, deniz çekirgesi	Dissolves kidney and bladder stones
148	Hacerü'l yehud	Israel olive	İsrail zeytini	Dissolves kidney and bladder stones
150	Hacerü'l isfenc	modo pumice	Sünger taşı	Dissolves kidney and bladder stones
152	Hacerü'l mesane	Human bladder stone	İnsan mesane taşı	Dissolves kidney and bladder stones
152	Hacerü'l hut	White stone in fish brain	Balık beyninde bulunan ak taş	Dissolves kidney and bladder stones
159	Hazenbel حرنبل	Myriophyllum verticillatum	Eğir kökü	Dissolves kidney and bladder stones
237	Zücac زجاج	Glass	Sırça (cam)	Dissolves bladder stones
257	Sukulufenderyun سقولوقندريون	Scolopendrium vulgare	Altun otu Talak otu	Dissolves kidney and bladder stones, prevents urinary dripping
259	Sekbinec سكبينج	Ferula szowitsiana	At kasnisi	Diuretic Dissolves kidney and bladder stones
265	Sümana سمانا	Quail (Coturnix coturnix)	bıldırcın	Diuretic Dissolves kidney and bladder stones
270	Sisenber	Thymus glaber	Marsama	Prevents urinary dripping, dissolves kidney and bladder stones
277	Şuniz شونيز	Nigella sativa	Çörek otu	Dissolves kidney and bladder stones
280	Şirruk (şirzak)	Bat feces	Yarasa dışkısı (idrarı)	Dissolves bladder stones
298	Akrep	Scorpion	Akrep	Dissolves kidney and bladder stones
311	Ferahu'l-himam Firahu'l-hamam	Pigeon cub	Güvercin yavrusu	Dissolves kidney and bladder stones
315	Kakule قاقوله	A cardamon	Kakule	Dissolves kidney stones
316	Kurretü'l-ayn قرتت العين	S. latifolium	Su kerevizi	Dissolves kidney stones, prevents urinary retention
326	Kebabe كبابه	P. cubeba	Kebebe, Hind biberi	Diuretic, clearance of urinary tract, Dissolves kidney and bladder stones
338	Lisanü'l asafur	Fraxinus exelsior	Kuş dili ağacı	Dissolves urinary stones, prevents urinary dripping
378	Heylun (helyun) هيلون	Asparagus officinalis	Kolan kuyruğu	Dissolves kidney and bladder stones Diuretic, stimulates kidneys and bladder

Table 4. Analgesic drugs for the urinary tract in the Ibn Al-Baitar's manuscript.[1]

Page	Drug name	Latin name	Turkish name	Effect on urinary tract
63	Anagalis اناغاليس	Anagyris foetida	Domuz dikeni, katır kuyruğu	Useful for kidney and groin pain
104	Benefşe بنفشه	V. odorata	Menekşe	Relieves kidney and bladder pain Diuretic
110	Binat-ı verdan بنات وردان	Cockroach	Düdül cerad Hamam böceği	Relieves kidney pain Diuretic
112	Bunyun بنيون	Bunium pumila	Kereviz	Relieves kidney and bladder pain Diuretic
151	Hacer-i ıraki		Bileği taşı	Relieves kidney pain
205	Dühnü'l merzencuş دهن المرزنجوش	Majorana hortensis	Merzencuş yağı Mercanköşk yağı	Relieves back pain and kidney pain
214	Dühnü'l hasek خسک	Tribulus terrestris	Demir dikeni yağı	Relieves back pain and kidney pain
214	Dühnü nüvari'l kundud (dühnü nevari'l kandul) نوار القندود	Tree in Jerusalem mountain	Kudüs dağı ağacı	Relieves bladder and kidney pain
216	Dühnü'l-levzi'l-mürr	P. amygdalus amara	Acı badem yağı	Relieves bladder and kidney pain prevents urinary retention dissolves kidney and bladder stones
217	Dühnü'l-levzi'l-hulv	P. amygdalus	Tatlı badem yağı	Relieves bladder and kidney pain prevents urinary retention
228	Ravend-i çini راوند	Rheum officinale	Ravend-i çini	Useful for kidney and bladder pain
261	seliha سلبيجه	Cinnamomum aromaticum	Yalan tarçını	Diuretic Useful for kidney pain
267	Semmur	Sable fur	Semmur	Fur coat wear is useful for kidney pain
267	Sünbül سنبل	Hyacinthus	Sünbül	Useful for kidney and bladder pain Diuretic
285	Suf	wool	Yün	Fur coat wear is useful for kidney and bladder pain
302	Unnab عناب	Ziziphus sativa	Hünnab	Useful for kidney and bladder pain
305	Garikun غاريقون	Polyporus officinalis	Katran köpüğü	Useful for kidney pain
308	Fucl فجل	Raphanus sativus	Turp	Useful for kidney and bladder pain Diuretic
310	Ferasiyün فراسيون	Marrubium alysson	Kavkaz	Useful for kidney pain
316	Kardamana قردمانه	Lagoecia cuminoides	Yaban kimyonu	Useful for kidney pain Prevents urinary retention
328	Kürras كراث	Allium porrum	Kendene Pırasa	Useful for bladder pain Diuretic,
367	Nebiz نبيذ	Wine made from grapes, barley, wheat, honey and dates	Üzüm, arpa, buğday, bal ve hurmadan yapılan şarap	Useful for kidney pain, diuretic, stimulates kidney and bladder, dissolves kidney and bladder stones, relieves dysuria
372	Nilüfer نيلوفر	Nymphaea lotus	Nilüfer çiçeği	Useful for bladder pain

4. DISCUSSION

'Kitab Al-Jami Li-Mufradat Al-Adwiya Wa Al-Aghdhiya' is Ibn Al-Baitar's best-known work, acknowledged as the largest plant and drug book of the Middle Ages. In this book, he examines almost 1,400 different drugs under 2,330 titles. The most cited authors are Dioscorides, Galen, Ibn Sina and al-Razi.[4–7]

In literature, there are several studies examining the works of Ibn Al-Baitar. These mention several drugs that can be used in treating different diseases, such as alopecia and leucorrhea, without explaining their active ingredients, herbal drugs used in the treatment of freckles and aphrodisiac formulas.[8–11]

Ibn Al-Baitar contributed greatly to the development of essential oils, particularly those used in therapies. He used a distillation method (using steam to remove oil from the plant) to obtain essential oils.[12]

To the best of our knowledge, so far drugs effective for the UT in Kitab Al-Jami have not been separately reported in the literature. We searched these drugs in this book.

Although most of these substances have mixed action, they are divided into 4 different groups, according to their main actions. Those with diuretic effects, those beneficial for UT infections, those dissolving urinary stones, and those useful in urinary system pain (analgesic drugs) (tables 1–4).

All of those drugs are the product of vast experience and observations. Modern medicine studies have demonstrated that they contain many active substances. However, it is hard to determine exactly which substance had a specific effect on the urinary system. All of them should be investigated pharmacologically with detailed laboratory studies. We hope that the active molecules of those substances, discovered by pharmacological research, can be introduced to the medical world as new therapeutic agents for UT problems.

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ΠΕΡΙΛΗΨΗ

Ibn Al-Baitar: Ένας επιστήμονας Βοτανολογίας του 13ου αιώνα και οι προτάσεις του για τα προβλήματα του ουροποιητικού συστήματος

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ΣΚΟΠΟΣ: Ο Ibn Al-Baitar γεννήθηκε στη Μάλαγα της Ανδαλουσίας το τελευταίο τέταρτο του 12ου αιώνα. Έλαβε βοτανική εκπαίδευση στην Ανδαλουσία και διεξήγαγε εκτεταμένες έρευνες στη βοτανική, συγκέντρωσε πολλά φάρμακα, λαχανικά, ζωικά προϊόντα και τα παρουσίασε στον ιατρικό κόσμο. Αναγνωρίστηκε ως ο μεγαλύτερος βοτανολόγος επιστήμονας και φαρμακοποιός της εποχής του. Το "Kitab Al-Jami Li-Mufradat Al-Adwiya Wa Al-Aghdhiya" είναι το πιο γνωστό έργο του Ibn Al-Baitar, αναγνωρισμένο ως το μεγαλύτερο βιβλίο φυτών και φαρμάκων του Μεσαίωνα. Εκδόθηκε στα Αραβικά το 1875 και μεταφράστηκε στα Λατινικά, τα Γερμανικά και τα Γαλλικά. Από όσο γνωρίζουμε, μέχρι στιγμής δεν έχουν αναφερθεί στη βιβλιογραφία τα φάρμακα για προβλήματα ουροφόρων οδών (UT) στο έργο του Ibn Al-Baitar. Στην παρούσα μελέτη, συνοψίσαμε τις προτάσεις του Ibn Al Baitar για προβλήματα των ουροφόρων οδών. **ΜΕΘΟΔΟΣ:** Για τη μελέτη αυτή, εξετάσαμε ένα από τα αντίγραφα του χειρόγραφου του Ibn Al Baitar στα αρχεία της Τουρκίας. Αυτό το αντίγραφο εκδόθηκε στα τουρκικά από το Τμήμα Ιατρικής Ιστορίας και Δεοντολογίας του Πανεπιστημίου Επιστημών Υγείας το 2017 και το πρωτότυπο αντίγραφό του (που γράφτηκε το 1573) φυλάσσεται στη συλλογή Αγία Σοφία στη Βιβλιοθήκη χειρογράφων İstanbul Süleymaniye (αρ. βιβλιοθήκης: 3745). Προσδιορίσαμε τα φάρμακα που έχουν επίδραση στο ουροποιητικό σύστημα. **ΑΠΟΤΕΛΕΣΜΑΤΑ:** Σε αυτό το βιβλίο, τα ονόματα των φυτών, των ζώων και των μεταλλικών στοιχείων που χρησιμοποιούνται ως φάρμακα ταξινομούνται αλφαβητικά και ο τρόπος παρασκευής και χρήσης τους περιγράφεται λεπτομερώς. Έχει βρεθεί ότι σχεδόν 175 φάρμακα ήταν αποτε-

λεσματικά για τις ουροφόρες οδούς, εκ των οποίων τα 150 ήταν βότανα. Οι κύριες επιδράσεις τους ήταν η διούρηση, η θεραπεία της λοίμωξης του ουροποιητικού συστήματος, η διάλυση των ουρολίθων και η αναλγησία. **ΣΥΜΠΕΡΑΣΜΑΤΑ:** Η πλειοψηφία των φαρμάκων που αναφέρονται στο "Kitab Al-Jami Li-Mufradat Al-Adwiya Wa Al-Aghdhiya" για τις ουροφόρες οδούς αποτελούν προϊόν μείξης και προϊόν τεράστιας εμπειρίας και παρατηρήσεων. Αν και οι μελέτες της σύγχρονης ιατρικής έχουν αποδείξει ότι περιέχουν πολλές δραστικές ουσίες, είναι δύσκολο να προσδιοριστεί με ακρίβεια ποια ουσία είχε συγκεκριμένο αποτέλεσμα στο ουροποιητικό σύστημα.

Λέξεις ευρετηρίου: Ibn Al Baitar, Kitab Al Cami, Παθήσεις του ουροποιητικού συστήματος στην Ανδαλουσιανική Ιατρική

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ΒΟΤΑΝΟΛΟΓΙΚΗ ΘΕΡΑΠΕΙΑ

The treatment of urinary diseases in Moroccan traditional pharmacopoeia
Elements of ethnology and historical epistemology

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ΑΡΧΕΙΑ ΕΛΛΗΝΙΚΗΣ ΙΑΤΡΙΚΗΣ 2020, 37(Συμπλ 2):156–165

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Η θεραπεία των νοσημάτων του ουροποιητικού στην παραδοσιακή φαρμακοποιία του Μαρόκου: Στοιχεία εθνολογίας και ιστορικής επιστημολογίας

Περίληψη στο τέλος του άρθρου

This work, based mainly on ethnobotany, contributes to the knowledge of the Moroccan pharmacopoeia concerning the treatment of urinary system diseases. Our approach, both synchronic and diachronic, seeks to highlight the historical anchoring of current traditional medical practices through a comparative study of recipes of the Moroccan traditional pharmacopoeia for urinary diseases and Arabic medical reference texts. I strive to show the persistence of historical medical knowledge in traditional medical practices, posing, in this sense, the fundamental question of the legitimacy of the presumed epistemological break between traditional medical knowledge and scholarly discourse.

Key words

Arabic historical medical knowledge
Ethnobotany
Moroccan pharmacopoeia
Urinary diseases Morocco

1. INTRODUCTION

Although it has been banished from the market-place in Morocco and deprived of its official status by modern medicine, traditional medical practice continues to serve many, and its prestige in the eyes of masses remains virtually undiminished.

It should be noted that one of the strengths of traditional medicine is that it is a practical art, well rooted in the local culture, and the relationship between the patient and the therapist is simple and close.[7]

Traditional medicine deals with all the ramifications of disease and approaches health as a necessary balance between physical, mental, emotional, moral and social well-being.

It would be wrong to underestimate the role of subjective factors in the survival of traditional medicine. These arise partly from the complete integration of traditional systems of care into the socio-cultural environment, which makes patients particularly receptive to them.

When we examine social behaviour in regard to illness, we see a number of different attitudes to traditional medicine. In the first place, there are the traditionalist and cultural positions, which are often experienced with anti-colonialism and exalt the prestigious past of Arab and Islamic civilisation, art and science. They refuse depersonalisation, and show a devotion to the arts and skills of Arab scholars. The confidence with which these attitudes are held is naturally strengthened with every error of modern medicine.

The major fault in this quarrel is that it sees the relationship between traditional and modern medicine as mutually exclusive and may even present an opposition between local and foreign medicine that does not exist. Although contemporary medicine has developed mainly in the West in recent times, since the development of medicine is closely bound with the development of technology, it must not be forgotten that many civilisations have contributed to the base of modern experimental medicine. It should not be seen as Western medicine but as universal medicine. Therefore, there is no part of the world where it can be considered foreign.

The second type of position, which is characteristically found in western countries but has also filtered through to the middle and upper classes in third-World counties, is critical of modern chemotherapy and advocates a return to natural therapy, as a reaction against the over-medicalisation of industrial societies. This tendency is in the mainstream of ecological thinking but unfortunately has some extreme views.

The third group of positions, which is much more eclec-

tic and less well organised and structured than the first two groups, is taken by those who have lost the faculty of critical judgment and who see traditional medicine only in terms of its irrational and mysterious aspect, with its supernatural and miraculous elements. These positions are very common at grass-roots level but are unfortunately being propagated in some intellectual circles as well. Anything that appears to be supernatural has a great hold on people's minds in this time of moral crisis in our societies. Hence the multiplicity of stories about the "miracles" performed by traditional practitioners. At the other end of scale, but equally eclectic, there are those who see only the irrational aspect of traditional medicine and therefore condemn it out of hand just as categorically as it has been exalted by their opponents.[7]

The purpose of this paper will be to emphasise the social and cultural relevance of traditional medicine in Morocco, especially in the rural areas. We try to highlight the role of knowledge transmission in preservation of old Moroccan medicine and the intangible heritage. Taking this into account, some examples of these traditional practices will be analysed, especially in urinary diseases.

Furthermore, this study aims at showing that these social and cultural practices are enacting the transmission of knowledge, especially in rural areas.

Another aspect that will be treated is the role of traditional actors in natural medicine in rural areas as main actors of practices linked to the production and transmission of these medical traditions. Some aspects of my approach will focus on certain practices of traditional Moroccan medicine by bringing back particular recipes, which have become increasingly rare, because of the disappearance of the modes of transmission maintained for generations.

All our data are based on anthropological and fieldwork conducted in some areas of Morocco in the last years. In Morocco, there is a paradox between cities and rural areas regarding access to medical care. However, remote areas are a good reservoir of ancestral medical knowledge and country people are a very important field of study for examining the persistence of ancient medical recipes.

How to explain this possible persistence; medical history or biogeographic and cultural determinism? To try to answer these questions we used an anthropological and epistemological approach: both synchronic and diachronic analyses.

The analysis of the nature of "traditional medicine" will go through an epistemological approach. Indeed, the legitimate way to analyse popular medicine is to refer it to its historical scientific sources, not to contemporary medical science.[13]

The fact that medicinal plants are used by people, especially in remote areas, to overcome medical problems, the material support, constituted by the vegetal drugs, is the most credible way to bring out tangible information on the history and culture of local society, which requires long-term ethnological and botanical work.

MATERIAL AND METHODS

To try to approach this problem, ethno-botanic studies and historical epistemology study (critical and comparative analysis of some Arabic reference books on kidney diseases) were carried out.

The ethno-botanical studies were carried out in three regions of Morocco: Sahara (especially Draa Vall ey), Rif Mountains and High Atlas Mountains. This ethno-botanical work is part of a research project on traditional medical knowledge in different regions of Morocco; general ethno-botanical work has already been carried out.[6,9,20]

The historical epistemology approach consists of a comparative study between bookish medical recipes and the traditional recipes of pharmacopoeia. The concept of historical epistemology that I use refers in its widest meaning to the long-term study of scientific developments.[10] It is important to follow the evolution of the remedies in time and then to compare the time-resistant remedies with those of the traditional Moroccan pharmacopoeia.

The books Studied are: *Treatise on stones in the kidneys and bladder* by Abu Bakr Al-Razi (Razes) (9, 10th century) analysed by Pieter de Koning,1896 (Frankfurt); *Canon of Avicenna* (Chapter about treatment of kidney stones) (10th century); Ninth section of the first part of the complete *Book on Medicine* named *the Royal book*, by Al-Madjusi (10th century); *Viaticum* of Ibn al-Jazzar of Kairouan (10th century); *Tayssir*: the book of simplification of Avenzoar (Andalusia) (11th century); *Book of the best in medicine*, by Mohaddab-addine Ibn-al-Habal (12th century).*

Umdat-attabib (Abu lkhayr al-Ichbili)** (12th century), Jamia Al-mufradat, treatise of simples (Ibn-al Baytar) (13th century); Hadiqat al-Azhar: the garden of flowers (Al wazir al-Ghassani) (16th century),

* The Kitab almukhtar (al-mukhtarat) fi l-tibb ("Selections on medicine") was written in Mosul in 560/1164–5. This is primarily based on the Kitab al-Qanun fi l-tibb of Ibn Sina (d. 428/1037), although he also cites other authors, including Hippocrates (fl. c. 450 B.C.E.), Galen (d. c. 216 C.E.), Masarjawayh (second-third/eighth-ninth centuries), al-Kindi (d. c. 256/870), and Ali b. al-Abbas al-Majusi (d.c. 384/994). This book is extant and has been edited twice; an important, though fragmentary, manuscript copy of it (MS Marsh 379, item 2, in the Bodleian Library, Oxford) was read and collated in the presence of Ibn Habal himself (Savage-Smith) (Alasdair Watson, Encyclopedia of Islam).

** Two books on medical botany, one by Al-Ichbili (Umdat A-ttabib) and the other by Alghassani (Hadiqat al -Azhar) have already been the subject of a botanical-historical analysis by Bammi (2012).5

Tuhfat al-ahbab: A work for loved ones (anonymous) (16th or 17th century), kachf arumuz (Ibn hamadouch al-jazaïri) (18th century).

Note that the authors selected for the study belong to two different cultural fields: Maghreb and Andalusia on the one hand (Ibn al-Jazzar, Avenzoar, Al-Ichbili, Ibn-al Baytar, Al-Ghassani, Ibn Hamadouch) and the East, especially Persia (Razes, Avicenna, Ibn-al-Habal, Al-Madjusi) on the other.

RESULTS AND DISCUSSION

Before presenting the main part of my results, I would like to stress that, despite the progress made by the Arabs in the field of experimental medicine, the contribution of Greek-Latin medicine in Arab medicine is obvious. The influence of Hippocrates and Galen's medicine on Arab authors is another subject though.

After analysing the selected historical books of medicine, the therapeutic protocol about kidney diseases is summarised in:

The prescription of: diuretics, drugs against kidney stones, Anti-inflammatory oral or in the form of friction. In case of pain, the prescription of narcotics, the use of sitz baths to fight inflammation, activate circulation and stop bleeding. In case of flatulence aggravating the pains, they associate diuretics and carminatives; the use of mucilage as emollients and against irritation of the urinary tract.

According to Razes, kidney calculi would be treated with baths, dietary restriction (particularly milk) and melon pips, Indian beans, and a pill made from burnt scorpions.

The same author, after bathing, rubs loins and hypochondria with chamomile oil or dill oil (*Anethum graveolens)* if there is violent irritation. "And when he is in the sitz bath give him what is diuretic and what breaks the kidney stone".[2]

The results of the historical epistemology study are summarised in the table 1.

The main innovation is that some remedies are considered, unanimously, as effective against renal diseases. Concerning diuretics, we noticed the predominance of species belonging to the *Cucurbitaceae* family (Melon, Cucumber, pumpkin) and the *Ombellifereae* family (Parsley, Celery, Cumin, caraway, Anise, Khella, carrot); these two botanical families dominate treatment.

Concerning kidney stones, we noticed the predominance of *Cucurbitaceae, Ombilleferae* and *Malvaceae* (Marshmallow, mauve).

Table 1. Treatment of urinary diseases, according to certain Arab-Muslim authors.

Treatments according to authors	Water retention	Kidney stones	Renal inflammation	Flatulence increasing pain
RAZES	Alfalfa, marshmallow, melon, cucumber	Bark caper root, celery, melon, cucumber, pumpkin seeds, flax-seed, marshmallow	Psyllium, violets, alfalfa, chamomile, flax-seeds, sesame	Rue, anise, dill, Khella, cumin, caraway, Nigella
(IBN SINA) AVICENNA	Fenugreek carrot Khella, fennel chaste tree seed	Alfalfa, marshmallow, cumin, Parsley, Celery, Henna root, Squill, cinnamon, cucumber, Quackgrass, Rue	Rose, chamomile, flaxseed, dill, marshmallow, carrot, liquorice	Rue, Celery, Khella, anise, caraway, Nigella
IBN AL-JAZZAR	Anise, Nigella, celery, pennyroyal, Mahleb	Melon, cucumber, pumpkin seeds, marshmallow, flaxseed, bark caper root, nigella, anise, Celery, marrube, cinnamon	Myrtle, rose, Tamarind, psyllium, marshmallow, flaxseed, fenugreek, bryone	
IBN AL-HABAL		Alfalfa, marshmallow, celery, cucumber, Quagrass, chaste tree root, cumin, fennel, Rue		
AVENZOAR	Melon, Cucumber, Carrot, Celery, Fennel roots, Asparagus	Nettle seeds, carrot seeds, Celery, melon seeds	Cucumber, chamomile, celery, rose, saffron, flax seeds, pyrethrum, liquorice	
IBN ALBAYTAR	Cucumber seeds, Southern maidenhair fern	Marshmallow	Mauve, Flaxseed chamomile, fenugreek	
Al-MADJUSI		Celery, fennel, pennyroyal, Khella Marshmallow, flax seed, Mauve, melon, cucumber	Bladder inflammation: caper, Khella, Pyrethrum, Nettle, fennel, Marrube, caste tree, Harmel	

Other remedies repeated by our authors belong to minority families, such as Flaxseed *(Linceae),* Almond *(Rosacea),* Caper *(Capparidaceae)*, Quackgrass *(Poaceae)*, Cinnamon *(Lauracea)* Asparagus *(Asparagaceae)*, Psyllium *(Plantaginaceae)*, Chamomile *(Asteraceae)*, Fenugreek, Alfalfa *(Fabaceae)*.

Note that great interest is placed in mucilage, as present, in large quantities, in the *Malvaceae* family.

Concerning the ethno-botanical study, some plants are used in traditional Moroccan pharmacopoeia according to the ancient theory of signature. For example, stinking wood *(Anagyris foetida)* whose kidney-shaped seeds are prescribed for kidney diseases and *Medicago sativa* seeds (Alfalfa), used against kidney inflammation.

Below, I present the results of the comparison of the recipes collected by the ethno-botanical study with those of traditional Arab medicine; for methodological reasons, I separated diuretic plants from plants used against kidney pathologies. The table 2 concerns diuretics.

We noted that 80% of diuretics used in traditional medicine are cited by ancient authors (especially from Maghreb and Andalusia). The remaining 20% are, in general, endemic or introduced plants.

Most plants considered as diuretics in traditional Moroccan medicine are cited by ancient authors, from Maghreb and Andalusia. Only some of these are also mentioned by oriental authors (Celery, parsley, cumin, anise).

Some recipes with a high cultural significance are worth noting: the young leaves of Borago officinalis (Borage) are specially used to prepare Khli'a Couscous broth (dried and salted meat). Given the large amounts of brine it contains, this dish is likely to cause water retention. This is why borage, whose diuretic properties are known, is added to the broth. In other Couscous recipes, borage is not usually used.[8] *Leptadenia pyrotechnica* (a Saharan plant not cited by ancient authors), is used by nomads; when they walk barefoot in the sun and the burning sensation in their feet extends to the navel to the point where they can no longer urinate, they drink a decoction made from this (tab. 3).

It is noted that, unlike diuretics, anti-lithiasis and anti-inflammatory plants are cited for the same effects, by both oriental authors and western authors (Maghreb and Andalusia). It is plausible that this indicates that, for severe pathologies, they rely on medical history, while for diuretics, it is rather local experience that is decisive.

Note that some plants used against kidney disease are not mentioned in historical books: *Herniaria hirsuta*, Chestnut, Eucalyptus, Corn (styles), Prickly pear (flowers), *Juncus maritimus*. The introduction of these plants into the pharmacopoeia has given rise to new recipes where old plants and new plants are mixed. This, in our view, represents a form of renovation in traditional treatments.

As an example, we present an anti-inflammatory mixture against kidney diseases in the Moroccan pharmacopeia, which contains: Chestnut, Eucalyptus leaves, Corn styles, Prickly pear flowers, Pennyroyal *(Mentha pulegium)*, Lavender, Indian nard, Rye seeds, Chamomile, Quackgrass and Juncus.

Table 2. Comparison between recipes collected by the ethno-botanical study and those of traditional Arab medicine (diuretics).

Diuretic plants in Moroccan pharmacopeia	Historical use (cited as diuretic by)	Diuretic plants in Moroccan pharmacopeia	Historical use (cited as diuretic by)
Celery	All authors	Lentisk	All Maghreban and Andalusian authors
Absinthe	All authors	Purple viper's-bugloss	Only by Ibn Al-Baytar
Parsley	All Maghreban and Andalusian authors and Avicenna	Field eryngo and Holly-leaved eryngo	All Maghreban and Andalusian authors
Red Bryony	Ibn Al-Jazzar as anti-inflammatory	Squill	All authors
Mediterranean Heath	Ibn Al-baytar and Al-*Ichbili*	Globe artichoke	All Maghreban and Andalusian authors
Caraway	All authors only as carminative	Borage	All Maghreban and Andalusian authors
Sarghina	All Maghreban and Andalusian authors, not by oriental authors	Statice	Not cited
Alfalfa dodder	All Maghreban and Andalusian authors	Silvery paronychia	Not cited
Anise	All Maghreban and Andalusian authors, Avicenna and RAZES	Broom Brush	Not cited
Black pepper	All Maghreban and Andalusian authors	Bouhmama's cauliflower	Not cited
Camel grass	All Maghreban and Andalusian authors	Hibiscus sabdariffa	Not cited

Table 3. Comparison between recipes collected by the ethno-botanical study and those of scientific Arab medicine (kidney diseases).

Medicinal plant	Therapeutic use	Historical use (cited by)
Celery	Anti-inflammatory	Panacea for all authors (in the occident and orient)
Mediterranean Heath	Urinary antiseptic	IBN Al-Baytar and AL-Ichbili
hairy rupture-wort	Kidney stones	Not cited
Onion	Dropsy, water retention; urination disorders, bladder diseases, with seeds of Radish, carrot and parsley	All Maghreban and Andalusian authors
Jujube	Urinary antiseptic, cystitis	All Maghreban and Andalusian authors
Lesser galangal	In decoction, against renal inflammations	All Maghreban and Andalusian authors except Ibn Hamadouch
Marshmallow	Decoction of roots to calm painful urination	Panacea usually used in kidney diseases
Khella	Decoction against kidney and bladder pain, antispasmodic	Used by Razes, Madjusi and Ibn AL-Habal
Asparagus	Unblocks all obstructions and facilitates secretions, used against syphilis and gonorrhoea	All authors
English lavender	Urinary antiseptic	Used by ancient physicians as anti-inflammatory
Psyllium	Inflammation of the kidneys, bladder and urinary tract	All Maghreban, Andalusian authors and Razes
Olibanum	Kidney stones, cystitis and oliguria	Maghreban and Andalusian authors
Roman nettle	Kidney stones, cystitis and oliguria	Maghreban and Andalusian authors
Opium poppy	Cystitis	Maghreban and Andalusian authors
Harmel	With Nigella, cumin, garlic, rance butter and honey (Kidney stones)	Avicenna and Ibn AL-Habal (Kidney stones)
Carrot (seeds)	Renal colic, oliguria	Panacea against kidney stones
Savory	Painful urination	Ibn Al-Baytar and Ibn Hamadouch
Bermuda grass and couch grass	Rhizome against kidney stones and urinary disorders	Maghreban and Andalusian authors
Sea urchin spurge and Resin Spurge	Cooling and affections of a kidney	Ibn Al-Baytar and Ibn Hamadouch
Barley	Against vesico-urinary irritations and against gonorrhoea	All authors
White henbane and black henbane	Low dose, sedative and antispasmodic in bladder pain	All authors as narcotic
Fringed lavender	Kidney stones	Only Tuhfat Al-Ahbab
Tailed pepper	Antiseptic in the treatment of urinary and bladder diseases	Maghreban and Andalusian authors
Capper	At Tissint, the dried root, reduced to powder is mixed with honey, is used against gonorrhoea, as diuretic	IBN al-Jazzar, Razes

3.1. Transmission of knowledge

3.1.1. The potential scientific base of traditional medical practice in Morocco. The remoteness of rural areas from official health centres helps traditional medicine in retaining a certain following, always represented locally by a practitioner, even if he sometimes earns his living in another occupation. The sedentary and urban-centred nature of modern medicine is thus a factor that militates in favour of traditional practitioners.

Care is very often given in patients' homes. The best-known example is that of traditional birth attendants who look after mothers in their own homes, but there are also many *fuqaha* who are willing to visit their patients on their sickbeds, wherever they may be.

Moreover, traditional therapy remains overall a "soft" type of medicine, using treatments that are mainly oral or topical and very rarely drawing blood. The medicinal herbs are used in decoctions, oleates, sugary pastes etc. in which the active principle is greatly diluted so that its effects are spread out over time, thus avoiding therapeutic shock. Progressive dosage is always the rule, which makes for easier surveillance of treatment. Moroccan pharmacopoeia only contains few dangerous products, and all of them are familiar to people in rural areas.

The materials for traditional medications were local plants, as well as exotic plants supplied by herbalists during the weekly rural souks.

The Faqihs, in mosques, having Arabic medicine books, contribute to perpetuating medical knowledge and to relieving the pains of people in the village.

How has this ancestral scientific knowledge reached remote areas in the mountains; how did this bookish knowledge come to them?

Al-Qaraouyine University in Fez –and the Fez schools that were annexes of the University– was, since the 13th century, a scientific centre attracting scholars –from all fields– who came from all over Morocco and from outside the country to complete their academic studies. On returning to their villages, they carried with them knowledge, which they passed on to others interested in science, but they also carried books with them. These books became private property or were placed in libraries, especially in the zaouïas, which provided religious, social and educational functions. Over time, this bookish medical knowledge has been transformed into popular knowledge, distorted certainly in its purely academic aspects, but keeping the essence of the recipes in their natural form.

Pilgrimages also contribute to the spread of medical knowledge, The Senegalese of the Tijania brotherhood, who come to the pilgrimage to Fez, often bring back to Morocco dried calices of *Hibiscus sabdariffa*, with a diuretic and urinary antiseptic effect, to offer to their guests.[8]

4. CONCLUSIONS

Without natural medicines, these mountain people would be in a dismal situation. However, economic aspects alone do not justify the use of medicinal plants. Indeed, ancient remedies help fight the ills of people in remote areas, who also benefit from science-proven remedies. The country people, especially in remote areas, benefit older scientists more than contemporary scholars.

Modern phytotherapy has drawn a lot and still draws from ancestral therapeutic heritage. This therapeutic continuity deserves to be studied and medicine from nature deserves to be re-examined. Traditional medicine is still popular in Morocco since it is an important form of healthcare for many. Its positive aspects could be encouraged if it were officially recognised and given a place in the health system. In Morocco today a new attitude is developing with regard to traditional medicine, and this can be seen particularly in *the emphasis now being placed on research into the history of Arab medicine and the pharmaco-chemistry of the medicinal plants commonly used by the people*. This new attitude has led to a more objective approach to traditional medicine in Morocco so that it is now possible to contemplate involving all facets of the country's potential –human, intellectual and material, modern and traditional– in developing a public health policy founded on improved management and optimum utilisation of the country's resources and efforts. This means recognition of the past and present accomplishments of the people in caring for the sick and in controlling disease.[7]

If we examine modern herbal medicine in its most credible sources, we find that several plants used in Arab and Greco-Latin medicine are successfully used in contemporary natural medicine:

Erica and Calluna, containing Arbutin, are very efficient urinary antiseptics; Quack-grass root, containing Agropyrene, potassium, silice, malic acid, Inositol, has a high antibiotic effect. *Plantago psyllium*, rich in mucilage, has an anti-inflammatory effect; marshmallow, rich in mucilage has anti-inflammatory and emollient effects; Borage, containing mucilage and potassium, is highly diuretic; corn style and Hibiscus are highly diuretic while Pumpkin seed oil is used against prostate hypertrophy. This encourages us to reframe traditional medicine and integrate it further into the public health system.

Public health officials must not lose sight of the vital importance of using the material and human resources available in the country, be they traditional or modern, to achieve optimum management of their own potential and thus improve the provision of public health.

Indeed, there is no foreseeable hope of extending health coverage in many countries today unless we adopt unorthodox measures such as the involvement of traditional practitioners and the use of medicines based on local plants, especially in rural and remote areas.

However, all this should not discourage attempts to involve traditional medicine in basic health care coverage in the framework of a pragmatic health policy. It will require a careful and critical analysis of the situation prevailing in the sector so that unverified assumptions can be discarded, but, at the same time, *any prejudice against traditional medicine must also be set aside. Only then will it be possible to attain the impartiality that is necessary to achieve the best in public health and to draw on all the resources of the nation, human and material, traditional and modern, for the greater benefit of underserved populations.*

Finally, the idea of considering the opposition between "scientific medicine" based on causality and laws and "traditional medicine" based on direct and limited experience deserves to be re-questioned.

ΠΕΡΙΛΗΨΗ

Η θεραπεία των νοσημάτων του ουροποιητικού στην παραδοσιακή φαρμακοποιία του Μαρόκου: Στοιχεία εθνολογίας και ιστορικής επιστημολογίας

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Το έργο αυτό, που βασίζεται κυρίως στην εθνοβοτανική, συμβάλλει στη γνώση της φαρμακοποιίας του Μαρόκου σχετικά με τη θεραπεία των ασθενειών του ουροποιητικού συστήματος. Η προσέγγισή μας, τόσο συγχρονική όσο και διαχρονική, επιδιώκει να τονίσει την ιστορική αγκύρωση των σημερινών παραδοσιακών ιατρικών πρακτικών μέσω μιας συγκριτικής μελέτης των συνταγών της μαροκινής παραδοσιακής φαρμακοποιίας για τις ουρολογικές ασθένειες και τα κείμενα ιατρικής αναφοράς της Αραβικής. Προσπαθώ να δείξω τη διαχρονικότητα της ιστορικής ιατρικής γνώσης στις παραδοσιακές ιατρικές πρακτικές, θέτοντας, υπό αυτή την έννοια, το θεμελιώδες ζήτημα της εγκυρότητας του υποτιθέμενου επιστημολογικού διαχωρισμού μεταξύ της παραδοσιακής ιατρικής γνώσης και του επιστημονικού λόγου.

Λέξεις ευρετηρίου: Αραβικές ιστορικές ιατρικές γνώσεις, Ασθένειες των ουροφόρων οδών του Μαρόκου, Εθνοβοτανική, Φαρμακοποιία του Μαρόκου

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Appendix 1. Scientific names of the plants mentioned.

Absinthe: *Artemisia absinthium*
Alfalfa: Medicago sativa
Alfalfa dodder: Cuscuta epithymum
Anise: Pimpinella anisum
Asparagus: Asparagus officinalis
Barley: Hordeum vulgare
Bermuda grass: Cynodon dactylon
Black henbane: Hyoscyamus niger
Black pepper: Piper nigrum
Borage: Borago officinalis
Bouhmama's cauliflower: Fredolia aretioides
Broom Brush: Leptadenia pyrotechnica
Camel grass: Cymbopogon schoenanthus
Caper: Capparis spinosa
Caraway: Carum carvi
Carrot: Daucus carota
Celery: Apium graveolens
Chamomile: Matricaria camomilla
Chaste tree: Vitex agnus-Castus
Cinnamon: Cinnamomum zeylanicum
Common rue: Ruta graveolens
Cucumber: Cucumis sativus
Cumin: Cyminum Cuminum
Dill: Anethum graveolens
English lavender: Lavandula vera
Fennel: Foeniculum vulgare
Fenugreek: Trigonella foenum-graecum
Field eryngo: Eryngium campestre
Flax-seed: Linum usitatissimum
Fringed lavender: Lavandula dentata
Globe artichoke: Cynara scolymus
Hairy rupturewort: Herniaria hirsuta
Harmel: Peganum harmala
Heartsease: Viola tricolor
Henna: Lasonia inermis
Holly-leaved eryngo: Eryngium ilicifolium
Jujube: Ziziphus lotus
Jujube: Ziziphus vulgaris
Khella: Ammi visnaga
Lentisk: Pistacia lentiscus
Lesser galangal: Alpinia officinarum
Liquorice: Chicorium intybus
Mahleb: Prunus mahaleb
Marrube: Marrubium vulgare
Marshmallow: Althea officinalis
Mauve: Malva sylvestris
Mediterranean Heath: Erica multiflora
Melon: Cucumis melo
Myrtle: Myrtus communis
Nettle: Urtica dioïca
Nigella: Nigella sativa
Olibanum: Boswellia carterii
Onion: *Allium cepa*
Opium poppy: Papaver somniferum
Parsley: Petroselinum sativum
Pennyroyal: Mentha pulegium
Psyllium: Plantago psyllium
Pumpkin: Cucurbita pepo
Purple viper's-bugloss: Echium plantagineum
Pyrethrum: Anacyclus pyrethrum
Quackgrass: Agrophyrum rupens
Red Bryony: Bryonia dioïca
Resin Spurge: Euphorbia resinifera
Roman nettle: Urtica pilulifera
Rose: Rosa damascena
Roselle: Hibiscus sabdariffa
Saffron: Crocus sativus
Sarghina: Corrigiola telephiifolia
Savory: Satureja calamintha
Sea urchin spurge: Euphorbia echinus
Sesame: Sesamum indicum
Silvery paronychia: Paronychia argentea
Southern maidenhair fern: Adianthum Capillus-veneris
Squill: Drimia maritima
Statice: Limonium bonduelli
Tailed pepper: Piper cubeba
Tamarind:Tamarindus indica
White henbane: *Hyoscyamus albus*

Appendix 2. Photos.

Old man harvesting a medicinal plant for self-medication in the Talouat region (Western High Atlas).

Talouat village, one among the study areas (Western High Atlas).

The author during the ethno-botanical investigation in the Laâyoune region (Atlantic Sahara).

Leptadenia pyrotechnica (not cited by ancient authors).

Fredolia aretoïdes (not cited by ancient authors).

Euphorbia echinus in Tata region (endemic plant of south Morocco).

Paronychia argentea (not cited by ancient authors).

Capparis spinosa in Tissint oasis (South Morocco).

Medicago sativa seeds and Anagyris foetida seeds (kidney-shaped).

Limonium bonduelli (not cited by ancient authors).

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CLINICAL CASE
ΚΛΙΝΙΚΗ ΠΕΡΙΠΤΩΣΗ

Research on the kidney and hair loss based on ancient Chinese medical literature

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ΑΡΧΕΙΑ ΕΛΛΗΝΙΚΗΣ ΙΑΤΡΙΚΗΣ 2020, 37(Συμπλ 2):166–170

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Huang Di Nei Jing (Inner Canon of the Yellow Emperor) embodies the fundamental view of the human body in the Chinese medical system. Its important concepts are based on the interpretation of the natural rhythms and human physiology. In the book's first part of *Su Wen* (Plain Questions), it is underlined that the kidney governs growth in general and stores the essence (*jing*), with hair being its external manifestation. According to the text, kidney qi is associated with the production and growth of hair, as well as their diseases, like hair loss or greying. With the kidney association in mind, over 400 Chinese medical books were investigated to collect the materia medica and formulas recommended for the treatment of hair loss created by the Chinese physicians of the past. This huge volume of information was categorised in three groups, according to the historical periods and their simple and compound drugs were compared, to create a list with possible candidates for future research. Indeed, a scholastic review of these texts from the past dynasties revealed an enormous wealth of ideas on hair disease pathogenesis and the formulas for its treatment. Several of these methods for nourishing the hair seem to have scientific and practical value.

Έρευνα όσον αφορά στα νεφρά και την απώλεια μαλλιών με βάση την αρχαία κινεζική ιατρική βιβλιογραφία

Περίληψη στο τέλος του άρθρου

Key words

Chinese ancient medicine
Hair loss
Inner Canon of the Yellow Emperor
Kidneys' qi
Su Wen

1. INTRODUCTION

Hair loss is a symptom of common skin diseases, like alopecia seborrheica and alopecia areata. The first one is also known as male pattern hair loss or androgenetic alopecia, with increased seborrhoea, dandruff, hair dryness and pruritus, while alopecia areata usually has a sudden onset, with severe hair loss and normal skin. In severe cases, it develops to alopecia totalis (total hair loss of the skull) or alopecia universalis (total loss of body hair).

Based on the records of ancient Chinese medical texts, this article systematically summarises the information on hair loss (*fa luo* or *fa duo*) and body hair loss (*mao luo*) which include withered skin, alopecia areata, hair loss and reduced growth (*fa tuo bu zhang*), loss of hair and eyebrows, glossy scalp wind (*you feng*) etc. Through time, people's understanding of hair loss became more elaborate, driving to a deeper analysis of its pathogenesis. In Sui, Tang and later dynasties, new terms appeared, suggesting that hair loss could also be associated with "wind" (*feng*) pathology (e.g. "ghost licking hair", "head wind white scaling", "white scaling and wind itching").

2. UNDERSTANDING OF HAIR PHYSIOLOGY IN ANCIENT CHINESE MEDICAL LITERATURE

The pathology of hair in Chinese medicine is based on its physiology and more specifically on the concepts of the eight principles (yin-yang, hot-cold, external-internal and excess-deficiency), the five zang-six fu organs, correlated with the five elements (*wu xing*), as well as the six level theory (*taiyang*, *yangming*, *shaoyang*, *taiyin*, *shaoyin*, *jueyin*). In the classical medical texts, there are many references explaining the mechanism of hair growth and consequently their possible ailments. The most important remarks include the following:

- The kidney stores the essence (*jing*) and transforms it to blood (*xue*). This essence is the root of the body.[1]

- The hairs are considered the surplus of blood. Their condition (colour, shape, growth, texture and density) is related to the condition of the brain and marrow that depend on the kidney essence.[2,3] This is why excessive seminal emission will lead to hair loss and consumptive diseases.[1]
- The body hair, including the eyebrows, beard etc., reflect the internal condition of the human body. There is a further distinction between hairs in various body parts.[4] The hair on the head is an expression of the heart and the element of fire; the eyebrows are related to the liver and the element of wood, while the beard depicts the condition of the kidneys and the element of water. In some of the texts, the eyebrows are also related to the lung (metal element), while the beard can also be associated with the gall bladder (wood element).[5]
- Blood is associated with the essence of water and grains; it is produced and transformed in the spleen. Since blood is controlled by the heart, stored in the liver, distributed by the lungs and drained by the kidneys to nourish the whole body, the body hair are actually related to all the zang organs.
- The chong mai and ren mai extraordinary meridians are both associated with the beard, since they reach the upper lip. In Chinese medicine, the eight extraordinary meridians are considered to circulate the essence.

2.1. Treatment

In Chinese medical classics, the treatment of hair ailments in general was a sign of expertise among physicians. The condition of the hair could also be used by a skilled physician for correct diagnosis and prognosis.[6] The main syndromes causing hair problems are kidney qi deficiency and kidney essence deficiency. Other syndromes include pathogenic wind, due to blood heat, deficiency or stasis, but since they are not directly connected to the kidney, they are not going to be examined here.

2.1.1. Kidney qi deficiency. The kidney qi is the general expression of the kidney's strength and ability to fulfil its function. Especially important for the understanding of this concept is the primordial qi (*yuan qi*), part of which is inherited by the parents. The Chinese herbal pharmacopoeia includes several natural substances that are considered kidney qi tonics, usually included in the categories of herbs that tonify the qi (e.g. *shan yao*, root of *Dioscorea opposita* Thunb.), nourish the blood (e.g. *shu di huang*, root of *Rehmannia glutinosa* (Gaertn.) Steud.), tonify the kidney yang (e.g. *lu rong*, Cornu Cervi Parvum) or nourish the kidney yin (e.g. *nu zhen zi*, the fruit of *Ligustrum lucidum* W. T. Aiton). Chinese herbal formularies include several interesting prescriptions in the categories of nourishing the yin and tonifying the yang. Examples of formulas in the first category are the *Zuo gui yin* (Restore the left kidney decoction), for kidney yin deficiency and most importantly the *Qi bao mei ran dan* (Seven-treasure special pill for beautiful whiskers), mentioned for the first time in the *Yi Fang Ji Jie* (Analytic Collection of Medical Formulas), by Ang Wang (1615-1694), and used primarily for treating premature greying of the hair, through nourishing the kidney yin and liver blood. This formula includes *he shou wu* (root of *Polygonum multiflorum* Thunb.) probably the most famous Chinese herb for restoring hair vitality.

2.1.2. Kidney essence deficiency. The essence deficiency presents the symptoms and signs of diseases of the five zang and six fu organs, resulting in exhaustion of the body, with blurred vision, withered teeth and hair loss.[7] There are two major categories of suitable substances in Chinese materia medica: herbs nourishing the essence and those that stabilise and bind (styptic action). Some, like *yi zhi ren* (the fruit of *Alpinia oxyphylla* Miq.) have both properties, warming the kidney and retaining the essence, being particularly useful for spermatorrhea or urinary incontinence. For example in *Jin Gui Yao Lue* (Synopsis of Prescriptions of the Golden Chamber), it is mentioned that the *Gui zhi jia long gu mu li tang* (Cinnamon Twig Decoction, with Dragon Bone and Oyster Shell) could be used to treat hair loss due to seminal loss.

Some formulas can be used for either category. For example in the *Wai Tai Mi Yao* (Medical Secrets from the Royal Library), the formula *Zhu shi ren shen wan* (Shen Shi's Ginseng Pill) is used to treat hair loss caused by kidney qi deficiency, failure to store the essence or seminal loss, due to consumptive diseases.

According to the records of ancient texts, as well as the *Zhong Yao Da Ci Dian* (Great Dictionary of Chinese Medicine), there are 24 herbs that can be used for hair growth, belonging to several categories: regulating qi and blood, clearing heat, eliminating dampness and warming the interior. According to the different types of hair loss, the herbs can be categorised as tonics, diaphoretics, qi and blood regulating, clearing the heart, eliminating dampness and warming the interior. Half of them (12 herbs), enter the kidney meridian, which affirms the importance of this organ in treating hair loss.

Actually, the records of formulas for hair loss in the ancient texts are scattered, with many repetitions. More than 400 books, from various historical periods, were in-

Table 1. The most regularly found herbs in the texts of the three historical periods of Chinese medicine.

Period		266–907	960–1368		1368–1911		Total
Herbs		No of formulas	No of formulas		No of formulas		
		External	External	Internal	External	Internal	
Chinese terms	**Binomial name and plant part**						
Bai zhi	Angelica dahurica (Fisch. ex Hoffm.) Benth & Hook (root)	17	11		31		59
Fang feng	Saposhnilcovia divaricata (Turcz.) Schischk. (root)	15	8		33		56
Sesame oil	Sesamum indicum L. (seed)	15	16		42		73
Man jing zi	Vitis trifolia L. (fruit)	14	17		43		74
Fu zi	Aconitum carmichaeli Debx. (prepared lateral root)	14	13	6	25	12	70
Song ye	Pinus spp. (leaf)	10	7		20		37
Xin yi	Magnolia spp. (flower)	10	5		19		34
Sheng Lou Le	Ocimum tenuiflorum L. (herb)	9	11		27		47
Chuan xiong	Ligusticum wallichii Franch [syn. L. chuanxiong Hort.] (root)	8	7		18	15	48
Ce bai zhi jie	Platycladus orientalis (L.) Franco [syn. Thuja orientalis L.] (twig)	8			25		33
almond	Prunus dulcis (Mill.) D.A. Webb (seed)	5					5
Sheng ma	Cimicifuga foetida L. (rhizome)	4					4
Gao gui chun huang ju	Chamaemelum nobile (L.) All. (flower)		5				5
Huā jiāo	Zanthoxylum simulans Hance (fruit)		9		25		34
Sang bai pi	Morus alba L. (root bark)		12		16		28
Liao Xi Xin	Asarum heterotropoides F. Schmidt var. mandshuricum (herb)		6		21		27
Gan song	Nardostachys jatamansi (D. Don) Candolle (syn. Nardostachys chinensis Batalin) (root)		5		19		24
Gan cao	Glycyrrhiza uralensis Fisch. ex DC (root)			10		25	35
Sheng di huang	Rehmannia glutinosa (Gaertn.) Steud. (root)			9		21	30
Shu di huang	Rehmannia glutinosa (Gaertn.) Steud. (prepared root)			7		19	26
Ren shen	Panax ginseng C.A. Meyer (root)			8		20	28
Yuan zhi	Polygala tenuifolia Willd. (root)			5		11	16
Fu ling	Wolfiporia extensa (Peck) Ginns [syn. Poria cocos (Schw.) Wolf] (mushroom)			8		22	30
Gan jiang	Zingiber officinale Rosc. (root)			8	13	19	40
Huang qi	Astragalus propinquus Schischkin [syn. A. membranaceus (Fisch.) Bge.] (root)			6		15	21
Long gu	Fossilia Ossis Mastodi			6			6
Mai men dong	Ophiopogon japonicus (L.f.) Ker-Gawl. (root)			12		14	26
Bai shao	Paeonia lactiflora Pall. (syn. Paeonia albiflora Pall.) (root)			6		20	26
Zào jia	Gleditsia sinensis Lam. (fruit)				12		12
Guǎng huò xiāng	Pogostemon cablin (Blanco) Benth. (herb)				19		19

Table 1. (continued) The most regularly found herbs in the texts of the three historical periods of Chinese medicine.

Period / Herbs		266–907 No of formulas External	960–1368 No of formulas		1368–1911 No of formulas		Total
Chinese terms	**Binomial name and plant part**		**External**	**Internal**	**External**	**Internal**	
Mo han lian	Eclipta prostrata (L.) L. (herb)				16		16
Dang gui	Angelica sinensis (Oliv.) Diels (root)					26	26
Bu gu zhi	Psoralea corylifolia L. (fruit)					8	8
Bai zhu	Atractylodes macrocephala Koidz. (rhizome)					12	12
Niu xi	Achyranthes bidentata Blume					19	19
Lu jiao jiao	Colla Cervi Cornus					15	15
La jiao	Capsicum annuum L. (fruit)					6	6
Rou cong rong	Cistanche deserticola Ma (herb)					8	8
Tu si zi	Cuscuta chinensis Lam. (seed)					12	12
Shi hu	Dendrobium nobile Lindl. (stem)					6	6

vestigated to collect the interesting formulas and medical substances used. The main list includes 44 famous formulas, which appear in multiple records. Most of them (80%) tonify and nourish the kidney qi and replenish the essence and marrow. Some of the works have a wealth of information on the subject, including formulas for both oral administration and external use, such as the *Xi tou fa* (Shampoo Formula), the *Mo fa gao* (Hair-massage Cream), the *Xi fa ju hua san* (Hair-washing Chrysanthemum Powder) and the San sheng gao (Three Sages Paste), providing us with a vast field for future herbal research. The best example comes from the Ming Dynasty, when Li Shizhen recorded nearly 60 substances that treat hair loss, in his monumental *Bencao Gangmu* (Compendium of Materia Medica, printed 1596).

Several stories in these texts became a standard for Chinese Medicine. *Gu Jin Yi An An* (Interpretations of Ancient and Modern Medical Records 7) describes the successful treatment of a patient suffering from hair loss due to diet, labour and anger, with the administration of the formula *Bu zhong yi qi* (Tonifying the Middle and Replenishing Qi) plus *mai men dong* (root of *Ophiopogon japonicus* (L.f.) Ker-Gawl.) and *wu wei zi* (fruit of *Schisandra chinensis* (Turcz.) Baill.), together with the formula *Liu wei di huang wan* (Six Ingredients Including Rehmannia), plus *wu wei zi*.[8] Another story involves the treatment of a case of eyebrow loss, treated with "one or two pieces of *Lu jiao jiao* (deer antler gelatine, Colla Cervi Cornus) with wine for a year", a remedy suggested to him by an alchemist.[8] In *Bencao Jing Ji Zhu* (Annotations to the Divine Husbandman's Classic of the Materia Medica, c. 500 AD), there were 12 herbs, including Chinese taxillus, Sichuan pepper, simple leaf shrub chastetree fruit, white mulberry root – bark, leaf of oriental variegated coralbean, hemp seed, root of Chinese date, pine needle, wild goose fat, horse fat, lard, and chicken fat; and in *Bencao Gangmu*, there were more than 60 herbs for treating hair loss.

The formularies were roughly separated into three major historical periods:

– From the Jin to Tang dynasty (266 CE–907 CE)

– The Song and Yuan dynasties (960–1368) and

– The Ming to Qing dynasty period (1368–1911).

In the first period, 58 formulas for hair loss treatment were found in four important texts, including 51 external formulas and 7 internal. Most of them came from *Wai Tai Mi Yao* (27 external and 4 internal). The main syndromes addressed were consumptive disease, blood deficiency and qi deficiency. More than 20 formula books from the second period were studied, with 74 compound drugs, including 46 external and 28 internal formulas. Most of the formulas of this period were collected from *Tai Ping Sheng Hui Fang* (31) and *Sheng Ji Zong Lu* (11). The Ming Dynasty made unprecedented achievements in formula books, including the *Pu Ji Fan*, the largest formulary in Chinese history. Over 30 important books on formulas and related surgical subjects were investigated, to collect a total of 265 formulas for hair loss, including 178 external and 87 internal formulas. More than half of them were recorded in the abovementioned *Pu Ji Fang* (142) and *Bencao Gangmu* (33). The Table contains the most regularly found herbs in the texts of the three historical periods of Chinese Medicine. It is interesting to note that the materia medica – 40 ingredients in total – can be roughly distinguished in

external (21) and internal (22) groups. Especially the first nine herbs on the table 1 are common ingredients in all historical periods (e.g. *bai zhi*, *fang feng*, *man jing zi*). In the group of internal ingredients, there are herbs like *gan cao*, *sheng di huang* and *shu di huang*, *ren shen*, *bai shao* and *dang gui*, which are quite common in TCM use. Only three herbs are recommended for both external and internal use: *fu zi*, *chuan xiong* and *gan jiang*.

ΠΕΡΙΛΗΨΗ

Έρευνα όσον αφορά στα νεφρά και την απώλεια μαλλιών με βάση την αρχαία κινεζική ιατρική βιβλιογραφία

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Το «Κλασικό του Κίτρινου Αυτοκράτορα» (*Huang Di Nei Jing*) εμπεριέχει τις θεμελιώδεις ιδέες του Κινεζικού ιατρικού συστήματος για το ανθρώπινο σώμα. Οι βασικές του έννοιες βασίζονται στην ερμηνεία των φυσικών ρυθμών και της ανθρώπινης φυσιολογίας. Στο πρώτο μέρος του έργου, με τον τίτλο «Απλές Ερωτήσεις» (*Su Wen*) υπογραμμίζεται ότι οι νεφροί κυβερνούν γενικώς την ανάπτυξη και αποθηκεύουν την πεμπτουσία (*jing*), ενώ η εξωτερική τους έκφραση είναι οι τρίχες. Το qi των νεφρών σχετίζεται με την παραγωγή και ανάπτυξη των τριχών, καθώς και με τις παθήσεις τους, όπως η τριχόπτωση και το γκριζάρισμα. Με γνώμονα τη σχέση με τους νεφρούς, εξετάστηκαν περισσότερα από 400 Κινεζικά ιατρικά βιβλία, για να επιλεχθούν οι φαρμακευτικές ύλες και οι συνταγές που συνιστώνται για τη θεραπεία της τριχόπτωσης, από τους Κινέζους ιατρούς του παρελθόντος. Αυτός ο μεγάλος όγκος πληροφορίας κατηγοριοποιήθηκε σε τρεις ομάδες, σύμφωνα με την ιστορική περίοδο και παραλληλίστηκαν τόσο τα απλά, όσο και τα σύνθετα φάρμακα, ώστε να δημιουργηθεί ένας κατάλογος με πιθανούς υποψηφίους για μελλοντική έρευνα. Πράγματι, μια σχολαστική εξέταση αυτών των κειμένων από τις παλιές δυναστείες αποκάλυψε έναν τεράστιο πλούτο ιδεών για την παθογένεια των μαλλιών και τριχών, καθώς και συνταγών για τη θεραπεία τους. Αρκετές από αυτές τις μεθόδους θρέψης των μαλλιών φαίνεται να έχουν επιστημονική και πρακτική αξία.

Λέξεις ευρετηρίου: Αρχαία κινεζική Ιατρική, Εσωτερικός κανόνας του Κίτρινου Αυτοκράτορα, Νεφρικό qi, *Su Wen*, Τριχόπτωση

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CLINICAL CASE
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Urolithiasis and hypertension
The apparent and the hidden in the Ancient Greek and Oriental medical traditions

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Ουρολιθίαση και υπέρταση:
Το εμφανές και το κρυμμένο στις αρχαίες ελληνικές και ανατολικές ιατρικές παραδόσεις

Περίληψη στο τέλος του άρθρου

In the systems of traditional medicine, symptoms like renal colic, dysuria and haematuria were easily associated with the urinary system and urolithiasis. On the contrary, a modern symptom like hypertension could not be readily identified with a specific pathology. The investigation in the Greek, Ayurvedic, Chinese and Tibetan medical systems on the pathology, diagnosis and treatment of urolithiasis and hypertension was based on the classical texts and the long tradition of application. Although the causation of disease varied in the different medical systems, it was possible to detect similarities in both the theory and the treatment, some of which still play an important role in Greece, India and China. Several herbs present a widespread distribution of usage, common in most of the traditions studied. The careful examination of these data can contribute to a better understanding of medical thought in different civilisations, enlightening their similarities and differences. It could also reveal a possible and plausible materia medica for modern applications.

Key words

Ayurveda
Chinese medicine
Greek medicine
Hypertension
Urolithiasis
Tibetan medicine

1. INTRODUCTION

Comparing different medical systems is not a new idea. Prestigious personalities in various traditions felt curiosity towards other cultures, eager to understand the possible differences and similarities. Only recently has this direction attracted the attention of scholars and researchers from various scientific disciplines. Two of the most persistent problems affecting these comparisons are compatibility issues between traditional and modern medical systems, as well as the different cultural background of the various medical traditions themselves. Two extreme examples –urolithiasis and hypertension– were used to further investigate these questions. Urolithiasis on the one hand is a very obvious internal disease, in terms of pathogenesis. Ancient physicians had no doubt about the causes of colic pain and their association with the kidney or urinary stones. On the contrary, hypertension is a condition that has developed from symptom to disease only in recent times. The suggested treatments covered the whole medical arsenal of antiquity, from surgical operations, like perineal lithotomy for cystolithiasis, mentioned in Sushruta Samhita,[1] to bloodletting and leeches, a rational way to relieve excess blood and hypertension. The present study focused on the herbal remedies used extensively in the treatment of urolithiasis and hypertension, and are still preferred by a considerable number of patients around the Mediterranean, in India and China.

The main questions that have to be addressed are the possibility and usefulness of comparing different traditional systems, as well as the best approach to be followed.

2. METHODOLOGY

This research was conducted with horizontal comparisons, between different geographical areas (the Mediterranean, India, China and Tibet), as well as vertical ones, between different historical periods. The traditional pathology and the respective diagnostic methods had to be examined, so as to understand the fundamental ideas on the disease. All four medical traditions (Greek, Indian, Chinese and Tibetan) mainly used the diagnostic methods of pulse taking and uroscopy, offering a relatively common ground, keeping in mind the differences in terminology. Furthermore, it was necessary to investigate the treatment methods for the specific ailments, both in terms of single herbs, as well as compound ones (formulas), although the results presented here belong only to the first category. Typically, all herb names were identified taxonomically

and their habitats were taken into account. Herbs with a geographically limited distribution were excluded. The traditional plant uses were based on textual sources, like the Corpus Hippocraticum (CH), the works of Aretaeus of Cappadocia (1st c. CE),* Dioscorides (1st c. CE)** and Galen (129–210? CE),*** in the Greek tradition. The Ayurvedic texts included *Caraka Samhita*, *Sushruta Samhita* and *Ashtanga Hridaya*. Two major works on Chinese pharmacopoeia, separated by almost fourteen centuries, were consulted: the *Shennong Bencao Jing* (possibly 200–250 CE) and *Bencao Gangmu* (1578 CE). The major Tibetan medical work of *rgyud bzhi* (Four Tantras, 12th c.?) was also examined.

2.1. Urolithiasis

All of the examined medical traditions perceive urolithiasis as a blockage somewhere in the urinary system. The causes may vary, but water quality was identified as one of them quite early, for example in the CH (*De aere aquis et locis* 9.1). In the same paragraph, the writer describes the stone formation and observes that women are less likely to have kidney stones than men, something that is still correct.[2] Both Dioscorides and Galen use the term "stone-breaking" *power* (*lithōn thruptikas dunameis*) (DSMTF 11.711.13 Kühn). Furthermore, Galen clearly differentiates between diuretic and stone-breaking actions (for example in DSMTF 12.89.13 Kühn). As explained in the case of the blackberry root (*Rubus fruticosus* L.), the combination of astringent (*stuptikon*) and fine-grained (*leptomeres*) qualities allow the herb to break the kidney stones (DSMTF 11.849.1 Kühn).

The Ayurvedic text *Sushruta Samhita* describes four types of lithiasis (*ashmari*), according to the dogma of *tridosha*:**** *vatashmari*, *pittashmari*, *shleshmashmari* and *shukrashmari*. In Chinese Medicine, the term *lín zhèng* (literally "pour disease") is used to describe painful urinary dysfunction, which can be distinguished in nine different categories, one of which is urolithiasis (*shí lín*).[3] The causes behind these categories can be mainly Damp-Heat in Kidneys and Urinary Bladder, Spleen and Kidney Excess or Liver Qi Stagnation. Tibetan Medicine is even more thorough in terms of classification. According to *rgyud bzhi* (91) dysuria has 12 types in total. One of them is urinary stones.[4]

* De causis et signis acutorum morborum, De causis et signis diuturnorum morborum, De curatione acutorum morborum and De curatione diuturnorum morborum.

** De materia medica (DMM).

*** De simplicium medicamentorum temperamentis ac facultatibus (DSMTF), De compositione medicamentorum per genera (DCMG), De compositione medicamentorum secundum locos (DCML) and De alimentorum facultatibus (DAF).

**** The dogma of *tridosha* (three aggravates), common in Ayurveda and Tibetan Medicine, involves *vata* (air), *pitta* (bile) and *kapha* (phlegm).

2.2. Herbal treatment for urolithiasis

In DMM, there are 37 substances used for dissolving the stones, most of them of herbal origin (32 or 86.5%). Galen confirms the stone-breaking and/or diuretic use of 23 out of the 37 drugs (62.2%), while 5 are not mentioned at all. Nevertheless, Galen adds 7 more drugs that are useful in his experience, like blackberry root (*Rubus fruticosus* L.) (DSMTF 11.849.1 Kühn). The list of herbs suggested by both Dioscorides and Galen includes some that are widely used for kidney stones, even in contemporary folk treatment. The best examples are the fruit of *tribolos (Tribulus terrestris* L.*)*, rustyback fern *(Asplenium ceterach* L.*)*, chamomile roots, leaves and herb *(Matricaria chamomilla* L.*)*, marshmallow root *(Althaea officinalis* L.*)* and Venus hair fern *(Adiantum capillus-veneris* L.*)*. Cardamom *(Elettaria cardamomum* [L.] Maton.), imported from India, is considered lithotryptic only in DMM. In an 18th c. *iatrosofion* influenced by Michael Kontopides Markellos (1651–1717),[5] several interesting species are proposed as stone-breaking herbs: the seeds of *malathron* (105, *Foeniculum vulgare* L.), *pentaneuro* leaves (123, *Plantago* spp.), corn leaves (*fylla kalampoukou,* 123, *Zea mays* L.) and *Malva* spp. root (*agriomolocha*, 137). The later work titled *Akeso or Unified Pharmacopoea and Pharmacology* (f. 155v), by Charisios Megdanis (1768–1823) mentions tobacco *(Nicotiana tabacum* L.*)* as a useful remedy in urinary bladder and kidney stones, "since we don't have stone-breaking drugs", an astonishing statement. As noted by the editor Agamemnon Tselikas, the specific text deviates from the Greek tradition and has much to share with the contemporary Vienna Pharmacopoeia.[6] In the ethnobotanical collection by Fragkaki[7] there are in total 15 herbs used for kidney stones, out of which only three (25%) are actually included in DMM:***** *Asplenium ceterach* L., *Cynodon dactylon* (L.) Pers., and *Prunus avium* L.

In Chinese Medicine, there are some similar herbs used for urolithiasis:

- dōng kuí zǐ (the seed of *Malva verticillata* L. or *Abutilon theophrasti* Medik.), in *Bencao Gangmu* (16.12)
- jīn qián cǎo, the herb from several species, according to geographical area (*Lysimachia christinae* Hance, *Desmodium styracifolium* (Osbeck) Merr., *Glechoma longituba* (Nakai) Kuprian., *Hydrocotyle sibthorpioides* var. *batrachium* (Hance) Handel-Mazzetti ex R.H. Shan, and *Dichondra repens* (J.R. Forst. & G. Forst), often used alone for expelling stones[8]

***** A fourth herb called *atrivolos* is usually identified with *Medicago disciformis* DC., but it could also be associated with *Tribulus terrestris* L. (*trivolos* in DMM).

- jīn shā téng (the herb of *Lygodium japonicum* (Thunb.) Sw.), mentioned in the *Bencao Gangmu* (16.63) as especially effective in Damp-Heat urolithiasis
- bái jí lí (the fruit of *Tribulus terrestris* L.), first mentioned in *Shennong Bencao Jing* for dissolving hard masses and accumulations,[8] while in *Bencao Gangmu* (16.61) it is noted to "treat haematuria with swelling and pain", and
- yù mǐ xū (the stylus of *Zea mays* L., an American species), is mentioned in *Bencao Gangmu* (23.4) as Yushushu, a plant from the West, not cultivated in a large scale in China. The corn leaf and root is indicated for stranguria due to urolithiasis with intolerable pain.

Although rustyback *(Asplenium ceterach* L.*)*, a famous lithotryptic herb in the Mediterranean region, actually exists in Xinjiang (Uyghur) & N. Xizang (Tibet) at an altitude of 1400–2600 m,[9,10] it is not mentioned in *Bencao Gangmu* (1578), the modern herbal pharmacopeias of Traditional Chinese Medicine (TCM) or in the Tibetan Medicine herbals examined. It seems that its limited distribution in western China and its high-altitude habitat contributed to its noted absence in the texts.

In Tibetan Medicine, the fruits of *Tribulus terrestris* L. (gze ma), *Elettaria cardamomum* (L.) Maton (sug smel), *Malva verticillata* L. (lcam pa ma ning), the roots and flowers of *Alcea rosea* L. (mdog ldan), as well as the herb *Pedicularis pyramidata* Royle ex Benth (glang sna), are all used for kidney disorders (cold, hot or wind type), including dysuria and stones.[4,11–14]

It is quite interesting that similar herbs are used in Ayurveda for kidney disorders, including urolithiasis: the root and flower of *Elettaria cardamomum* (L.) Maton (elā), the roots of *Cynodon dactylon* L. (doorva), the herb and fruit of *Tribulus terrestris* L. (gokshura), the fern *Asplenium polyodon* G. Forst (pana), the root of *Althaea officinalis* L. (khatmi) and the stylus of *Zea mays* L. (makkaya).[15]

3. HYPERTENSION

Hypertension is a symptom defined after the invention of the sphygmomanometer by Samuel Siegfried Karl Ritter von Basch (1837–1905). Today it is distinguished into primary (90–95% of cases), attributed to nonspecific lifestyle and genetic factors and the secondary hypertension, due to identifiable causes. Possible symptoms include headache, epistaxis, shortness of breath, light-headedness, vertigo, tinnitus, altered vision or fainting episodes. These symptoms, however, might be related to associated anxiety, rather than the high blood pressure itself. Therefore, in traditional medical systems, hypertension, contrary to urolithiasis, needs an indirect approach, based on the pathological theories and some characteristic symptoms, like headache, epistaxis etc.

In the TCM, the related pathology is divided into four different patterns, three of deficiency (Liver Yang Rising types) and one of excess (Liver Phlegm Fire). The diagnosis is based on the different pulse motifs, but all types share the same "chord-like" pulse.* Jú huā (flowers of *Chrysanthemum morifolium* Ramat.) was mentioned for the first time in the Shennong Bencao Jing, while according to Bencao Gangmu (15.1): "When severe intermittent headache is to be treated, white chrysanthemum is the best among all the species". In the TCM, it is used for headaches and hypertension caused by Liver Wind syndrome, with Liver Yang Rising (Liver and Kidney Yin Deficiency).[8] Mulberry (*Morus alba* L.) root bark or sāng bái pí was originally used to drain Heat from the Lungs (to stop coughing and calm wheezing), though more recently it is used in hypertension.[8] This application is still based on old texts, since Bencao Gangmu (36.1) notes that: "it brings down ascending Wind" and "is good for smoothing urination". Hawthorn fruit or shān zhā (*Crataegus pinnatifida* Bge. var. *major* N.E.Br. or *Crataegus cuneata* Sieb. & Zucc.) was used to disperse Qi Stagnation (Bencao Gangmu 30.9) and more recently for the treatment of hypertension, coronary artery disease and elevated serum cholesterol.[8] Another example, following this same motif, is dà jì (the herb and root of *Cirsium japonicum* DC.), mentioned in Bencao Gangmu (15.30) for stopping hematemesis and epistaxis, while more recently it is used against hypertension, especially due to Liver Heat.[8]

Ayurvedic texts include several interesting herbs, like sarpagandha (the root of *Rauwolfia serpentina* Benth ex. Kurz.), mentioned already in *Caraka Samhita* (Chikitsa Sthana 9), that balances Vata and Pitta, reduces heart rate and dilates blood vessels, as well as lowering blood pressure.[15,16] One of its drastic constituents, reserpine, is used specifically in hypertension and the treatment of psychiatric patients. In China, the same herb (yìn dù luó fú mù or the "Indian vine tree") is mentioned in modern pharmacopoeias, but not in traditional texts. Garlic or rasonam (*Allium sativum* L.), is a well-known herbal treatment for hypertension, mentioned already in *Caraka Samhita* (Sutra Sthana 27), for its quality of balancing Vata and Kapha. With the Chinese name dà suàn, it is mentioned in Bencao Jingji Zhu (500

* This is usually translated as "wiry pulse". The correct version would be "chord-like pulse", in total agreement with the galenic term spasmodic pulse (*spasmōdēs*, *De Differentia Pulsuum* 8.554.18 Kühn) that has a tensed chord-like sensation, comparing the feeling with that of a string from a musical instrument and not a wire.

AD). Bencao Gangmu (26.9) informs us that garlic was brought to Han China by Zhang Qian, a renowned envoy to the western regions (206 BC- 220 AD), and can disperse pathogenic Wind, Cold and Damp, dissolve hard masses and undigested food.

Ashwagandha (the root of *Withania somnifera* (L.) Dunal), is considered today one of the most important Ayurvedic herbs, administered mainly to relax the nervous system.[15,17] In *Caraka Samhita,* there are 28 references to ashwagandha for neurological disorders (Chikitsa Sthana 28.166, 28.170 and 28.173, Siddhi Sthana 4.4 and 9.87). In Ashtanga Hridaya, there are 20 references, again on the treatment of neurological disorders (13.41) and epilepsy (14.14). Although ashwagandha is mentioned (cuī mián shuì qié) in the modern Chinese pharmacopoeias, it is absent in the examined traditional texts. It does not seem to be a part of the Tibetan flora, but it has a name (ba dzi gandha) probably for imported quantities.[11] Another famous Ayurvedic herb, used for hypertension today, is the amla or amalaki fruit (*Phyllanthus emblica* L.), mentioned in *Caraka Samhita* (Sutra Sthana 27) for balancing Kapha and Pitta, a property found also in Tibetan medical texts.[11]

In the Hippocratic world, hypertension could be categorised as abundance of blood (*plethora*). In Greek medical texts, there are several herbs associated with the treatment of hypertension. Similar species with those already mentioned in the oriental traditions include the three chamomiles (*anthemides* are identified with *Matricaria recutita* (L.) Rausch, *Chamaemelum nobile* (L.) All and possibly other *Anthemis* spp.) mentioned in DMM (3.137), their roots and flowers considered diuretic and lithotryptic,* effective also for jaundice and liver diseases, coinciding with the use of chrysanthemum in Chinese Medicine. Galen suggested the use of chamomile oil in headaches from intoxication or fever (DCMSL 12.507.10, 12.519.2, 12.561.1), a condition similar with the Ascending Yang Fire in TCM. In DMM (1.126), the cooling effect of mulberry leaves (*Morus nigra* L.) was used externally to soothe burns, but Galen administered the leaf extract in hypertension caused by heat or cold (DCMSL 12.502 and 12.507). *Mespilon* or *arōnia* in DMM (1.118) (very possibly *Crataegus monogyna* Jacq., *Crataegus orientalis* Pallas ex M.Bieb. or *Crataegus azarolus* L.) was considered to have styptic fruits, used for the treatment of diarrhoea, but in recent centuries were found effective against both hypertension and hypotension, in insomnia related with stress, arteriosclerosis and atherosclerosis. In DMM (2.152) garlic (*skordon,* the bulb of *Allium sativa* L.), a well-known hypotensive today, is considered wind-expelling and diuretic, among else. Galen regards *skorodon* (*De Alimentorum Facultatibus* 6.659.1 Kühn) as an unblocking and differentiating medicine, especially when taken raw.

Withania somnifera (L.) Dunal is recorded in various regions of Greece (Sterea, Peloponnesus, Crete, East and North Aegean Islands)[18] and it has been identified with the *struchnos upnōtikos* in DMM (4.72), although its uses diverge from the Ayurvedic ashwagandha: the root bark is considered a hypnotic, the fruit a strong diuretic, but in a larger quantity it can induce ecstasy. In any case, the particular root it did not seem to play such an important role as in the case of Ayurveda.

4. CONCLUSIONS

In some cases, the pathology in traditional medical systems can be easily associated with the modern terminology, as for example with urolithiasis, while in other cases, contemporary diseases, like hypertension, cannot be readily identified with the traditional terms. Yet, the old texts can be used as valuable sources in terms of the traditional diagnostic methods, in relation to the symptoms (e.g. the "chord-like" pulse as a criterion for hypertension). Simple ailments can be addressed successfully with single herbs (monotherapy in urolithiasis), while more complicate conditions can be treated with herbal formulas (hypertension).

Medical traditions are not homogenous and they actually represent a matrix of interconnected information from a multitude of sources. Therefore, we should take into consideration the primary and secondary sources of a text, as well as the MSS tree. Materia medica texts – including the practical Greek *iatrosofia* – are actually complicate collections, heavily influenced by cultural backgrounds, locale and historical period. The actual goal of their writers or compilers was not to reproduce exact copies of previous texts, but to

Table 1. Herbs used for urolithiasis.

Greek	Ayurveda	Tibetan	Chinese
Asplenium ceterach	(Asplenium polyodon)		
Cynodon dactylon	X		
Althaea officinalis and Malva spp.	(Malva verticillata)	X	(Malva verticillata)
Elettaria cardamomum	X	X	
Tribulus terrestris	X	X	X
Zea mays	X		X

* Used especially in that fashion by Rufus the Ephesian (*De renum et vesicae morbis* 1.12, 3.13 and 12.1).

provide useful lists of medical substances. In that context, the dissemination of knowledge for the American herbs was quite rapid, since within a century they were established in both East & West (e.g. *Zea mays* L.). As evident in tables 1 and 2, *Tribulus terrestris* L. and *Malva* spp. are used against urolithiasis in all of the medical systems examined, while *Elettaria cardamomum* (L.) Maton and *Zea mays* L. in three of them. In the hypertension group, three species are used in all the medical systems: *Allium sativum* L., *Crataegus* spp. and *Morus* spp. A few species remain problematic, like the examples of *Asplenium ceterach* L. and *Withania somnifera* (L.) Dunal. In any case, the systematic and interdisciplinary study of such sources can provide valuable information for future drug research.

Table 2. Herbs used for hypertension.

Chinese	Tibetan	Ayurveda	Greek
Chrysanthemum morifolium			Matricaria recutita/Chamaemelum nobile
Morus alba	X	X	Morus nigra
Crataegus spp.	X	X (ethnobotanical use)	X
Cirsium japonicum	(Cirsium souliei)		Not present
	Not present	Rauwolfia serpentina	Not present
X (Western origin)	X	Allium sativum	X
Present	Not present?	Withania somnifera	Present
	X	Phyllanthus emblica	Not present

ΠΕΡΙΛΗΨΗ

Ουρολιθίαση και υπέρταση: Το εμφανές και το κρυμμένο στις αρχαίες ελληνικές και ανατολικές ιατρικές παραδόσεις

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Στα παραδοσιακά ιατρικά συστήματα τα συμπτώματα όπως ο κολικός των νεφρών, η δυσουρία και η αιματουρία συνδέονται εύκολα με το ουροποιητικό σύστημα και την ουρολιθίαση. Αντίθετα, η υπέρταση, τουλάχιστον ως ορολογία, δεν υπήρχε πριν την εφεύρεση του σφυγμομανόμετρου και δεν ήταν άμεσα συνδεδεμένη με κάποια συγκεκριμένη παθογένεια. Η έρευνα πάνω στην παθολογία, τη διάγνωση και τη θεραπεία της ουρολιθίασης και της υπέρτασης, όπως τα αντιλαμβάνονταν η αρχαία ελληνική και οι ανατολικές Ιατρικές, βασίστηκε τόσο στα κλασικά κείμενα, όσο και στη μακρόχρονη παράδοση. Παρ' όλο που η αιτιολογία της νόσου μπορεί να διαφέρει, κατέστη εφικτό να εντοπιστούν ομοιότητες, τόσο στη θεωρία, όσο και στην πράξη. Κάποια βότανα παρουσίασαν ευρύτητα εφαρμογής, στα περισσότερα συστήματα που εξετάστηκαν. Η προσεκτική μελέτη των δεδομένων αυτών μπορεί να συνεισφέρει στην καλύτερη κατανόηση της ιατρικής σκέψης στους διαφορετικούς πολιτισμούς, υπογραμμίζοντας τις ομοιότητες και τις διαφορές τους, ενώ θα μπορούσε να αποτελέσει μια πιθανή πηγή φαρμακευτικών υλών για το άμεσο μέλλον.

Λέξεις ευρετηρίου: Ayurveda, Ελληνική Ιατρική, Θιβετανική Ιατρική, Κινεζική Ιατρική, Ουρολιθίαση, Υπέρταση

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CLINICAL CASE
ΚΛΙΝΙΚΗ ΠΕΡΙΠΤΩΣΗ

Papal deaths caused by cardiorenal disease
First approach

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ΑΡΧΕΙΑ ΕΛΛΗΝΙΚΗΣ ΙΑΤΡΙΚΗΣ 2020, 37(Συμπλ 2):177–181

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Οι θάνατοι Παπών που προήλθαν από καρδιονεφρικές νόσους: Πρώτη προσέγγιση

Περίληψη στο τέλος του άρθρου

We know a lot on the history of the Roman Pontiffs, we know enough about their diseases and their deaths. By contrast, we have scarce data on cardiorenal deaths. The aim of this paper is to provide the preliminary results of a study that up to now includes 83 out 264 popes. An additional 40 popes reigning in the years 1700–2019 have been studied only as to their mean ages at death. Sixteen died of gout and its renal complication, 6 because kidney and bladder stones, 4 had nephritis, 4 disease of the prostate, 1 gonorrhoea, 1 syphilis, 1 died of crush syndrome. Nine popes died of stroke, 6 underwent cardiac deaths. Nine popes were murdered, 26 martyred. Among the 38 popes who died between 1700 and 1999, the average mean age at death was 75.05 years, for popes who died in the years 1700–1799 it was 77.8 years, for popes who died between 1800 and 1899, and 78.1 years for popes who died between 1900 and 1999. The two living popes (Benedict XVI, emeritus and Francis, reigning) are 92 and 82 years old, respectively. The majority of popes aged successfully and lived longer than their contemporaries. In Italy, in the 17th century, the mean age at death was below 40 years.

Key words

Cardiovascular deaths
Diseases of the popes
Gout
Kidney and bladder stones
Renal deaths
Stroke
Successful aging

1. INTRODUCTION

The lives of Roman Pontiffs are interesting from a historical and historiographic point of view.[1] The abundance of documents not only in the Vatican but everywhere in Europe makes popes a great topic of studies but all have been extensively studied by historians and a vast literature exists.[1–5] By contrast, few specific studies exist on their diseases and causes of death, even though a lot has been written about the popes' physicians, starting with Giovanni Castellomata.[6,7] The latter was the archiater *(medicus papae)* of Pope Innocent III (1161–1216), born Lothar of Segni, who reigned from 8 January 1198 to 16 July 1216. The topic of papal diseases was recently addressed by Agostino Paravicini Bagliani,[8] Giovanni Ceccarelli[9] and Giorgio Cosmacini.[10]

Cardiorenal diseases are primary and important causes of death today. No study of their prevalence in popes is available. The goal of this study is to explore the prevalence of cardiorenal deaths among popes, who are usually elected to office at advanced age and enjoy successful ageing.

2. POPES WHO DIED OF GOUT AND ITS COMPLICATIONS

Table 1 lists popes who died of gout and its complication (tab. 1), among them Boniface VIII, Sixtus IV and Clement VIII. Pope Boniface founded the University of Rome (*Studium Urbis,* 6 June 1303) without suppressing the *Studium curiae* (the university of the Pope's Court, a university located in the places where the court was settled, thus following the popes in their travels). Sixtus started the Hospital Santo Spirito, the Vatican Library and the Sistine Chapel. Pope Clement VIII sentenced Giordano Bruno to death.

Boniface VIII (Pope in 1283–1303) was born Benedetto Caetani at Anagni (c.1230). He was elected Pope after the withdrawal of Celestine V, and is considered one of the greatest popes in history, although Dante Alighieri accused him of simony and nepotism. "He was chronically affected by gout and renal stone disease and by the fear of death and the search for therapies capable to prolong life. Cosmacini says "podagroso e gottoso… the Pope is affected by arthritis and renal disease due to overalimentation of

Table 1. Popes who died of gout and its complications.

Sisinnius, born c.650 in Syria, Pope for 21 days in 708
Honorius IV, born in Rome in 1210, Pope in 1285–1287
Boniface VIII, born c.1230, Pope in 1294–1303
Pius II, born Enea Piccolomini in 1405, Pope in 1458–1464
Sixtus IV, born Francesco della Rovere in 1414, Pope in 1471-1474
Pius III, born in 1440, Pope for 16 days in 1503
Julius II, born Giuliano della Rovere in 1443, Pope in 1503–1516
Julius III, born in 1481, Pope in 1550–1555
Clement VIII, born Ippolito Aldobrandini, Pope in 1592–1605
Clement X, born Emilio Bonaventura Altieri in 1581, Pope in 1670–1676
Innocent XI, born in the family Odescalchi at Como in 1681, Pope in 1676–1689
Innocent XII, born Antonio Pignatelli di Spinazzola in 1615, Pope in 1691-1700
Innocent XIII, born Michelangelo Conti a Poli (Vatican State) in 1655, Pope in 1721-1724
Clement XI, born in Urbino as Gianfrancesco Albani in 1649, Pope in 1700–1721
Benedict XIV, born Prospero Lorenzo Lambertini in 1765, Pope in 1740–1758
Pius VIII, born Francesco Saverio Castiglioni near Ancona in 1761, Pope in 1829–1830

food very rich (*straricca*) in meat".[11] He had great interest in Roger Bacon's theories on *De retardatione accidentium senectutis (On retarding the accidents of ageing)*. Boniface enrolled various archiaters, among them Taddeo Alderotti (1223–1295), Pietro da Abano (1257–1315), Anselmo da Bergamo *(artis physicae professor)*, Simone of Genova (author of *Clavis sanationis*), Accursino from Pistoia, Manzia from Fabriano, Guglielmo da Brescia, Angelo da Camerino and Campano da Novara *(Magister Campanus)*, a naturalist also affected by renal stone disease.

Pope Boniface VIII was the founder of the Holy Year in 1300 and author of the *Bulla detestandi feritatis* (against the dismemberment and evisceration of cadavers) issued on 27 September 1299). For this *Bulla* during the subsequent centuries he was wrongly accused even by Herman Boerhaave and Albrecht von Haller to have delayed the advancement of medicine by impeding anatomy. This was a misinterpretation since a special permission was granted for teaching purposes.

Sisto IV (1471–1484), born Francesco della Rovere in 1414, suffered of a disease affecting his joints, probably gout, and died following apoplexy. He is remembered for the splendour of the Sistine Chapel (he enrolled Verrocchio, Botticelli, Pinturicchio, Perugino, Ghirlandaio, Melozzo). He also promoted the foundation of the Hospital Santo Spirito and the development of the Vatican Library (he nominated as its director the famous Bartolomeo Sacchi, known as Platina – as shown by a painting by Melozzo in the Vatican Museum). He also renamed the Jubilee1475 as Holy Year (*Anno Santo*). Sisto IV wrote an important short apostolic letter (*littera in forma brevis*) to the President of the University of Tubingen, who had inquired about the possibility of utilising the bodies of executed people for teaching anatomy. As Professor Cosmacini demonstrated[12] "we give you permission to utilise the corpses from those places where those persons were executed, to dissect them and to dismember them and thereafter to give them back to be buried" [according to the rules and tradition of the Church] (4 April 1582).

Clemente VIII (1592–1605), born Ippolito Aldobrandini, was the pope who convicted Giordano Bruno. In 1597, he continually suffered from gout attacks. In 1598, in a travel note, he wrote "nos quidem in ipso itinere chiragra et podagra liquanto tentati sumus/in that travel we suffered of Chiragra and podagra".[13] He also had gouty arthritis in his hands and feet. Crippling arthritis was associated with nephritis. His pallor makes a diagnosis of chronic kidney disease probable. His physician prescribed that he drinks a lot. In his last months, he had various attacks of "podagra, with insomnia and lack of appetite". In January 1605, he suffered "mal di goccia" (cerebral haemorrhage).

3. POPES WHO DIED BECAUSE OF KIDNEY OR BLADDER STONES

Table 2 shows that six popes died of kidney or bladder stones (Boniface IX, Gregory XV, Clement IX, Pius V, Pius VI and Leo XII).

Boniface IX "afflitto da mal della pietra morì/died of renal stone disease". The final cause was a stroke. Autopsy found a stone in his bladder.[14] In Platina we read "Boniface who had complained of long-lasting flank pain, finally died".[15]

Gregory XV became pope at the age of 67. He canonised

Table 2. Popes who died of bladder and kidney stones.

Boniface IX (Pope 1389–1404), born Piero Tomacelli
Pious VI (Pope 1775–1799), born Giovann'Angelo Braschi
Gregory XV (Pope 1621–1623), born Alessandro Ludovisi
Clement IX (Pope 1667–1669), born Giulio Rospigliosi
Pious V (Pope 1566–1572) born Michele Ghisleri in 1504
Leo XII (Pope 1823–1829), born Annibale Della Genga

Teresa d'Avila, Francesco Xavier, Filippo Neri and Ignatius of Loyola and in 1522 founded the institution known as *De propaganda Fide*, giving the congregation a great palace, known as the ministry of missions. He suffered from renal stone disease, fever, nausea and vomiting. Having luckily passed the stone he died of acute sepsis and diarrhoea, aged 70.

At autopsy, Pius V's three stones were found complicated by urinary sepsis. Pius VI died aged 82 in Valence, France. He was the last pope to have died abroad. The narratives about his death report strangury, repeated bladder catheterisations and bloody urine.

The death of Leo XII was also associated with strangury and haematuria.

4. POPES WHO DIED OF NEPHRITIS, PROSTATE DISEASE, GONORRHOEA AND SYPHILIS

Four popes had nephritis: Marcellus II (1501–1545) Pope for 22 days, Hadrian VI (born in 1459 in Utrecht, Pope in 1522–1523), Clement X (born in 1591, Pope in 1670–1676), Pius VII (born in Cesena in 1742, Pope in 1800–1823).

Clement XI (born in Urbino in 1649, Pope in 1700–1721), Pius VII, Paul VI, John Paul II had prostate disease. Clement VI, Pope in Avignon, had severe gonorrhoea, while Julius II had syphilis.

5. CARDIAC DEATHS AND DEATH DUE TO STROKE

There were a few cardiac deaths: Clement XIII, Pope in 1758–1769 (he suffered of angina and died of an aortic aneurysm), Pius X (born in 1835 in Riese, Pope in 1903–1914), Pius XI (born in 1857 as Achille Ratti), Paul VI (born Giovan Battista Montini in 1897 in Concesio, Pope in 1953–1978), John Paul I (born Albino Luciani in 1912, pope for 33 days in 1978).

John Paul II was Pope in the years 1978–2005, having been born Karol Józef Wojtyła, in Wadowice in 1920 and died aged 86. According to Archiater Buzzonetti, his death was due to "Parkinson's disease, acute respiratory syndrome and tracheotomy, benign prostatic hyperplasia, hypertensive cardiopathy and ischemia".

Many popes died of a stroke. Among them Stephen II (Pope in 752–757), Sergius (Pope in 884–887), John XII (Pope in 955–964), Nicholas III (Pope in 1277–1280), Honorius IV (Pope in 1295–1297), Innocent VI (Pope in 1406), Martin V (Pope in 1431), Paul II (Pope in 1471), Clement XIII (Pope in 1758–1769).

Pope John XXI, born Pietro Hispano about 1205–1210, was Pope in 1276–1277. He died of crush syndrome. In the night of 10 August 1277, the ceiling of his office fell and he was severely injured. Although he was extracted alive from the rubble, he died a few days later.

6. DISCUSSION

6.1. Ageing well as a cause of death

In general, all Popes' age at death is higher than that of contemporary laymen. Celestine V, who refused the tiara, died aged 81 in prison. Pope Innocent XII was 85, John Paul II was nearly 86, Clement X was 86, Pius IX was 87 and died after 31 years of reign, Leo XIII was 93 and died after 25 years of reign. He was a frugal eater, drank two fingers of Bordeaux wine a day, sniffed tobacco, and was a regular walker in the Vatican Gardens.

Table 3, which is a compilation of age at death of popes who died in the XVII-XX centuries, demonstrates that popes enjoyed greater longevity than their contemporaries, thanks to their lifestyle, including good nutrition. Even in the XVII century, when male life expectancy in Italy was around thirty-five years, the mean age at death of popes was 75.

6.2. Martyrium

Many popes, especially in the early years of Christianity, were martyred. Table 4 accurately lists the 26 martyred popes, most belonging to the early church. St Peter, founder of the patriarchate of Antiochia, died in Rome by crucifixion. Linus was martyred in 78 AD, St. Clement thrown into the sea with an anchor around his neck, St Anacletus was martyred in 110 AD.

Nine popes were murdered: John VIII, Stephen VI, Leo V, John X, John XII, Benedict VI, John XIV, Clement II, Celestine V (tab. 5). It is uncertain if Boniface VIII died because of the attack in Anagni.

6.3. Crush syndrome

John XXI (1276–1277), born Peter Julianus in 1215, was identified with Petrus Hispanus, the author of a treatise *De Oculo* and physician to Pope Gregory IX (1271–1276). He was given a place of honour by Dante Alighieri in the sphere of the sun (*Divine Comedy*). He died of crush syndrome after the ceiling of his office fell.

Sifridus de Balnhusin (*Compendium historiarum Movimenta Germaniae Historica, Scriptorum*, 1880 XXV, 708) wrote "subito domus in qua sedebat super eum corruit tantumque concussit ut infra spatium quinque dierum

Table 3. Lifespan of popes who died in the XVII, XVIII, XIX and XX centuries.

Pope	Dates of birth and death	Age (years)	
XVII Century			
Clement VIII	1536/1605	69	
Leo XI	1535/1605	70	
Paul V	1552/1621	69	
Gregory XV	1554/1623	69	
Urban VIII	1568/1644	76	
Innocent X	1574/1655	81	
Alexander VII	1599/1667	68	
Clement IX	1600/1669	69	
Clement X	1590/1676	86	
Innocent XI	1611/1689	78	
Alexander VIII	1619/1691	81	
Innocent XII	1615/1700	85	*Mean 75.0*
XVIII Century			
Innocent XII	1615/1700	85	
Clement XI	1649/1721	71	
Innocent XIII	1655/1724	70	
Benedict XIII	1649/1730	82	
Clement XII	1652/1740	87	
Benedict XIV	1675/1758	83	
Clement XIII	1693/1769	76	
Clement XIV	1705/1774	69	*Mean 77.8*
XIX Century			
Pious VI	1717–1800	83	
Pious VII	1742–1823	81	
Leo XII	1760/1829	69	
Pious VIII	1761–1830	70	
Gregory XVI	1765–1846	81	
Pious IX	1792/1878	85	*Mean 78.1*
XX Century			
Leo XIII	1810/1903	93	
Pious X	1835/1914	79	
Benedict XIV	1854/1922	67	
Pious XI	1857/1839	81	
Pious XII	1876/1958	82	
John XXIII	1881/1963	82	
Paul VI	1887/1968	81	
John Paul I	1912/1978	65	
John Paul II	1920/2005	84	*Mean 79.3*
XXI Century			
Benedict XVI (emeritus)	Born 1927	92	
Francis	Born 1936		

Table 4. Martyred Popes (no 26).

Saint Peter, c.67, martyred by crucifixion
Pope Linus, c.67–c.76
Pope Clement I (c.92–c.99), thrown into sea with anchor around his neck
Pope Telesphorus (c.128–c.138)
Pope Soter (166–175)
Pope Anicetus (166–176)
Pope Eleuterius (175–189)
Pope Victor I (189–199)
Pope Calixtus I (217–222)
Pope Urban I (222–230)
Pope Pontian (230–235), condemned to mines in Sardinia, died on the Island of Tavolara
Pope Anterus (elected 21/12/235), martyred by Emperor Maximus
Pope Fabian (elected 11/10/236), martyred in 1/20/250 during persecution by Decius
Pope Cornelius (elected March 253), martyred in June 253
Pope Lucius (elected 6/25/253), martyred 3/5/254
Pope Stephen I (elected 5/12/254), martyred 8/2/257
Pope Sixtus II (elected 8/30/257), martyred 8/6/258
Pope Eutychian (elected 1/4/275), martyred 12/7/283
Pope Felix (elected 5/1/269), martyred 12/30/274
Pope Caius (elected 12/17/238), martyred 4/22/296
Pope Dionysius (elected 7/22/259), martyred 12/26/268
Pope Marcellinus (elected 6/30/296) martyred 10/25/304
Pope Marcellus (elected 5/27/308), martyred 1/16/309
Pope Eusebius (elected 4/18/309), martyred in Sicily 8/17/309
Pope John I (elected August 13, 523). Imprisoned by Theodoric and starved to death (5/18/526)
Pope Martin (elected in 649), died in exile on 9/16/655

Table 5. Murdered Popes (no 9).

John VIII (872–882): Allegedly poisoned and then clubbed to death
Stephen VI (896–897): Strangled
Leo V (903): Allegedly strangled
John X (914–928): Allegedly smothered with pillow
John XII (955–964): Allegedly murdered by the jealous husband of the woman with whom he was in bed
Benedict VI (973–974): Strangled
John XIV (983–984): Either by starvation, ill-treatment or direct murder
Clement II (1046–1047): Allegedly poisoned
Celestine V (1294–1296): Allegedly (unlikely) murdered while in post-abdication captivity; allegations blame his successor Boniface VIII

miserabiliter moreretur" (Agostino Paravicini Bagliani, *The Pope's Body*, 1994).

7. CONCLUSIONS

Cardiovascular and renal deaths were frequent among popes. Renal stone disease with or without gout was frequent. These preliminary findings warrant further studies; however, they point out that these narratives add another perspective to the popes' contribution to Medical Milieu, not only as founders of universities,[10] protectors of anatomists,[7] and enrollers of archiaters,[3,6] but also as patients.

ΠΕΡΙΛΗΨΗ

Οι θάνατοι Παπών που προήλθαν από καρδιονεφρικές νόσους: Πρώτη προσέγγιση

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Γνωρίζουμε πολλά για την ιστορία των Ρωμαίων Ποντιφήκων, γνωρίζουμε αρκετά για τις ασθένειες και τους θανάτους τους. Αντίθετα, διαθέτουμε ελάχιστα δεδομένα για καρδιοαναπνευστικούς θανάτους. Σκοπός της παρούσας εργασίας είναι να παράσχει τα προκαταρκτικά αποτελέσματα μιας μελέτης που μέχρι τώρα περιλαμβάνει 83 από 264 Πάπες. 40 ακόμα Πάπες που ηγεμόνευσαν κατά τα έτη 1700–2019 έχουν μελετηθεί μόνο ως προς τις μέσες ηλικίες τους κατά τον θάνατο. Δεκαέξι πέθαναν από ουρική αρθρίτιδα και νεφρική επιπλοκή, 6 από λίθους στους νεφρούς και την ουροδόχο κύστη, 4 είχαν νεφρίτιδα, 4 ασθένειες του προστάτη, 1 από γονόρροια, 1 από σύφιλη, 1 πέθανε από σύνδρομο σύνθλιψης. Εννέα Πάπες πέθαναν από αγγειακό εγκεφαλικό επεισόδιο, 6 από καρδιακούς θανάτους. Εννέα Πάπες δολοφονήθηκαν, 26 μαρτύρησαν. Μεταξύ των 38 Παπών που πέθαναν από το 1700 έως το 1999, η μέση ηλικία κατά τον θάνατο ήταν 75,05 χρόνια για τους Πάπες που πέθαναν κατά τα έτη 1700–1799, 77,8 χρόνια για τους Πάπες που πέθαναν μεταξύ 1800 και 1899, 78,1 χρόνια για τους Πάπες που πέθαναν μεταξύ 1900 και 1999. Οι δύο ζωντανοί Πάπες (Βενέδικτος ΙΣΤ΄, επίτιμος και Φραγκίσκος, ο νυν Πάπας) είναι 92 και 82 ετών, αντίστοιχα. Η πλειοψηφία των Παπών κατάφερε να φτάσει σε μεγάλη ηλικία και έζησε περισσότερο από τους συγχρόνους τους. Στην Ιταλία, τον 17ο αιώνα, η μέση ηλικία θανάτου ήταν κάτω των 40 ετών.

Λέξεις ευρετηρίου: Αγγειακό εγκεφαλικό επεισόδιο, Θάνατοι λόγω νεφρών, Καρδιαγγειακοί θάνατοι, Λίθοι στους νεφρούς και την ουροδόχο κύστη, Μεγάλη ηλικία επιτυχώς, Ουρική αρθρίτιδα, Παθήσεις Παπών

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CLINICAL CASE
ΚΛΙΝΙΚΗ ΠΕΡΙΠΤΩΣΗ

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Paroxysmal nocturnal haemoglobinuria
From the first case to the current complement inhibition therapies

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Paroxysmal nocturnal haemoglobinuria (PNH) is a rare clonal disorder that affects about 1-1.5 cases per million individuals, characterised by haemolysis, peripheral blood cytopenia, bone marrow dysfunction, thrombosis, renal impairment and arterial and pulmonary hypertension. The first case of PNH was described probably in 1793 by a surgeon, Dr Charles Stewart, in the medical commentaries "Account of a singular periodical discharge of blood from the urethra". In the following decades the most eminent physicians and scientists of the time reported several cases. In 1882, Paul Strübing was the first to identify PNH as a new disease entity. Hijmans in 1911 considered the possibility that the complement system mediated the haemolysis of PNH erythrocytes and, in the same year, Italian scientists Ettore Marchiafava and Alessio Nazari scrupulously described the pathogenesis of the condition. In 1925, Enneking introduced the name "paroxysmal nocturnal haemoglobinuria", to define this pathology. Despite increased knowledge about this syndrome, therapies for PNH were still only experimental and symptomatic, with the use of antimicrobial agents, corticosteroids and blood transfusions. The natural history of PNH changed remarkably only in 2007, with the introduction of the Eculizumab complement blockade agent. Ravulizumab, a long-acting C5 complement inhibitor, approved in December 2018 by the US Food and Drug Administration (FDA), and on July 2019 by the European Commission, represents a new promising instrument for PNH treatment. A second generation of anti-complement agents is currently under investigation, representing future promising instruments for the treatment of PNH.

Νυκτερινή παροξυντική αιμοσφαιρινουρία:
Από την πρώτη περίπτωση έως τις τρέχουσες θεραπείες αναστολής συμπληρώματος

Περίληψη στο τέλος του άρθρου

Key words

Complement inhibition
Eculizumab
Marchiafava – Micheli disease
Paroxysmal nocturnal haemoglobinuria
Ravulizumab

1. INTRODUCTION

Paroxysmal Nocturnal Haemoglobinuria (PNH) is a rare clonal disorder that affects about 1–1.5 cases per million individuals.[2] The condition takes its name from the characteristic severe haemolytic anaemia giving rise to episodes of haemoglobin in the urine, especially during the night.

The main features of PNH are haemolysis, peripheral blood cytopenia, bone marrow dysfunction, hypercoagulablilty, thrombosis, smooth muscle dystonia, all symptoms that can also lead to redoubtable complications such as renal failure, arterial and pulmonary hypertension and recurrent infections.[3,30]

2. HISTORY OF PAROXYSMAL NOCTURNAL HAEMOGLOBINURIA

2.1. The origins of PNH: First cases

The first case of PNH was described probably in 1794 by Dr Charles Stewart, a Scottish surgeon practicing in Archangel, a city in the north of European Russia. In the medical commentaries "Account of a singular periodical discharge of blood from the urethra", he reported the case of a 51-year-old man, much emaciated a complaining of *"constant severe pain in the loins, passing down to the pubes and groin, passed bloody urine at times for over eight months"*. He also reported that *"Each attack of haemorrhage lasted*

three days, he was cured by tincture of bark, port wine and good diet. The great wasting and constant pain, increased by movement, are unlike what is met with in paroxysmal haematuria".[4] This could be the first time that PNH has been documented in the history of the disease.

In the next decades, the most eminent physicians and scientists of the time reported several cases.

The French physician Dr Pierre François Olive Rayer in his three-volume book on diseases of the kidney titled "*Traité des maladies des reins"* (Treatise on Diseases of the Kidneys), published in 1841, gave a vague reference to the disease, describing a case of intermittent haematuria of unknown origin.[5]

The Jewish-American Cardiologist Dr William Dressler, in 1854, published a report of "Intermittent Albuminuria and Chromaturia", describing the case of a 10-year-old boy with urine containing brown amorphous pigments, the abundance of casts and no blood corpuscles.[6]

A first detailed account was described in 1866, when Sir William Gull reported a case of a young "anaemic looking" tanner with several episodes of dark urine, calling this condition "intermittent hematinuria". The patient was a leather-dye worker and in his work he was exposed to cold and humid conditions. Gull considered that this may have been a triggering cause for the syndrome. This raises the suspicion that it could have been Paroxysmal Cold Haematuria, a disease not yet distinguished from PNH at the time.

An interesting witness of the knowledge and methods used in nephrology in the XIX century came from thesis of G.H.K. Macalister for the M.D. degree at Cambridge University, in July 1909. He made a critical review on "The pathology of paroxysmal haemoglobinuria". He attributed the paternity of the definition "Paroxysmal Haemoglobinuria" to the work of Dr Secchi in 1872.[7]

The author also mentioned the experience of Dr George Johnson, who in 1873, under the name of "periodic or cyclic albuminuria", recognised a condition of intermittent haemoglobinuria, whose most commonly recognised causes were exercise, fatigue and exposure to the cold.

Macalister also reports that in 1877 Dr Stefanini and Dr Camillo Golgi performed in Pavia an autopsy on a patient who had suffered from *"emoglobinuria da freddo"* (cold haemoglobinuria) for five years. The arteries were atheromatous, the liver was quite normal, but the spleen was nearly twice the normal size. The kidneys were enlarged; the capsule fully stripped. The cortex was easily lacerated and the surface was marked with *"dark rose points"*. The medullary pyramids were hyperaemic and distinctly showed many red striae. Microscopically, they found *"una leggera nefrite diffusa e specialmente interstiziale"* (a mild diffuse and especially interstitial nephritis).

In 1880, Dr R. Lepine of Lyon published a report of a case mentioning the typical pattern of nocturnal haemoglobinuria: "It is only at night that urine was blood coloured, around 11:00 o'clock or midnight, the urine was blood-coloured and not the other specimens. The colouring was, moreover, as I have said, intense. On microscopic examination several times repeated, it demonstrated an absolute absence of red cells. The urine specimens which are not coloured are probably not entirely free of haemoglobin". Lepine contended that haemoglobinuria is in reality an unusual form of haematuria that the red cells are lost as such by the kidney, and are lysed in the very diluted urine in the renal tubules. He concluded, "In the immense majority of cases the crisis is the result of cold. But we need not believe that this is the only cause. My patient had his paroxysm at midnight when he had been in bed six hours. There are at least two distinct types of paroxysmal haemoglobinuria".[8]

In 1882, Paul Strübing identified PNH as a new disease entity, indicating that these patients could have an intravascular haemolysis with a defect of red blood cells.[9] He described a 29-year-old man who presented with fatigue, abdominal pain, and severe nocturnal paroxysms of haemoglobinuria. By provocative tests, he differentiated this affection from other forms of paroxysmal haemoglobinuria, proposing theories of pathogenesis based upon analysis of his clinical observations. He first hypothesised the nocturnal paroxysms of haemoglobinuria as a consequence of lysis of "abnormally sensitive erythrocytes" secondary to systemic acidosis from CO_2 accumulation during sleep.[10] Strübing described haemosiderinuria with these words: "a fine grained, yellowish-brown detritus and fine-grained casts of the same colour. Free in the sediment were found yellow-brown renal epithelial cells".

2.2. History of PNH: First decades of twentieth century

In 1894, Jules Bordet found that complement binds to antibody-antigen complexes regardless of the antigen or antibodies involved; for his research on the complement, he was awarded the 1919 Nobel Prize in Physiology or Medicine.[11] Fifteen years later, Dr Hijmans Van Den Bergh, in line with Bordet's discovery, considered the possibility that the complement system mediated the haemolysis of PNH erythrocytes.

He demonstrated that erythrocytes from a similar patient were lysed in normal serum as well as in the patient's

serum if the mixture was acidified with carbon dioxide.[12] He also confirmed that the haemolytic process was due to a defective red cell and related to complement dysregulation.[13]

The same year (1911), the Italian scientists Ettore Marchiafava and Alessio Nazari scrupulously described the pathogenesis of the condition. They believed that haemolysis occurred in the kidney: the scientists called the reported case "acquired haemolytic anemia, Widal-Abrami type", characterised by "massive amounts of haemosiderin in the urine".[14] In 1925, Dr Enneking introduced for the first time the name "paroxysmal nocturnal haemoglobinuria", to define this pathology.[1]

In 1928, Ettore Marchiafava reported a second case: he believed he had identified a new disease entity and he proposed that it be called "chronic haemolytic anaemia with perpetual haemosiderinuria".[15] In 1930, Micheli, Marchiafava's pupil, continued his mentor's research work. He studied Marchiafava's second patient and published his observations. Micheli termed this condition "splenomegalic haemolytic anaemia with haemoglobinuria-haemosiderinuria, Marchiafava type".[16]

In 1939, Sir Thomas Hale Ham[17] and Dr John Dingle devised the first diagnostic test for PNH based on the relationship of complement activation to the haemolysis in PNH, named the Ham test.[18]

In 1960, Metz et al[19] demonstrated that the degree of suppression of erythrocyte acetylcholinesterase activity is directly proportional to the severity of this disease.

In 1969, Aster and Enright[20] showed that PNH platelets and neutrophils are abnormally sensitive to complement-mediated lysis, providing evidence that the PNH defect arose in a primitive hematopoietic stem cell. The same year, Edward Hoffman described for the first time the decay accelerating factor (DAF) or CD 55. He found that this factor, prepared from human erythrocyte membranes, inhibited complement-mediated haemolysis. This substrate enhanced the rate at which the complement C3 convertase diminished over time.[21]

2.3. PNH: 1980s to current days

Dockter and Morrison,[22] in 1986, demonstrated with indirect immunofluorescence analysis of a monoclonal antibody specific for a surface epitope of human erythrocyte acetylcholinesterase, that the erythrocytes of PNH patients presented deficiencies in acetylcholinesterase, a GPI-anchored protein.

In 1989, Dr Charles Parker et al[23] isolated for the first time the membrane inhibitor of reactive lysis (MIRL, CD59), the encoding protein of (GPI)-anchored cell surface glycoprotein that inhibits the final step of membrane attack complex (MAC) formation.[24]

In the mid-1990s, a fundamental change was brought about in the diagnosis of PNH: flow cytometry of the peripheral blood superseded the Ham Test as the definitive clinical assay. Until 1994, patients were diagnosed using the Ham test or modified versions of the test.[25]

Brodsky et al[26] in the 2000 developed the Fluorescein-labelled proaerolysin reagent (FLAER), based on a fluorescently labelled inactive variant of the aerolysin protein that binds selectively to GPI anchors.

Despite increased knowledge of this syndrome, therapies for PNH were still only experimental and symptomatic, with the use of antimicrobial agents, corticosteroids and blood transfusions.

2.4. The present and future perspective of PNH therapy

The most significant development in PNH was the emergence and successful clinical trial of a humanised monoclonal antibody that inhibits terminal complement activation targeting haemolysis.[27] This agent is eculizumab, which, in 2007, remarkably changed the history of PNH.

Eculizumab radically modified the symptoms, biology, and natural history of PNH, strongly improving the quality of life of PNH patients.[28]

Ravulizumab, a long-acting C5 complement inhibitor approved in December 2018 by the US Food and Drug Administration (FDA), and in July 2019 by the European Commission, represents a new promising instrument for the treatment PNH. This drug is an eculizumab-like monoclonal antibody engineered to have a longer half-life. It is designed to produce the same benefits as eculizumab but with a more advantageous and effective dosing schedule.[29]

A second generation of anti-complement agents is currently under investigation, representing future promising instruments for the treatment of PNH.

3. CONCLUSIONS

The history of PNH shows many examples of the role of careful clinical observation and the application of the methods of science available at the time in unravelling this complex disorder.

As with all science, it is characterised by a series of "bricks", which solidify our understanding and which are built as more observations are made and better methods become available. The work of our eminent colleagues is an inspiration for both young and experienced researchers to unveil the mysteries of medicine.

ΠΕΡΙΛΗΨΗ

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Η νυκτερινή παροξυντική αιμοσφαιρινουρία (ΝΠΑ) είναι μια σπάνια κλωνική διαταραχή που επηρεάζει περίπου 1–1,5 ανά εκατομμύριο ατόμων. Χαρακτηρίζεται από αιμόλυση, κυτταροπενία περιφερικού αίματος, δυσλειτουργία μυελού των οστών, θρόμβωση, νεφρική ανεπάρκεια και αρτηριακή και πνευμονική υπέρταση. Η πρώτη περίπτωση ΝΠΑ περιγράφηκε πιθανότατα το 1793 από έναν χειρουργό, τον Dr Charles Stewart, στις ιατρικές σημειώσεις «Περιγραφή μιας ιδιαίτερης περιοδικής έκκρισης αίματος από την ουρήθρα». Τις επόμενες δεκαετίες αναφέρθηκαν αρκετές περιπτώσεις, από τους πιο διακεκριμένους ιατρούς και επιστήμονες της εποχής. Το 1882 ο Paul Strübing ήταν ο πρώτος που αναγνώρισε την ΝΠΑ ως μία νέα ασθένεια. Ο Hijmans το 1911 εξέτασε την πιθανότητα της διαμεσολάβησης του συστήματος συμπληρώματος στην αιμόλυση των ερυθροκυττάρων της ΝΠΑ και, το ίδιο έτος, οι Ιταλοί επιστήμονες Ettore Marchiafava και Alessio Nazari περιέγραψαν σχολαστικά την παθογένεση της ασθένειας. Το 1925 ο Enneking εισήγαγε για πρώτη φορά τον όρο «νυκτερινή παροξυντική αιμοσφαιρινουρία» για να περιγράψει την παθολογία. Παρά την αυξημένη γνώση περί αυτού του συνδρόμου, οι θεραπείες για την ΝΠΑ ήταν ακόμα μόνο πειραματικές και συμπτωματικές, με τη χρήση αντιμικροβιακών παραγόντων, κορτικοστεροειδών και μεταγγίσεων αίματος. Η φυσική ιστορία της ΝΠΑ άλλαξε αξιοσημείωτα μόνο το 2007, με την εισαγωγή του παράγοντα αποκλεισμού συμπληρώματος eculizumab. Το ravulizumab, ένας αναστολέας συμπληρώματος C5 μακράς δράσης που εγκρίθηκε το Δεκέμβριο του 2018 από τον Αμερικανικό Οργανισμό Τροφίμων και Φαρμάκων (FDA) και τον Ιούλιο του 2019 από την Ευρωπαϊκή Επιτροπή, αποτελεί ένα νέο πολλά υποσχόμενο μέσο για τη θεραπεία της ΝΠΑ. Η δεύτερη γενιά αντι-συμπληρωματικών παραγόντων βρίσκεται υπό έρευνα, αντιπροσωπεύοντας μελλοντικά ελπιδοφόρα μέσα για τη θεραπεία της ΝΠΑ.

Λέξεις ευρετηρίου: Αναστολή συμπληρώματος, Εκουλιζουμάμπη, Νόσος Marchiafava-Micheli, Νυκτερινή παροξυντική αιμοσφαιρινουρία, Ραβουλιζουμάμπη

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CLINICAL CASE
ΚΛΙΝΙΚΗ ΠΕΡΙΠΤΩΣΗ

A historical appraisal of lupus nephritis

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Μια ιστορική ανασκόπηση της νεφρίτιδας του λύκου

Περίληψη στο τέλος του άρθρου

The understanding of lupus nephritis over the past five decades has been phenomenal. Kidney biopsy is now the gold standard for its diagnosis, evaluation and management. However, lupus nephritis is a medical entity of recent vintage. The term "lupus", derived from Latin for wolf, was introduced in the Middle Ages to label nondescript erosive skin lesions resembling wolf bites. The specific dermatologic features of lupus were characterised as a non-erosive "erythematous" butterfly rash in 1828 and termed "lupus erythematosus" in 1850. Their association with systemic manifestations was described in 1872 as "disseminated lupus erythematosus". The generic term "nephritis" was first used to describe the renal lesions of systemic lupus erythematosus (SLE) in 1902. Although albuminuria and abnormal urine sediment were often noted in SLE patients, initial studies of their renal changes was limited to post-mortem studies. Clarification of the lesions of lupus nephritis came only after the introduction of kidney biopsies in the 1950s and was refined thereafter by immunofluorescent and electron microscopic studies. Subsequent studies of lupus nephritis paralleled the emerging discipline of immunology that identified autoimmunity as the cause of SLE. The varied lesions observed in lupus nephritis were classified by glomerular changes in 1975 and refined in 2003.

Key words

Collagen diseases
Lupus erythematosus
Lupus nephritis
Nephritis
Systemic lupus erythematosus

1. INTRODUCTION

Lupus nephritis, a serious manifestation of systemic lupus erythematosus (SLE), is an entity of recent vintage. SLE is a disease that can be difficult to diagnose because of the variable nature of its clinical manifestations, its recurrent episodes of recovery and relapse, and the numerous antigens and antibodies incriminated in its pathogenesis, especially since the failure to find them does not rule out the diagnosis of SLE while their presence is not invariably associated with clinical evidence of disease.[1] Kidney biopsy has become an essential component of the diagnosis, course, outcome and management of renal involvement in SLE.[2–5] The history of lupus nephritis can best be gleaned from an appraisal of how an ancient skin disease came to be identified as a systemic disease of varied manifestations, including that of kidney disease, which is now recognised as the most serious of its many complications.

2. LUPUS

2.1. An ancient skin disease

The term *lupus*, derived from the Latin for wolf, was introduced to label a vague group of ulcerative or necrotic skin lesions that resembled wolf bites.[6–11] As a lesion of external manifestation, it was readily observed and attracted medical attention early in the history of medicine. It is generally accepted now that the disease made its entry into the parlance of medicine in the fourth century BC, in the Hippocratic Corpus as *"herpes esthiomenos"*, designating an erosive or corroding lesion that gnaws at the skin (*esthiomenos*) and creeps like a snake (*herpes derived from the Greek "herpein" for the verb "to creep"; a compound word from the Greek verb esthio meaning "to eat" and herpein...*).[6–12] In earlier Cnidian medicine it had been referred to as *"serpiginous ulcers"*. The appearance and usually the spread of the lesion have continued to determine its nomenclature. Thus, it was likened to the crawling of ants by the Roman encyclopaedist Celsus (c. 25 BC–c. 50 AD) who dubbed it *"formica corrosiva"* and *"formica ambulativa"*, terms that entered Arabic medicine as a lesion that spreads like ants, *"namleh"*.[6–11] The preceding animal iconography of the skin lesions is likely what led in the Middle Ages to noting their resemblance to the bites of a hungry wolf that gnaws at the skin of its victims, hence their being termed *lupus*. This new nomenclature is likely due to the fact that it was in the Middle Ages that changes in landscape to ac-

commodate the expanding agricultural undertakings of feudal estates led to deforestation, changing the habitat of the native wolves who as predatory animals attacked the now adjoining farmers and their herds. It is also then that stories related to the "big bad wolf" began to appear in the literature of the period.[13]

Use of the term *"lupus"* for the Hippocratic herpetic lesions has been attributed to the Salertinian surgeon Rogerius dei Frugardi (c. 1140–c. 1195). Actually, lupus is mentioned in an earlier 10th century account of the magical healing of the skin disease of Heraclius (d. 971), bishop of Liège, by the intercession of St. Martin of Tours (d. 397) who appeared to him in a dream and miraculously saved the bishop from *"the point of death by the disease called lupus"*. The failure of the skin lesions to respond to treatment and their aggravation by the irritant agents used then led to their being also termed *"noli me tangere"*, the Latin version of the Biblical "touch me not" to indicate that they are best left alone rather than manipulated.[6–11] Under any circumstance, the skin lesion we now term lupus erythematosus may not have been called lupus throughout most of past medical history as the term was then applied to a varied cluster of nondescript erosive skin lesions.[14]

Some elucidation of the vague entity that was lupus began to surface in the 19th century, when medicine transitioned from its roots as a descriptive discipline into one based on explanatory and investigative studies (fig. 1). It was during this epochal transformative period that medical specialties began to emerge including that of dermatology whose studies were clarified by the publication of atlases of life-like coloured illustrations of skin lesions that allowed for the more accurate comparative study of specific skin diseases than that of their past rather ambiguous verbal description. This step forward was enhanced by improved histological techniques of examining skin biopsies that led to the use of morphological criteria in characterising skin lesions in general and of lupus in particular. It was then that the specific dermatologic features of lupus rather than being corrosive were characterised as a warm reddish rash that spread centrifugally (*érythéme centrifuge*) in 1828 by the French dermatologist Laurent T. Biett (1781–1840) and dubbed *"lupus érythémateux"* (lupus erythematosus) in 1850 by his student Pierre Alphée Cazenave (1795–1877).[6–11] This was the first qualification of the skin lesion of lupus by its colour as an erythematous rash that is circular and spreads centrifugally, and its differentiation from the host

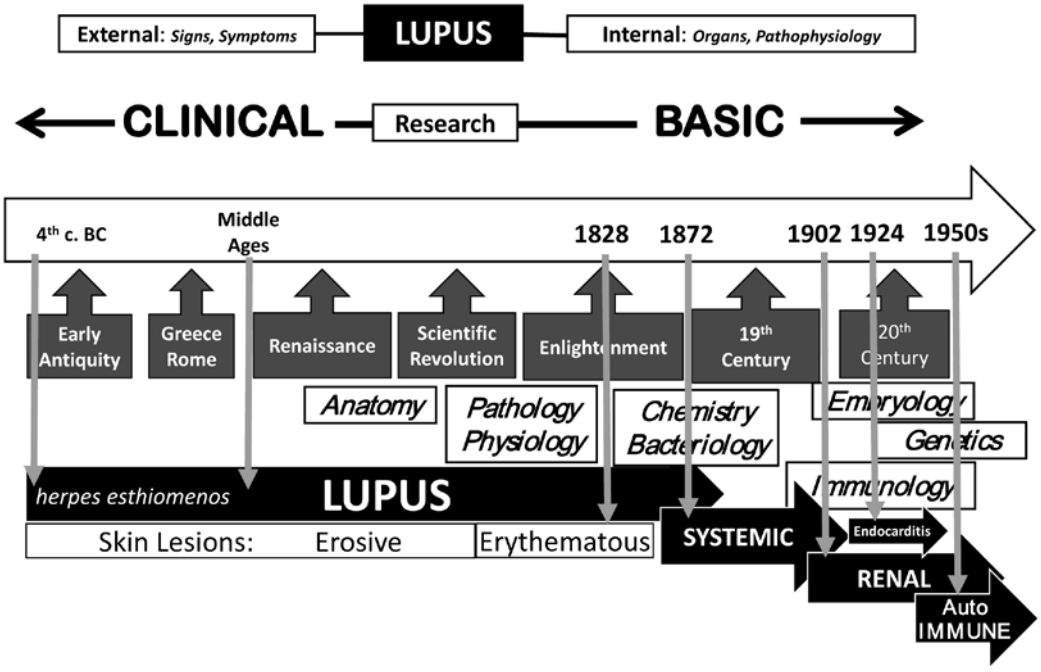

Figure 1. A timeline of the evolution of the disease that came to be called lupus and the emergence of lupus nephritis as a kidney disease. The upper part of the figure shows the conceptual evolution of diseases from a descriptive clinical phase of external findings to that of an investigative basic research phase of internal organ involvement and pathophysiology. The long arrow in the centre of the figure represents a time line of the classic historical periods shown in the black boxed arrows (with white lettering) below the long arrow. Immediately below those, shown in white rectangular boxes (with *italic* black lettering) are the corresponding temporal emergences of the basic sciences. The bottom arrows show the timeline of the evolution of lupus from its recognition in antiquity as an erosive skin lesion (*herpes esthiomenos, lupus*) to its identification as a systemic disease in 1872, affecting the kidneys in 1902, causing endocarditis in 1924 and its ultimate determination as an autoimmune disease.

of varied erosive skin lesions with which it had been classified theretofore, particularly those of then prevalent skin lesions of tuberculosis known as *"lupus vulgaris"*.[15]

Of note in this regard and relevant to the kidney is the two-volume illustrated atlas of skin diseases published in 1826–1827 by the French dermatologist, later nephrologist, Pierre Rayer (1793–1867), a contemporary of Biett and Cazenave in Paris.[16] In his book, published two years before Biett's report, Rayer classifies lupus as a tubercular lesion.

2.2. A systemic disease

Lupus erythematosus continued to be considered a skin disease until 1872, when the Austrian dermatologist Ferdinand von Hebra (1816–1880) and his son-in-law Moritz Kaposi (1837–1902) reported some of the systemic manifestations of the disease such as arthralgia, fever, weight loss, anaemia, amenorrhea, lymphadenopathy, and pulmonary inflammation. It is on this basis that Kaposi went on to separate the lesions of lupus erythematosus as limited to the skin only or *"discoid lupus"* as opposed to the one associated with systemic manifestations or *"lupus disseminates"* (disseminated lupus).[6–11] To avoid confusion in using the adjective "disseminated", it was proposed to replace it by "systemic" in 1904 by the German dermatologist Josef Jadassohn (1863–1936) (fig. 1).[11–17] Still, the use of "disseminated lupus" prevailed well into the 1960s, when it was finally replaced the more specific "systemic lupus erythematosus" now in use.

Even after the description of its systemic manifestations, lupus remained in the realm of dermatology until 1924 when the non-bacterial valvular and mural atypical verrucous cardiac lesions of SLE were described by Emmanuel Libman (1872–1946) and Benjamin Sacks (1896–1971), and achieved prominence as the eponymous *"Libman-Sacks endocarditis"*.[18] All glomerulonephritis. It was because of the prevailing interest in diseases of the heart at the time that this new cardiac feature more than any of the other reported systemic manifestations of the disease rekindled interest in SLE. It was in the course of studies of cases of Libman-Sacks disease that lupus nephritis was reported then by George Baehr (1887–1978), who had a standing interest in the glomerular lesions of endocarditis.[19,20]

It was from these studies of Libman-Sachs endocarditis that a distinctive pathologic feature of SLE was identified in the early decades of the 20th century as a mucoid degeneration of the collagen tissue of involved organs that was termed *"fibrinoid necrosis"* by the pathologist Paul Klemperer (1887–1964) and his associates.[19] In their original 1935 report of fibrinoid necrosis in the visceral lesions of 23 cases of SLE studied at post-mortem, all of their 23 cases had albuminuria or an abnormal urine sediment, and 18 of them had glomerular abnormalities on microscopy.[20] Also, it was within the concept of fibrinoid degeneration that the descriptive term "*wire loop*" lesion of the kidney was introduced and came to be considered pathognomonic of SLE, being observed in 20% to 60% of autopsied cases.[21]

2.3. A kidney disease

The further study of SLE led to the identification of a rapidly progressive so-called "active" form of the disease that was associated with grave complications and usually a fatal outcome within a period of weeks to five years. It was from the post-mortem studies of these "active" cases that the renal lesions of lupus were first identified. Credit for the early study of the kidney in SLE belongs to a forgotten nephrologist, Norman M. Keith (1885–1976), one of the many generalist pioneers of the 20th century who devoted most of their effort to the study of the kidney in the period that preceded the emergence of nephrology as a specialty in 1961.[22] Notable amongst his publications is one from 1922, describing four cases of SLE with definite renal manifestations (proteinuria, haematuria, casts, azotemia, elevated creatinine) and of glomerular proliferative lesions of the kidney in the one case that was studied at post-mortem.

Early attempts at describing lupus nephritis were all based on post-mortem observations. It was the advent of percutaneous needle biopsy of the kidney that would set the next stage for the emergence of the term "lupus nephritis".[23] In fact, one of the first applications of percutaneous kidney biopsies was to the study of SLE leading to a milestone article published in 1957 by the Chicago team of Robert Kark (1911–2002), Conrad L. Pirani (1914–2005), Robert Muehrcke (1921–2003) and Victor E. Pollak.[24] Based on kidney biopsies from 33 patients they demonstrated for the first time the different glomerular changes of lupus nephritis based principally on light microscopy. These initial studies enriched by immunofluorescent and electron microscopic studies on 87 patients was reported in yet another landmark paper on lupus nephritis in 1964 by the same authors.[25]

On the basis of these and subsequent studies, the varied renal lesions of SLE came to be classified as normal, glomerulitis, active glomerulonephritis and membranous glomerulonephritis. At the time, the mesangium was still not identified as a distinct structural component of the glomerulus, and glomerulitis referred to what would later become the mesangial lesions of SLE.[26] A first attempt to

classify the renal lesions of SLE was by the World Health Organization (WHO) that was published in 1975. With increased use of immunopathologic and electronmicroscopic studies attempts at refining the classification of lupus nephritis were formalised under the joint auspices of the International Society of Nephrology (ISN) and the Renal Pathology Society (RPS) in 2003. The six categories described are based primarily on the glomerular changes, but also include as subcategories those that affect the vasculature, tubules and interstitium.[27,28]

2.4. An autoimmune disease

Throughout the period when its clinical features were being identified SLE went on as a disease of unknown etiology.[29] The solution to its pathogenesis would come from the study of infectious diseases that solved the mystery of contagious diseases and launched the study of bacteria in the 1860s. The toxins produced by bacteria and their specific antitoxins produced by the defensive system of the body in time became the antigens and antibodies of immunology. It was the study of how the body protects itself against the threat of foreign pathogens that provided a better understanding of how the immune system senses, attacks and deals with these invaders without destroying the body's own cells and tissues.[29,30]

It was within these evolving early notions of immunology that a pathognomonic feature of SLE emerged from the observation of haematoxylin bodies in the cardiac lesions of Libman-Sacks disease in 1932. These were the damaged nucleoproteins of injured cells which when ingested by leukocytes became the LE cells first identified in 1948 by the haematologist Malcolm Hargraves (1903–1982) and his associates.[31,32] The discovery of LE cells resulted in the more accurate differentiation of SLE from other connective tissue disorders. Soon afterwards the serologic factor inducing the LE cell was identified as a gamma globulin in 1958 and termed antinuclear antibody (ANA).[32] The almost simultaneous availability of antibiotics, adrenocorticotropic hormone and adrenal corticosteroids to control the clinical manifestations of SLE led to improved survival of SLE patients and allowed for the long-term studies of the evolution of lupus nephritis by repeated kidney biopsies.

As originally defined, the immune system was conceived as a defender of the self from exterior attacks. When the possibility that the immune system can malfunction and unleash its destructive forces upon the body began to be recognised in the 1950s it was considered anathema to the wisdom of the body as a well-ordered machine in which the immune system was the protector of the self. This betrayal, dubbed *"horror autointoxicus"* by Paul Ehrlich (1854–1915), was ultimately shown to be the inability of the body to maintain immune tolerance against its own cells and identified as the cause of autoimmune diseases.[33,34] By the 1960s autoimmunity as the mechanism underlying a variety of chronic ailments was established, with SLE as the prototypic autoimmune disease in the lead (fig. 1). That was just about the time that nephrology was flourishing as a discipline and autoimmunity came to be identified as the cause of a growing number of renal diseases and in fact immunology itself was enriched by studies of kidney disease and renal transplantation.

ΠΕΡΙΛΗΨΗ

Μια ιστορική ανασκόπηση της νεφρίτιδας του λύκου

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Η κατανόηση της νεφρίτιδας του λύκου τις τελευταίες πέντε δεκαετίες ήταν εκπληκτική. Η βιοψία των νεφρών είναι πλέον το χρυσό πρότυπο για τη διάγνωση, την αξιολόγηση και τη διαχείρισή της. Ωστόσο, η νεφρίτιδα του λύκου είναι πρόσφατη ιατρική νόσος. Ο όρος «λύκος», που προέρχεται από τη λατινική λέξη για τον λύκο, εισήχθη στον Μεσαίωνα για να επισημάνει κοινές διαβρωτικές αλλοιώσεις του δέρματος που ομοιάζουν με δαγκώματα λύκου. Τα συγκεκριμένα δερματολογικά χαρακτηριστικά του λύκου χαρακτηρίστηκαν ως μη διαβρωτικό «ερυθηματώδες» εξάνθημα πεταλούδας το 1828 και ονομάστηκε «ερυθηματώδης λύκος» το 1850. Η συσχέτισή τους με συστηματικές εκδηλώσεις περιγράφηκε το 1872 ως «διάχυτος ερυθηματώδης λύκος». Ο γενικός όρος «νεφρίτιδα» χρησιμοποιήθηκε αρχικά για να περιγράψει τις νεφρικές αλλοιώσεις του συστηματικού ερυθηματώδους λύκου (SLE) το 1902. Παρ' όλο που παρατηρήθηκε συχνά λευκωματουρία και μη φυσιολογικά ιζήματα ούρων σε ασθενείς με SLE, οι αρχικές μελέτες των

νεφρικών τους αλλαγών περιορίστηκαν σε μεταθανάτιες μελέτες. Η διευκρίνιση των αλλοιώσεων της νεφρίτιδας του λύκου ήρθε μόνο μετά την εισαγωγή βιοψιών νεφρού στη δεκαετία του 1950 και στη συνέχεια βελτιώθηκε με ανοσοφθορισμούς και με ηλεκτρονικές μικροσκοπικές μελέτες. Οι μεταγενέστερες μελέτες της νεφρίτιδας του λύκου κινούνταν παράλληλα με την αναδυόμενη επιστήμη της Ανοσολογίας που αναγνώρισε την αυτοανοσία ως την αιτία του SLE. Οι ποικίλες αλλοιώσεις που παρατηρήθηκαν στη νεφρίτιδα του λύκου ταξινομήθηκαν με σπειραματικές αλλαγές το 1975 και βελτιστοποιήθηκαν το 2003.

Λέξεις ευρετηρίου: Ερυθηματώδης λύκος, Νεφρίτιδα, Νεφρίτιδα του λύκου, Παθήσεις κολλαγόνου, Συστηματικός ερυθηματώδης λύκος

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Nephro-urology in Greek-Roman medicine
A solid catheter from the Lisbon National Museum of Archaeology

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Νεφρο-ουρολογία στην ελληνορωμαϊκή Ιατρική. Ένας συμπαγής καθετήρας από το Εθνικό Αρχαιολογικό Μουσείο της Λισαβόνας

Περίληψη στο τέλος του άρθρου

This paper discusses a solid thin catheter-shaped tube of copper alloy ending in a small scoop, found during the excavations of a Roman salting factory in the beautiful archaeological site of Troia by the sea, in the peninsula of Setubal near Lisbon. The finding shares similarities with the published hollow Roman catheters, being compared with the items. Its function was described in the medical literature on the urologic procedures and studies on Greek-Roman instruments, the finding fitting into the typology of instruments for unclogging the bladder neck from a stone blocking the passage of urine and combining the function of the ear probes, probes and catheters described in the literature for this purpose. A second similar device, in poor condition, presenting a broken end and bent in its distal part was found in the same archaeological site. These findings indicate a high prevalence of urinary lithiasis, induced by a diet rich in fish, shellfish and garum, itself used as a medicine, but containing a high amount of purines.

Key words

Catheters
Greek-roman surgical instruments
History of nephrology
History of urology
Urinary lithiasis

1. INTRODUCTION

Troia, an archaeological site facing the city of Setubal near Lisbon, was a Roman settlement from the 1st to the 5/6th cent. AD. The words Setubal and Troia share the same origin, deriving from the Latin word Cetobriga, as André de Resende (1500–1573), a Dominican friar, theologist and classicist, credited as being the first Portuguese archaeologist, reported: *"In ancient times it had flourished in the village of Cetobriga, which the inhabitants of the land call Troia"*.[1] The beauty of the ruins by the sea has attracted interest over time. However, there is still much to excavate and interpret. The main activities were fishing and the production of garum, a spiced sauce made of fermented fish, used as a condiment, and for medical uses:

"Of the therapeutic value of fish sauce, the ancient physicians, in general, are in agreement. In the treatment of internal conditions and diseases, fish sauce played an important role in the creation of medical foods administered by mouth or solutions injected as a clyster. The afflictions so remedied involved primarily the digestive tract".[2]

Alexander of Tralles (565–605 AD), one of the most prominent ancient physicians, correctly placed garum among the foods that should be avoided by patients suffering from "podagra" (gout): *"the patient should refrain from the following foods: pure wine, pork, veal and rabbit meat, and should beware of cabbage (Brassica oleracea L.), mustard, uncooked vegetables and watered garon and ensure good digestion"*.[3]

2. THE ARCHAEOLOGICAL SITE OF TROIA

During the 1st and 2nd centuries AD, salting factories produced large quantities of salted fish and fish sauces that were packed in amphorae, sold in the cities of Lusitania and exported mainly to Rome. The production was interrupted until the second half of the 2nd century. A new cycle encompassed the 3rd to the 5th century, when large factories were divided into smaller units. The diversified amphorae from that period suggest a greater variety of products, sardines being the main fish. The production of fish and salted products ceased in the first half of the 5th century, but the place continued to be occupied for at least another century. Evidence of numerous traces of salting factories with many tanks indicates that the Roman Troy was the largest centre for fish salting known in the Roman world. During the 5th and 6th century, salting factories slowly closed and the place was abandoned.[4]

The archaeological site comprises a housing area, baths, an incineration and cremation necropolis, a paleo-Christian basilica,

and industrial facilities. The houses formed blocks separated by alleys, some luxuriously decorated with mosaics and frescoes. The bath complex comprised an atrium, frigidarium, tepidarium and caldarium, hipocaustum, swimming pools, one of which decorated with mosaics, and exercise rooms. A large number of contiguous rectangular and square salting tanks were excavated near the baths.[5]

Medical-surgical instruments such as probes, spatula-probes, ear-probes, balsamaria were unearthed during the excavations. A solid tube of copper alloy shaped like a bladder catheter, ending in a small scoop, was found in the upper layer of rectangular salting workshop 22. A skeleton, a broken bone needle, two broken bone hairpins, a small bronze dish, a bronze nail, a hoop and an ear probe were found in workshop 22.[6]

Skeletons were found in some workshops that were used as tombs. In this case, it could well be the tomb of a physician. However, workshop 22 has not been interpreted as a tomb so far. The objects can be seen on the site of the National Museum of Archaeology.[7] Ana Patrícia Magalhães, the archaeologist who studied this factory, kindly conveyed her personal view concerning the probe which does not seem to have any relation with the skeleton. On the other hand, the reference to the skeleton does not indicate any tomb structure, so its type of deposition could indicate the burial of a slave, much more usual, and that would make sense given the area where it was found: a funerary space of an abandoned factory.

3. MANAGING URINARY LITHIASIS

In his work *"On Medicine"*, Caius Cornelius Celsus (25 BC–50 AD) described a large number of surgical operations performed for the first time in Western medicine. These included surgical management of urinary obstruction and bladder stone lithotomy, as a last resort when medical treatments failed. Celsus described some of these operations, probably with modifications. He described the operation of cutting for the stone into the bladder through the perineum as a hazardous procedure that should only be performed when there was no other option to relieve the patient. If the stone is large, he advised *"we must put over the upper part of it, the scoop must be rather long, for a short one has not enough strength to extract.*[8] The lithotomy scoops mentioned by Celsus have a straight shaft, the inner side of the scoop being rough to facilitate the adherence of the stone. These scoops are part of the ancient lithotomy instrumentarium. Ernst Künzl presented an example of this item.[9]

The existence of instruments devised explicitly for the procedure, such as special knives, hooks and hollow S-shaped catheters, adapted to the male urethra, is documented since the time of the Alexandrian physician Erasistratus (304–250 BC), and Pseudo-Galen, a variety of texts written in diverse periods inserted in the Galenic Corpus. In his text *"Introductio sive medicum"*, dealing with the medical management of urinary obstruction, Erasistratus praised the ability of the S-shaped catheter in emptying the bladder.[10] Celsus, referring to urinary catheterisation, advises an ear scoop to remove stones: *"Sometimes we are compelled to draw off the urine by hand when it is not passed naturally; either because in an old man the passage has collapsed, or because a stone or a blood-clot of some sort has formed an obstruction within it; but even a slight inflammation often prevents natural evacuation; and this treatment is needed not only for men but also sometimes for women. For this purpose, bronze tubes are made, and the surgeon must have three ready for males and two for females, in order that they may be suitable for everybody, large and small: those for males should be longest, fifteen finger-breadths in length, the medium twelve, the shortest nine; for females, the longest nine, the shortest six. They ought to be slightly curved, but more so for men, and they should be very smooth and neither too large nor too small".*[11]

Three Roman hollow catheters match Celsus' description (fig. 1).

According to Lawrence Bliquez, 15 male catheters and 2 female catheters have been found so far.[12] Celsus refers to the use of catheters in another condition: *"Sometimes too a stone slips into the urethra itself, and lodges not far from its orifice, because this becomes narrower further down. The stone should if possible be extracted either by an ear scoop or by the instrument with which a stone is drawn out in the course of lithotomy".*[13]

The Scottish surgeon John Stuart Milne, who carried

Figure 1. Roman catheters on display at the British museum. 1. and 2. Hollow male catheters. 3. Hollow female catheter. 1st century AD. Provenance: Italy. Credit: Wikimedia Commons file.

out the first throughout survey on Greek-Roman surgical instruments at the beginning of the 20th century, commented on this passage as follows: *"This shows that the scoop must have been quite a narrow instrument, or it could not have passed into the urethra"*.[14]

Milne questioned the existence of "solid bladder sounds" (instruments devised for probing and dilating passages within the body), some hints pointing to their use by Greek-Roman surgeons: "They must have been well aware of the characteristic grating sensation conveyed to the skilled hand on striking a stone with a metal instrument, for we have several references in the classics to a manoeuvre of pushing back by means of a catheter, a stone impacted in the urethra. […] Some instruments have come down to us, however, which seem undoubted solid bladder probes sounds.[15]

Milne gives the example of instrument no 3 on Plate XVI displaying catheters from the House of the Surgeon in Pompei (fig. 2).

Aretaeus of Cappadocia, a remarkable Greek physician from the 1st century BC, provides a similar description: *"But, if it is the impaction of calculi which stops the urine, we must push away the calculus and draw off the urine. With the instrument, the catheter, unless there be inflammations"*.[16]

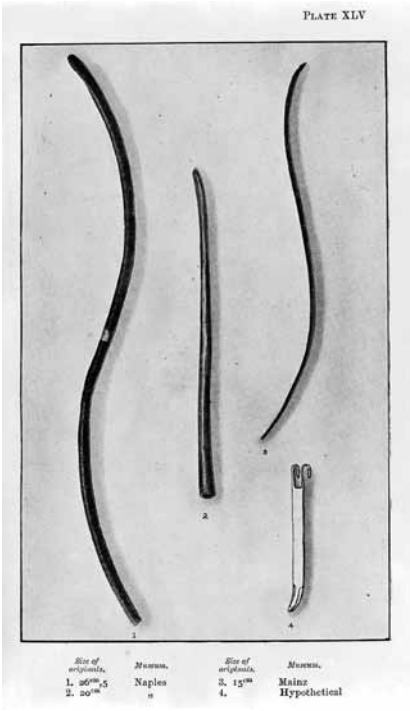

Figure 2. Milne JS. Surgical instruments in Greek and Roman times, Plate XVI.

Rufus of Ephesus (70–110 AD) refers to the manoeuvre when the physician did not want to perform the cutting operation: *"Si l'on ne veut pas recourir à l'incision pour les pierres engagés dans l'urètre, on doit les repousser avec la sonde"* (If we do not want to perform the incision when the stones are impacted in the ureter, we must push them with a probe).[17]

Caelius Aurelianus, a Roman physician from Sicca Venerea in Numidia, from c. 400 AD, provided information on the diagnostic use of a probe, a thin instrument that could be inserted through the urethra for the management of bladder obstruction: *"But, since the same symptoms occur in ulcerated bladder, stone of the bladder, and in cases of difficulty in urination due to the impediment of a blood clot, the suspicion that a stone has formed in the bladder will have to be corroborated by the use of a probe"*.[18]

Caelius Aurelianus reports having given details of the probe in his treatise "Answers". Unfortunately, the few extant manuscripts do not include the surgical part containing information on the probe.[19]

4. THE SOLID CATHETER FROM TROIA

The piece from Troia is a solid thin catheter-shaped tube of copper alloy ending in a small scoop. The distal end is broken (fig. 3).

Although with a less pronounced double curvature, it has a shape similar to the S-catheter introduced in Greek-Roman medicine by Erasistratus. Unlike catheters to void bladder urine, the device is thin and solid, ending in a small scoop, appearing to be devised to be introduced into the urethra to unclog stones from the bladder neck with the small scoop (fig. 4). Since the instrument is not well preserved, it is not possible to check the roughness of the inner side.

A similar piece was unearthed in the Troia excavations.

Figure 3. Solid catheter Inv. 983.47.19. Dimensions: length: 23.5 cm; thickness 0.12 cm. Credit: José Paulo Ruas (DGPC), National Museum of Archaeology.

Figure 4. Solid catheter. Detail of the scoop.

It is in poor condition, presenting a bent shaft and broken distal end. Inv. 983.3.290. Dimensions: length: 17 cm, thickness: 0.23 cm.[7]

For this study, catheters from the collections of Greek-Roman instruments have been compared to the Troia solid tube, aiming to find its place and possible function, based on the writings of classical medical authors on urologic manoeuvres. Caelius Aurelianus refers to an easy manoeuvre, although probably just occasionally successful in women with impacted calculi in the urethra: "And women patients even insert their fingers into the vagina, and themselves remove the stone by gradually working it forward.[20]

Apart from these cases, the ancient authors described a lesser complicated and lesser dangerous manoeuvre than the stone cutting operation left for large stones, as Caelius Aurelianus stated: "Prescribe lithotomy in cases where a larger stone has been formed.[21]

They mostly refer to three types of instruments for carrying out a less troublesome procedure: a scoop, a catheter and a probe. The instrument from Troia finds the most similar parallelism in Milne´s solid catheter from the House of the Surgeon in Pompei. Nevertheless, this catheter does not end in a scoop. The instrument is similar to an ear probe from the Roman city of Balsa in Algarve, South of Portugal, in Algarve, also housed in the Lisbon National Museum of Archaeology, but it is shorter and has a straight shaft (fig. 5).[18]

The device from Troia seems to combine this kind of ear probe with a thin solid catheter, devised by a physician to match the function described by Celsus and the similar manoeuvres described by Caelius Aurelianus, Areteus of Cappadocia and Rufus of Ephesus. Physicians invented the instruments that they needed as Galen of Pergamon (130–210 AD) sadly highlighted after losing valuable goods,

Figure 5. Ear probe. Inv. 983.288.21. Copper alloy. Length: 11.8 cm. Photo archive: Lisbon, National Museum of Archaeology.

including books and wax models for surgical tools after a fire: *"Some, valuable for medical purposes, I said I had lost but still hoped to replace, but other instruments I had invented myself, making models out of wax before handing them over to the bronze-smiths"*.[22]

The finding of two similar catheter-shaped ear probes in a salting factory could indicate a high prevalence of urolithiasis, induced by a diet rich in fish, shellfish and garum, containing a high amount of purines. Uric acid stones are one of the four major types of kidney stones, together with calcium stones (calcium oxalate and calcium phosphate), struvite stones and cystine stones.[23]

5. CONCLUSIONS

The extant instruments and textbooks appear to contain sufficient evidence for an alternative theory to place this piece, discovered in the ruins of Troia and housed in the Lisbon National Archaeological Museum. In our view, it plays the role of three types of instruments for dislodging stones from the bladder neck: a scoop, a catheter and a probe, finding its place within the instrumentation of Greek-Roman nephro-urology.

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ΠΕΡΙΛΗΨΗ

Νεφρο-ουρολογία στην ελληνορωμαϊκή Ιατρική. Ένας συμπαγής καθετήρας από το Εθνικό Αρχαιολογικό Μουσείο της Λισαβόνας

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Το παρόν άρθρο πραγματεύεται έναν συμπαγή λεπτό σωλήνα σε σχήμα καθετήρα από κράμα χαλκού που καταλήγει σε ένα μικρό κοχλιάριο, που βρέθηκε κατά τη διάρκεια των ανασκαφών ενός ρωμαϊκού εργοστασίου αλατιού στον όμορφο αρχαιολογικό χώρο της Τρόια, δίπλα στη θάλασσα, στη χερσόνησο του Setubal κοντά στη Λισαβόνα. Το εύρημα παρουσιάζει ομοιότητες με τους δημοσιευμένους κοίλους ρωμαϊκούς καθετήρες, οι οποίοι έχουν συγκριθεί με τα δημοσιευμένα αντικείμενα. Η λειτουργία του περιγράφηκε στην ιατρική βιβλιογραφία για τις ουρολογικές διαδικασίες και μελέτες για τα ελληνικο-ρωμαϊκά όργανα. Το όργανο ανήκει στην ομάδα οργάνων που χρησιμοποιούνται για την απόφραξη του αυχένα της ουροδόχου κύστης από μια πέτρα που εμποδίζει τη διέλευση ούρων και συνδυάζει τη λειτουργία των ανιχνευτών σημείων, ανιχνευτών και καθετήρων που περιγράφονται στη βιβλιογραφία για το σκοπό αυτό. Μια δεύτερη παρόμοια συσκευή, σε κακή κατάσταση, παρουσιάζοντας ένα σπασμένο άκρο και λυγισμένο στο περιφερικό τμήμα της, βρέθηκε στον ίδιο αρχαιολογικό χώρο. Αυτά τα ευρήματα υποδηλώνουν υψηλό επιπολασμό της λιθίασης του ουροποιητικού συστήματος, που προκαλείται από μια διατροφή πλούσια σε ψάρια, οστρακοειδή και γαύρο, η οποία χρησιμοποιείται ως φάρμακο, αλλά περιέχει μεγάλη ποσότητα πουρινών.

Λέξεις ευρετηρίου: Ελληνορωμαϊκά χειρουργικά εργαλεία, Ιστορία της Νεφρολογίας, Ιστορία της Ουρολογίας, Καθετήρες, Λιθίαση του ουροποιητικού συστήματος

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Another case of organ blindness in the history of combined eye-kidney disorders
Wilson's disease

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Wilson's disease, or hepatolenticular degeneration, is a rare genetic disorder of copper metabolism. The disease leads to the accumulation of copper in the brain, liver, eyes and kidney. The dominant triad of the syndrome is nodular liver cirrhosis, Kayser-Fleischer ring in the corneas, lesions of the cortex and basal ganglia. In addition, a defect in proximal tubule reabsorption has been noted. The syndrome has been named after Samuel Alexander Kinnier Wilson (1878–1937). It was initially considered a purely brain disease, described by Frerichs in 1861. In 1883, Carl Westphal in Germany described two cases of what he termed "pseudosclerosis". These and other reports led Wilson to propose the existence of the new clinical entity with degeneration of the brain lenticular nucleus and of the liver in 1912. "Pseudosclerosis" and "Wilson's disease" were later found to be the same disease. In 1913, Rumpel introduced the study of copper in the liver in a case of pseudosclerosis. The renal dysfunction included the discovery of aminoaciduria, glycosuria, increased urate excretion, reduced renal plasma flow (RPF) and glomerular filtration rate (GFR), and specific histological lesions. A complete physiological study of the kidney was then presented in 1957 by Bearn and Gutman, who confirmed the reduced RPF and reduced GFR, and reduced secretory and reabsorptive tubular function. The ocular findings in Wilson's disease were identified in 1902 by Bernhard Kayser and Bruno Fleischer in Germany, who first described the typical ring in the cornea that still brings their names. In conclusion, the history of renal and eye involvement in Wilson's disease appears as another case of organ blindness; that is, attention to the predominant symptom leads to neglecting the involvement of other organs in multisystemic diseases. The sequence of discoveries and hypotheses reflects the technical advancement of each specific historical period.

Μια ακόμη περίπτωση τύφλωσης οργάνων στο ιστορικό των συνδυασμών νεφρικών και οφθαλμικών διαταραχών: νόσος του Wilson

Περίληψη στο τέλος του άρθρου

Key words

Carl Westphal's pseudosclerosis
Organ blindness
Wilson's disease

1. INTRODUCTION

Wilson's disease, or hepatolenticular degeneration, is a rare genetic disorder of copper metabolism. The disease leads to the accumulation of copper in the brain, liver, eyes and kidney. The dominant triad of the syndrome is nodular liver cirrhosis, Kayser-Fleischer ring in the corneas, lesions of the cortex and basal ganglia. Besides, a defect in proximal tubule reabsorption has been noted.[1] The syndrome involving the basal ganglia degeneration and liver damage has been named after Samuel Alexander Kinnier Wilson (1878–1937).

The modern description of combined liver-brain disease probably starts with Frerichs in the 1850s, who focused on the liver damage, and Karl Westphal in 1883, who focused on the nervous disease. The kidney problem emerged many years afterward. Certainly, other cases of hepatolenticular degeneration were observed before; however, the neurological and neuro-pathological doctrines were not sufficiently mature to make them distinguishable from other cases, and the attention to liver cirrhosis was also immature. Regarding the kidney, we shall see that even though Bright's disease and the Fanconi Syndrome were formulated, they did not attract the physicians' attention enough, a phenomenon we call "organ blindness".

Concerning the neurological and neuropathological doctrine, the mid-1800s was a gold period, with a convergence of neurological anatomy and pathology, and

several important neurologists including: (a) Moritz Heinrich Romberg (1795–1873), who wrote the "Lehrbuch der Nervenkrankheiten des Menschen" in 1846, the first neurology textbook; (b) Theodor Meynert (1833–1892) who taught Sigmund Freud, Karl Wernicke, Sergei Korsakoff, Auguste-Henri Forel, Paul Flechsig, (c) Carl Westphal (1833–1890). Regarding liver disease, it is useful to remember that the term "cirrhosis" was introduced by Renè Laennec (the inventor of the stethoscope) in his treatise "De l'auscultation médiate" in 1819.[2] The term was then made common by William Osler (1849–1919) in his widely used textbook "Principles and Practice of Medicine" in 1892. However, "liver induration" had already received attention at the time; see e.g. John Browne (1642–1700)[3] and Matthew Baillie (1761–1823).[4] Baillie was also one of the fathers of pathology based on the study of organs of the body, which, as shown below, was part of the methodology used by Wilson. This suffices to explain Frerichs' interest.

1.1. From Frerichs to Wilson

Friedrich Theodor von Frerichs (1819–1885), head physician at the Charité in Berlin was an eminent physician of the time. He had very famous students such as Paul Ehrlich, a Nobel prize winner for his contribution to immunology and chemotherapy and Paul Langerhans, who discovered the cells producing insulin. He wrote the first German book on nephrology and made a microscopic study of Bright's disease (today called Chronic Kidney Disease). He first described aminoacids in urine and the theory of uremic intoxication or "Frerichs' theory".[5] He also gave a first description of the hepato-renal syndrome. Frerichs was greatly interested in liver diseases, which he studied using autopsy, and in 1854 wrote the classic "Treatise on Diseases of the Liver".

In the second volume of the treatise, he reported a case of combined brain and liver disease (Observation no VIII). The patient, named Carl Zeppner, was 10 years old and suffered from progressive, rapid neurological deterioration (dysphagia, anarthria, tremor); the boy died after a few days. At autopsy, Frerichs observed a small liver "its surface was covered with nodules, varying in size from a pea to a bean". This case later came to Wilson's attention, who acknowledged the famous physician for this early observation. However, Frerichs described this case as part of a series of liver diseases in the chapter "Varieties of granular induration of the Liver, and Illustrative cases". He was not interested in the neurological symptoms, and the autopsy of the boy was indeed focused on the liver and did not cover the brain.

At the extreme opposite, a contemporary famous neurologist, Carl Friedrich Otto Westphal (1833–1930), in Germany, focused entirely on the neurological symptoms and failed to focus on the liver. Westphal was an influential psychiatrist who worked in Berlin at Charitè. The nucleus of the third pair of cranial nerves is named after him (Edinger-Westphal nucleus). He had Arnold Pick and Karl Wernicke as students. In 1883, he described two cases of what was almost certainly Wilson's disease: neurological aspects similar to "multiple sclerosis", but without white matter degeneration at autopsy.[6] Westphal named the disease "pseudosclerosis", without noticing the liver involvement. Wilson knew this work.

Afterward, five other physicians reported cases of combined liver-brain diseases:

- Adolph Strümpell in Germany in 1898 described other cases of Westphal's pseudosclerosis, and in one case also the presence of liver cirrhosis.[7,8] These were also noted by Wilson. After Westphal and Strümpell, the term "Pseudosklerose" gained ground and was also used by Spiller in 1898[9] and Jakob in 1921.[10] No neurologist or liver physician at the time could recognise that Pseudosklerose and hepato-lenticular degeneration were the same entity, and two separate streams of studies started.
- Sir William Gowers reported a case (later cited by Wilson), published in 1906, of a fatal case of a girl of 15 with "Tetanoid chorea and its association with cirrhosis of the liver". "Tetanoid chorea" and Westphal's "pseudosclerosis" were likely the same disease. This work too was then reported by Wilson.[11]
- Gabriel Anton of Halle also published a separate case under the title "Dementia choreo-asthenica with juvenile nodular cirrhosis of the liver",[12] which Wilson later devised as a case of congenital syphilis.
- One case of combined brain and liver disease was also furnished by J.A. Ormerod in 1890.[11]
- Three other cases by Homén, of Helsingfors in 1890.[11]

These reports finally led Wilson in the UK to propose the existence of a new clinical entity with degeneration of the brain lenticular nucleus and of the liver, in 1911.[13]

Wilson was a British neurologist at the National Hospital, Queen Square, London. He presented a thesis entitled "Progressive lenticular degeneration: a familial nervous disease associated with cirrhosis of the liver", and the year after a famous paper in the journal *"Brain"*.[11] In his seminal work, Wilson recognised both Sir William Gowers and Dr JA Ormerod "for permission to utilise their notes".

It is not surprising that the same disease was renamed and re-discovered several times (granular induration of the liver, pseudosclerosis, tetanoid chorea, hepatolenticular degeneration with cirrhosis) over about 60 years. The methods were similar: neurological examination and autopsy. However, each author prioritised a specific symptom (neurological or liver disease) assigning secondary relevance to other symptoms. We already see here the origin of what we call "organ blindness". Such "blindness" or inattention meant it took 60 years to establish a clinical entity that was in essence already known.

Wilson was possibly aided by his knowledge of the latest advances in neuroanatomy and by his attention to liver disease during dissection. The personal story of Kynnier Wilson is instructive in this regard.

He was born in 1878, the second son of Agnes MacIntosh, the daughter of Hately, a composer and precentor of the Free Church in Edinburgh and of the Reverend James Kinnier Wilson (their daughter Anne was born in 1878). James, a Presbyterian minister from Ireland, studied at Princeton and was a renowned Assyriologist.

However, Samuel Alexander never knew his father because James died in 1879 from malaria. The family hence returned in Edinburgh, were his mother married Henry McIntosh and in 1882 had a son, Henry Walter McIntosh. The family's good financial status allowed Samuel to study medicine at Edinburgh and to make a stage in Neurology in Paris, with the famous Pierre-Marie and Babinski.[14]

Due to these studies, he was aware, and used, the Nissl staining to visualise neuronal bodies, invented by the Nobel-prize laureate Franz Nissl in Germany in 1885. He also used the staining of nerve fibres/myelin, invented by Karl Weigert in 1882. He knew (and cited) the famous neurologist sir William Gowers and Hughlings Jackson.

Moreover, at the time of his dissertation for the MD title in Edinburgh, when his seminal paper "Progressive lenticular degeneration: a familial nervous disease associated with cirrhosis of the liver" was published,[11] there was great attention to the "extrapyramidal system" and hence to the lenticular nucleus.

Finally, possibly the period was mature for greater attention to both the brain and liver because of the work on Kernicterus, cited by Wilson, by Schmorl (1861–1932): brain disease in neonatal jaundice.[15] In a series of 120 brains from jaundiced individuals, Schmorl observed intense yellow colouring in the basal ganglia (which include the lenticular nucleus). The pattern was previously also described in a case reported by Johannes Orth in 1875. Therefore, the time was ready for greater attention to the liver in case of damage to the basal ganglia.

Before leaving Wilson, we should remark on his hypotheses on the origin of the disease, which are reasoned by him as follows:

- "It seems certain that the disease is not due to a congenital or abiotrophic defect
- The presumption therefore is strong that the disease is acquired
- There is evidence to show that the disease is toxic in origin, but none to suggest that this toxin is syphilitic
- It is possible that this toxin may be elaborated in the liver
- The toxin has a specific action on the lenticular nucleus
- The nature of the toxin is unknown: it is almost certainly not microbial. Possibly it is chemical and of the nature of a lipoid."

It is remarkable that almost all hypotheses have since been confirmed. Wilson was wrong only when thinking about a lipoid toxin and that it was acquired, whereas it is inherited.

After Wilson, two major steps occurred: the fusion of the "Pseudosklerose" and "hepatolenticular degeneration" streams of study, and the recognition of corneal deposits.

1.2. "Pseudosclerosis" and "Wilson's disease" were found to be the same disease

After 1911, a debate started as to whether pseudosclerosis and hepato-lenticular disease were the same clinical entity. For instance, Fleischer noted the corneal pigmentation that carries his name in a case of pseudosclerosis in 1912. The work by Alzheimer and von Hosslin in 1912 demonstrated diffuse gliosis in the case of pseudosclerosis. Spielmeyer was the first, to our knowledge, to analyse the similarity (from a histological point of view) of pseudosclerosis and hepatolenticular disease, in 1920. In his work, Spielmeyer says "This seemed to support the opinion of leading neurologists that the clinical pictures mentioned are expressions of one and the same process - that Wilson's disease and pseudosclerosis mean the same suffering". According to Spielmeyer's report, Bielschowsky also did a histopathological comparison of pseudosclerosis and hepatolenticular disease, but concluded that there is a difference between the two.

In 1921, Hans Christian Hall also proposed that the two were identical.[16] Derek Denny-Brown reviewed the subject

in 1946 (in: Diseases of the Basal Ganglia and Subthalamic Nuclei), pointing out that "the work of Hall [...] had obscured the remarkable differences between the two syndromes" (citation from Homburger).

Therefore, Homburger and Kozol revised additional cases in 1946. They favoured the Hall hypothesis and concluded that some cases of hepatolenticular degeneration may have been misdiagnosed in the past as parkinsonism, psychoneurosis or multiple sclerosis.[17]

Thereafter, the term pseudosclerosis was not used anymore and scientists focused on the causes of the disease.

1.3. Ocular findings

The field of ocular diseases was made mature by the invention of the ophthalmoscope by Hermann Ludwig Ferdinand von Helmholtz (1821–1894). This revealed a large number of ocular findings in many known diseases.

The ocular findings in Wilson's disease were identified in 1902 by Bernhard Kayser (1896–1954) and in 1912 Bruno Fleischer (1874–1965) in Germany who first described the typical ring in the cornea that still brings their names.

Kayser made his observation in 1902, describing annular "congenital [sic] greenish discoloration of the cornea" in a patient with nervous symptoms, incorrectly attributed to multiple sclerosis.[18]

Wilson did not appreciate the work by Bernard Kayser in 1902, who described the greenish corneal pigment in a case of pseudosclerosis.

Conversely, Bruno Fleischer was not studying hepatolenticular degeneration, but, rather, pseudosclerosis. In 1912, he reported the ring in a case of cirrhosis and neuropsychiatric abnormalities. He knew the observation by Kayser, which was similar to what he was describing: "I have recently had the opportunity to see two more such cases and to repeatedly examine them in detail. The result is in both cases completely consistent with the Kayser case". Fleischer recognised that the ring heralded a neurological disorder associated with cirrhosis, shown at autopsy.

1.4. Renal involvement

In 1913, Rumpel introduced the study of copper in the liver in a case of pseudosclerosis,[19] which was confirmed by Malory in 1925; Cumings, and in parallel Denny-Brown and Porter, in 1951, definitely supported the role of copper and the use of copper ligands as therapy.

The same Denny-Brown, with Uzman, was the first to report a case of aminoaciduria in hepato-lenticular degeneration, in 1948.[20] In 1950, Cooper et al confirmed the presence of aminoaciduria.[21] Copper accumulation in the kidney was described by Wintrobe in 1954.

Stein et al and Bickel et al characterised aminoaciduria and found a loss of glycine, histidine, threonine, cysteine, serine, alanine, glutamine, tyrosine, lysine, glutamic acid, leucine, phenylalanine. Their findings definitely excluded that Wildon's syndrome was an innate metabolism disorder. A complete physiological study of the kidney was then presented in 1957 by Bearn and Gutman, who confirmed the reduced RPF and reduced GFR, and reduced secretory and reabsorptive tubular function.

1.5. Organ blindness

A simple analysis of "discovery retardation" can be obtained using technical milestones as time points that should then enable scientists to make a new discovery.

The neurological examination was very mature in the mid-1800s. Specifically, Charcot introduced brain pathology in 1868. Therefore, it took only about 12 years for Westphal to identify the "pseudosclerosis" in the 1880s.

As for liver disease, considering the work by Laennec in 1819, it took about 40 years to have the first liver degeneration case described by Frerich. Surprisingly, with a delay of 50 years, Wilson merged the liver and cerebral diseases in 1912. No technical reasons could explain such a delay. It took only 10 years to merge the pseudosclerosis and hepatolenticular degeneration by Hall in 1921, even if the debate continued for more than 20 years, up to 1946! The third characteristic, the corneal ring, was discovered with a delay of 50 years from von Helmoltz's invention of the ophthalmoscope in 1851. Even then, 10 years passed before the ring was connected to pseudosclerosis in 1912 by Fleischer, and a further 10 years before it was linked to hepatolenticular degeneration.

As for renal defects, the technique to detect aminoaciduria was available since 1861, thanks to the work of Von Frerichs, and of G. Fanconi in 1831. Therefore, the late discovery of aminoaciduria in Wilson's disease by Uzman in 1948 cannot be ascribed to a problem in the techniques or lack of paradigms. We are here with a delay of almost 100 years! This is not the only case of such a phenomenon.[22]

2. CONCLUSIONS

The history of renal and eye involvement in Wilson's disease appears as another case of organ blindness; that is, the attention to predominant symptoms leads to ne-

glecting the involvement of other organs in multisystemic diseases. The sequence of discoveries and hypotheses reflects the technical advancement of each specific historical period.

ΠΕΡΙΛΗΨΗ

Μια ακόμη περίπτωση τύφλωσης οργάνων στο ιστορικό των συνδυασμών νεφρικών και οφθαλμικών διαταραχών: νόσος του Wilson

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Η νόσος του Wilson ή ηπατοφακοειδής εκφύλιση είναι μια σπάνια γενετική διαταραχή του μεταβολισμού του χαλκού. Η ασθένεια οδηγεί στη συσσώρευση χαλκού στον εγκέφαλο, στο ήπαρ, στα μάτια και στους νεφρούς. Η κυρίαρχη τριάδα του συνδρόμου είναι η κνίδωση με κίρρωση, ο δακτύλιος Kayser-Fleischer στους κερατοειδείς χιτώδες, οι βλάβες του φλοιού και των βασικών γαγγλίων. Επιπλέον, έχει παρατηρηθεί ένα ελάττωμα στην επαναρροή της εγγύς σωληναρίου. Το σύνδρομο πήρε το όνομά του από τον Samuel Alexander Kinnier Wilson (1878–1937). Αρχικά θεωρήθηκε μια καθαρά εγκεφαλική νόσος, που περιγράφεται από τον Frerichs το 1861. Το 1883, ο Carl Westphal στη Γερμανία περιγράφει δύο περιπτώσεις αυτού που ονομάζεται «ψευδοσκλήρυνση». Αυτές και άλλες αναφορές οδήγησαν τον Wilson να προτείνει την ύπαρξη της νέας κλινικής οντότητας με εκφυλισμό του εγκεφαλικού φακού και του ήπατος το 1912. Η «ψευδοσκλήρυνση» και η «ασθένεια του Wilson» βρέθηκαν αργότερα ως η ίδια ασθένεια. Το 1913, ο Rumpel εισήγαγε τη μελέτη του χαλκού στο ήπαρ σε περίπτωση ψευδοσκληρώσεως. Η νεφρική δυσλειτουργία περιελάμβανε την ανακάλυψη της αμινοξονουρίας, τη γλυκοζουρία, την αυξημένη απέκκριση ουρικών ενώσεων, τη μειωμένη ροή του νεφρικού πλάσματος (RPF) και την ταχύτητα σπειραματικής διήθησης (GFR) και συγκεκριμένες ιστολογικές αλλοιώσεις. Μια πλήρης φυσιολογική μελέτη του νεφρού στη συνέχεια παρουσιάστηκε το 1957 από τους Bearn και Gutman, οι οποίοι επιβεβαίωσαν το μειωμένο RPF και την μειωμένη GFR και τη μειωμένη εκκριτική και επαναπορροφητική λειτουργία των σωληναρίων. Τα οφθαλμικά ευρήματα της νόσου του Wilson εντοπίστηκαν το 1902 από τους Bernhard Kayser και Bruno Fleischer στη Γερμανία, που περιέγραψαν για πρώτη φορά τον τυπικό δακτύλιο στον κερατοειδή που φέρνει ακόμα τα ονόματά τους. Συμπερασματικά, το ιστορικό νεφρικής και οφθαλμικής εμπλοκής στη νόσο του Wilson εμφανίζεται ως μια άλλη περίπτωση τύφλωσης για τον ρόλο άλλων οργάνων. Δηλαδή, η προσοχή στο κυρίαρχο σύμπτωμα οδηγεί στην παραμέληση της εμπλοκής άλλων οργάνων σε πολυσυστηματικές ασθένειες. Η ακολουθία των ανακαλύψεων και των υποθέσεων αντανακλά την τεχνολογική πρόοδο κάθε συγκεκριμένης ιστορικής περιόδου.

Λέξεις ευρετηρίου: Νόσος του Wilson, Τύφλωση για τον ρόλο άλλων οργάνων, Ψευδοσκλήρυνση Carl Westphal

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DIALYSIS/TRANSPLANTATION
ΑΙΜΟΚΑΘΑΡΣΗ/ΜΕΤΑΜΟΣΧΕΥΣΗ

A journey through the history of dialysis in sub-Saharan Africa

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ΑΡΧΕΙΑ ΕΛΛΗΝΙΚΗΣ ΙΑΤΡΙΚΗΣ 2020, 37(Συμπλ 2):203–207

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Ένα ταξίδι στην ιστορία της εξωνεφρικής κάθαρσης στην υποσαχάρια Αφρική

Περίληψη στο τέλος του άρθρου

Sub-Saharan Africa (SSA) is a heterogeneous region with 47 countries, almost one billion people, and a gross domestic product of 1.7 trillion USD in 2017. The development of dialysis in Africa reflects the local socio-political circumstances. Up to seventies, Africa was recovering from long years of colonisation and political turmoil, so limited countries were able to establish dialysis centres. (a) *Before the seventies:* South Africa was the first country in SSA that started dialysis, when, in 1957, a general practitioner in Krugersdorp hospital dialysed 2 patients with acute kidney injury (AKI). In Kenya, acute haemodialysis (HD) was started in 1961 by Professor *L.S. Otieno*, followed by peritoneal dialysis (PD) two years later. In Nigeria, limited acute dialysis has been available in Lagos since 1965 and acute PD in Ibadan since 1967. Regular HD was firstly established at Lagos Teaching Hospital in 1981 by Professor *T.A. Odutola*. In Sudan, the first dialysis centre was a home dialysis unit, established in 1968, supervised by Mr. *Osman Awadalla.* (b) *After the seventies:* In Côte d'Ivoire, the first acute PD was performed in 1974 in Abidjan by Professor *Alain Bondurand* to treat a black fever patient with AKI. In Zimbabwe, *Drs John Forbes and Janet Seggie* placed a dialysis machine in Harare Central Hospital in the early 1970s; yet the machine was only occasionally used for the treatment of AKI until 1980. In Ethiopia, PD dialysis and less often HD was started in 1980 as reported by Dr *Berhanu Habte* to treat AKI at Addis-Ababa University Hospital. In Tanzania, Dr *J. P. Miabaji* reported that two dialysis machines were available at Dar-El-Salam University Hospital in the early 1980s, to treat AKI or important patients with plans for transplantation abroad. In Ghana, Dr *T.C. Ankrah* provided acute PD and sometimes HD for AKI in 1980. Other SSA countries started to establish dialysis units afterwards. However, dialysis services are still sparse in most countries due to the high costs and shortage of skilled personnel.

Key words

Haemodialysis AKI
Haemodialysis black fever
Haemodialysis sub-Saharan Africa after the seventies
Haemodialysis sub-Saharan Africa before the seventies
Home dialysis Sudan

1. INTRODUCTION

Sub-Saharan Africa (SSA) is the area of Africa that lies south of the Sahara desert. It is a vast and heterogeneous region, comprising 47 countries and a population of almost one billion people. In 2018, the aggregate gross domestic product (GDP) per capita in SSA amounted to 4,097.85 USD. About 65% of the population lives in rural settings, at significant distances from cities, where most of the organised health-care delivery systems are located.[1]

Chronic kidney disease (CKD) and its severe form, end stage kidney disease (ESKD) are a global public health problem with a high economic cost for the health system. Epidemiological data on CKD and ESKD in SSA are sparse and those existing are of limited reliability due to the dearth of renal registries in most countries. According to recently published data, the burden of CKD in SSA is determined to be around 14%,[2,3] close to the global CKD prevalence (13.4%).[4]

Since the end of the previous century, there has been an upsurge in the number of people with ESKD requiring renal replacement therapy (RRT).[5] Globally, the number of people requiring RRT was estimated at 4.9–9 million. Only 3.3 million people are receiving RRT, the majority of which in the developed world, while less than 5% of the pool of global RRT is available in SSA.[6,7] Of all world regions, Africa has an immense RRT gap between people needing and receiving RRT, of over 80%. Even though it is projected that people receiving RRT will double from 2010 to 2030 in Asia and Africa, the number of people without access to treatment is expected to remain excessively high.[8]

The evolution of dialysis in different African countries has been almost the same, with differences only in timing. Acute peritoneal dialysis (PD) was often the first available modality, soon followed by acute haemodialysis (HD). With the introduction of RRT, intermittent PD and HD were used according to the feasibility and availability of monetary and human resources. Continuous ambulatory peritoneal dialysis (CAPD) usually came later, and had an initial glamour that soon faded owing to the high cost of imported dialysis fluid.[9]

In this review, we tried to provide an overview of the history of dialysis in different SSA countries based on available data. In addition, we focused on the difficulties SSA faces in implementing national dialysis programs. We illustrated the starting year of dialysis in different sub-Saharan African countries in figure 1.

2. FROM THE SEVENTIES TO THE CURRENT ERA

Democracy brought about many changes in Africa after the seventies. Before this, colonialism was responsible for Africa's difficulties, which affected all aspects of life and development in different countries. The diverse and heterogeneous post-independence political turmoil in individual countries was reflected in the timing, quality, and spread of dialysis services in different regions. Within this environment of political instability, certain countries were lucky enough to have a "powerful patient" with ESKD who had the power and influence to push the introduction of dialysis services. In the absence of personal motivation however, most political regimes regarded dialysis as an unaffordable luxury, and definitely not a priority issue.[10]

2.1. The first step

South Africa hosted the first dialysis in the African continent. In 1957, an amateur general practitioner at a state hospital in the small town of Krugersdorp built the first dialysis machine, based on his observations in the United Kingdom, as a hybrid between a Kloff coil and a rotating drum. This machine was used to dialyse two acute kidney injury (AKI) patients, who unfortunately died later (as noted by Professor Anthony Meyers).[9]

2.2. Steps forward

This was followed by the initiation of dialysis in Kenya by Professor L.S. Otieno at Nairobi General Hospital in 1961. It started with the introduction of acute HD, followed by acute PD two years later. In 1984, regular HD for ESKD started and after 3 years, Professor Seth O. McLigeyo introduced CAPD, while haemofiltration was established in 1992.[9]

Nigeria was the first country to start dialysis in West Africa. Limited acute HD had been available in Lagos since 1965 and acute PD in Ibadan since 1967. Regular HD began later due to the sociopolitical instability prevailing for many years. In 1981, the Lagos University teaching hospital implemented regular HD, on the initiative of Professor T.A. Odutola. This progressed into a national program in 1985, where several other centres providing regular HD and occasional CAPD to several hundreds of patients, as reported by Dr Fatiu Arogundade.[9]

At the end of the sixties, Sudan established the first home dialysis unit to treat an important Sudanese citizen, under the supervision of Mr. Osman Awadalla, who received his training in the USA and returned home with a Kiil dialyzer. After the patient's death, the machine was transported to Khartoum General Hospital, where it became the seedling for the first hospital dialysis centre in the country. The same centre also introduced PD and included a chemistry laboratory, sponsored by the Korkain Skendrian family. In 1985, Khartoum University built an independent dialysis centre in Soba, largely sponsored by individual donations. This was directed by Prof. Omar Abboud, considered the Father of the progress of dialysis in Sudan. He was aided by Dr Salma Suliman, who developed the first paediatric dialysis service in the country. This service was later named after her, following her tragic death in the Nile, during her daughter's marriage celebrations. Suliman's centre remains one of the pillars of the national CAPD program adopted in 2005 at two paediatric and seven adult centres.[11–13]

2.3. After the seventies

In 1974, the first acute PD was performed by Professor Alain Bondurand on a case of black water fever diagnosed in Côte d'Ivoire in Abidjan. Two years later, HD was initiated. Both modalities used for the treatment of malarial AKI. Regular HD was started at the same time; however, patients did not follow the plans regularly, as they were not convinced to continue treatment while feeling well. This in turn led to a 30% survival rate, as reported by Professor Gnionsahe Daze.[9]

In parallel to these developments in Côte d'Ivoire, both Drs John Forbes and Janet Seggie placed a dialysis machine in Harare Central Hospital in Zimbabwe. This machine was only used for the treatment of AKI until the early eighties. Later, the country's first lady, Sally Mugabe, received

regular HD in the UK; after returning to her country, she brought her own machine and treating doctor, who was responsible for developing a chronic dialysis program in the country. In May 1988, the Minister of Health declared RRT a national commitment, and set up a Renal Committee at Parirenyatwa Hospital for patient selection on the sole basis of medical criteria (information kindly provided by Dr Chiratidzo Ndhlovu).[9]

In Ethiopia, Dr Berhanu Habte showed a great interest in renal diseases. In 1987, during an African countries meeting, he mentioned that PD and, less often, HD were sporadically available for AKI at Addis-Ababa University Hospital. In 2002, dialysis was no longer available in Ethiopia. Later on, an agreement with Professor Marc De-Broe was established to provide them with PD catheters, lab quality control, and a water treatment plant. Two more fellows were trained in South Africa, in 2005 and 2007, but no organised RRT program has been available so far.[9]

During the African Association of Nephrology (AFRAN) meeting in 1987, Dr J.P. Miabaji indicated that two dialysis machines were available at Dar-El-Salam University Hospital, and were used only for AKI or when VIPs with ESRD planned receiving a transplant abroad. Sixteen years later, a young physician called Linda Ezekiel received an International Society of Nephrology (ISN) fellowship in South Africa. Upon her return home, she managed to convince Baxter Healthcare Corporation to support a pilot acute PD program for pregnant women and children with AKI –called the "Access to Care" project– in Tanzania, to be implemented at two of the four main hospitals in the country. Unfortunately, the program stumbled in bureaucratic debates, leading to the withdrawal of the Baxter grant and the program's collapse even before it started.[9]

In 1987, Dr T.C. Ankrah, from Ghana, reported that acute PD and sporadic HD were provided for the treatment of AKI at Accra University. Afterwards, two doctors received training in the UK and South Africa as part of an international society of nephrology training programs. Nowadays, both acute and chronic dialysis are currently available at the Komfo Anokye Teaching Hospital in Kumasi and the Korre-Bu Teaching Hospital in Accra.[9]

3. CURRENT ERA

3.1.The current situation of dialysis therapy in sub-Saharan Africa

There are progressing steps towards the management of CKD in SSA; however, the burden of CKD continues to increase. Though the incidence of infection-related CKD may be declining, the overall incidence of ESKD is escalating in parallel to the increasing rates of diabetes mellitus, hypertension, and obesity. In addition, access to dialysis for ESKD is limited by insufficient infrastructure and catastrophic out-of-pocket costs. Most patients remain undiagnosed, untreated, and die.[14]

There is no available information on dialysis services in other East African countries, although some activity may be taking off in Uganda. Two nephrologists are available in the countries of Benin, Mauritania, and Togo, and one in Cape Verde and Niger. Limited acute dialysis is provided at university hospitals in eight other countries in the West region. South Africa was instrumental in starting dialysis programs in neighbouring countries during the late 1990s, following its sociopolitical reform. As regards Central Africa, only acute dialysis is offered at a few of the large hospitals in the main cities.[9] Maintenance dialysis programs were established in twelve SSA countries and out of them, there were five national dialysis programs.[15] The situation changed over time, as other new countries introduced dialysis programs but other countries could not support the cost of these national programs. Some countries offer limited short-term dialysis, including transient treatment to bridge an episode of reduced kidney function, preparation for a transplant, or managing the patient until travelling abroad for further management.[15]

3.2. Challenges faced by dialysis treatment in sub-Saharan Africa

Access to dialysis for ESKD is influenced by several impediments, such as local health indexes, the high prevalence of undernutrition and chronic infections; low per capita gross domestic product; national expenditures on health and increase of these expenditures with incremental demand; availability and adequate training of health care providers; and literacy.[15] Most patients remain undiagnosed, untreated, and die. Ashuntantang G. et al reported in their systematic review that more than 95% of all adults and children who could not access dialysis in SSA died and of those who accessed dialysis, 88% of adults with incident ESKD, 16% of adults with prevalent ESKD, and 36% of children with ESKD died.[17]

Globally, the cost of HD care ranges from $100 to $200, but in some SSA countries, it ranges from $80 to $160, $130 to $200, $10 to $120, $50 to $100, $70 to $110, and $120 in South Africa, Uganda, Cameroon, Kenya, Ethiopia, and Nigeria, respectively. PD is still in its infancy in most SSA countries.[6] Government provides financial support for patients on HD in some African countries such as South

Africa, Malawi, Sudan, Tanzania, and Nigeria, but not so in other countries; for example, a study conducted in Nigeria shows that <1% of patients can afford treatment for more than three months mainly because of financial constraints.[5]

The shortage of adequately trained personnel has always been a critical barrier to dialysis services in Africa. France takes the credit of independently providing physicians and nurses with training as part of free technical support in francophone countries such as Côte d'Ivoire (1980) and Senegal (2004). The International Society of Nephrology stepped in with an escalating impact since 1987 through its fellowship program, training 23–102 young physicians from 20 African countries in ten developed countries in North and South Africa and Egypt. The number of trainees sponsored by this initiative has multiplied eightfold in 20 years.[17]

Another problem is patients' non-adherence to treatment, including skipping dialysis sessions when feeling well, disregarding dietary constraints, and neglecting interdialytic medications, thereby leading to poor dialysis outcomes.[18]

In conclusion, this review describes the history of dialysis in sub-Saharan Africa until now based on available information. It also discusses the challenges faced by different countries that hinder the progress of dialysis services in this region. To overcome these difficulties, we need a competent workforce, with commitment from the government to focus on training and retention of nephrologists and nephrology nurses and the development of policies and strategies to increase the number of RRT centres available to prepare for the potential need for RRT. Moreover, proper planning, multidisciplinary work with the different health authorities, media and stakeholders, and a good record system should be established to diagnose patients early while an accurate referral system needs to be implemented.

ΠΕΡΙΛΗΨΗ

Ένα ταξίδι στην ιστορία της εξωνεφρικής κάθαρσης στην υποσαχάρια Αφρική

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Η υποσαχάρια Αφρική είναι μια ετερογενής περιοχή με 47 χώρες, πληθυσμό σχεδόν ένα δισεκατομμύριο ανθρώπους και ένα ακαθάριστο εγχώριο προϊόν 1,7 τρισεκατομμυρίων το 2017. Η ανάπτυξη της εξωνεφρικής κάθαρσης στην Αφρική αντικατοπτρίζει τις τοπικές κοινωνικοπολιτικές συνθήκες. Μέχρι τη δεκαετία των 1970, η Αφρική ανέκαμπτε από μια μακρά περίοδο αποικιοκρατίας και πολιτικών αναταραχών, έτσι ώστε μόνο λίγες χώρες μπόρεσαν να ιδρύσουν κέντρα εξωνεφρικής κάθαρσης. (α) Η εποχή πριν τη δεκαετία του 1970: Η νότια Αφρική ήταν η πρώτη χώρα στην υποσαχάρια Αφρική στην οποία άρχισαν να διενεργούνται συνεδρίες αιμοκάθαρσης το 1957, από έναν γενικό ιατρό στο νοσοκομείο του Krugersdorp προκειμένου να θεραπεύσει 2 ασθενείς με οξεία νεφρική βλάβη. Στην Κένυα, η εφαρμογή οξείας αιμοκάθαρσης ξεκίνησε το 1961 από τον καθηγητή L.S. Otieno, ακολουθούμενη από την περιτοναϊκή κάθαρση δύο χρόνια αργότερα. Στη Νιγηρία, υπάρχει περιορισμένη δυνατότητα διενέργειας οξείας αιμοκάθαρσης στο Lagos από το 1965 και οξείας περιτοναϊκής κάθαρσης στο Ibadan από το 1967. Κέντρο χρόνιας αιμοκάθαρσης ιδρύθηκε αρχικά στο Lagos Teaching Hospital το 1981 από τον καθηγητή T.A. Odutola. Στο Σουδάν, η πρώτη διενέργεια αιμοκάθαρσης έγινε με την μορφή της κατ' οίκον αιμοκάθαρσης το 1968 και εποπτευόταν από τον κ. Osman Awadalla. (β) Η εποχή μετά τη δεκαετία του 1970: Στην Ακτή του Ελεφαντοστού, η πρώτη οξεία περιτοναϊκή κάθαρση διεξήχθη το 1974 στο Abidjan από τον καθηγητή Alain Bondurand για τη θεραπεία ασθενών με πανώλη και οξεία νεφρική ανεπάρκεια. Στη Ζιμπάμπουε, οι καθηγητές John Forbes και Janet Seggie εγκατέστησαν ένα μηχάνημα τεχνητού νεφρού για τη διενέργεια αιμοκάθαρσης στο κεντρικό νοσοκομείο Harare στις αρχές της δεκαετίας του 1970. Το μηχάνημα χρησιμοποιήθηκε περιστασιακά για τη θεραπεία ασθενών με οξεία νεφρική ανεπάρκεια μέχρι το 1980. Στην Αιθιοπία, η περιτοναϊκή κάθαρση και λιγότερο συχνά η αιμοκάθαρση άρχισαν να εφαρμόζονται στο Πανεπιστημιακό Νοσοκομείο της Αντίς Αμπέμπα το 1980 όπως αναφέρθηκε από τον Δρ Berhanu Habte για τη θεραπεία της οξείας νεφρικής ανεπάρκειας. Στην Τανζανία, ο Δρ J.P. Miabaji ανέφερε ότι δύο μηχανήματα αιμοκάθαρσης ήταν διαθέσιμα στο Πανεπιστημιακό Νοσοκομείο του Dar-El-Salam στις αρχές του 1980, για να θερα-

πεύσουν την οξεία νεφρική ανεπάρκεια ή σημαντικούς ασθενείς με χρόνια νεφρική νόσο τελικού σταδίου και προγραμματισμένη νεφρική μεταμόσχευση στο εξωτερικό. Στην Γκάνα, η Δρ Τ.Κ. Ankrah προσέφερε οξεία περιτοναϊκή κάθαρση και περιστασιακά αιμοκάθαρση για την θεραπεία της οξείας νεφρικής βλάβης από το 1980. Στη συνέχεια και άλλες χώρες της υποσαχάριας Αφρικής άρχισαν να εγκαθιστούν μονάδες αιμοκάθαρσης. Ωστόσο, τα κέντρα αιμοκάθαρσης εξακολουθούν να είναι σπάνια στις περισσότερες χώρες λόγω του υψηλού κόστους και της έλλειψης εξειδικευμένου προσωπικού.

Λέξεις ευρετηρίου: Αιμοκάθαρση μαύρος πυρετός, Αιμοκάθαρση ΟΝΑ, Αιμοκάθαρση στην υποσαχάρια Αφρική μετά το 1970, Αιμοκάθαρση στην υποσαχάρια Αφρική πριν το 1970, Κατ' οίκον αιμοκάθαρση Σουδάν

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DIALYSIS/TRANSPLANTATION
ΑΙΜΟΚΑΘΑΡΣΗ/ΜΕΤΑΜΟΣΧΕΥΣΗ

History of renal transplantation in the Arab World

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Ιστορία της μεταμόσχευσης νεφρού στον αραβικό κόσμο

Περίληψη στο τέλος του άρθρου

Key words

Cadaver donor transplantation
Living donor transplantation
Transplantation Arabic peninsula
Transplantation North Africa

The history of renal transplantation from 18 Arab countries will be highlighted. In Egypt, Mansoura led the transplantation program by performing the first two transplants in 1976. The Egyptian experience exceeds 19,000 transplants in 39 centres. Cairo University performed the first unrelated donor transplant in 1980 and the first deceased-donor transplant in 1992. In Algeria, the first two transplants were performed in 1986 and 1987. In total 220 transplants have been performed using live donors and 4 using deceased donors. In Sudan, the first case was in 1974, while overall experience exceeds 1,600 cases. In Iraq, the first case was in 1973 with overall experience of 5,000 cases. In Morocco, transplantation started in 1985. In 2015, they performed 56 transplants. In Saudi Arabia, the transplantation program was initiated in 1979. In total 6,939 transplants have been performed using live donors and 2038 using deceased donors. In Yemen, the first transplant was in 1998 with a total number of transplants exceeding 400 cases. In Syria, the first transplant was in 1979 while in Tunisia, transplants using live donors and deceased donors were performed in 1986 and 1988 respectively. In Jordan, transplantation started in 1972 using deceased donors and the total number of transplants is currently 4,500. In the United Arab Emirates, 160 transplants have been performed using live donors and 2 using deceased donors. In Libya, the transplant program started in 1989 and resumed activity in 2004. In Lebanon, the first transplant using a deceased donor was performed in 1990 while the first transplant using a live donor was in 1992. In Oman, 60 transplants had been performed up to 1998. In Kuwait, the program started in 1979. In total, 2,500 transplants have been performed. In Palestine, the first transplant was performed in 2003 in Nablus, while total experience covers 300 cases. In Qatar, the first transplant using a live donor was performed in 1986 and the first transplant using a deceased donor in 1996. In Bahrain, the first transplant using a live donor was performed in 1995 and a deceased donor in 2001. In total 100 transplants using live donors had been performed and 25 using deceased donors up to the end of 2017. I hope that in the near future, an Arab transplant committee will be established to supervise organ distribution, set up a regional database, raise funds for less privileged centres and support research.

1. INTRODUCTION

Arab physicians became interested in transplantation since the first transplant in 1954 in the USA. We will try to highlight the history of renal transplantation from 18 Arab countries.

1.1. Egypt

The first transplant was carried out in 1964 in Alexandria for a Greek woman who received a kidney from an Egyptian donor; the surgery was performed by an American surgeon. Mansoura University led the transplant program as Ghoneim performed the first two transplants, in March and August 1976. Arrangements took place at Kasr-El-Aini where Barsoum under the supervision of Hassaballah prepared one of his private patients who received a transplant in October 1976 with an uneventful post-operative period. Cairo University carried out the first unrelated transplant in 1983 after a long ethical discussion. The Mansoura team insisted on transplants using only living related donors.[1] Then, the Egyptian Society of

Nephrology held an extraordinary General Assembly that banned transplants using unrelated donors. In 1992, the Egyptian Attorney General approved the harvesting of kidneys from two executed criminals after obtaining their consent prior to their execution. Vigorous public debate ended in banning the use of transplants from executed prisoners. Moreover, other universities, military, general and private hospitals (39 centres) entered the field with an overall experience of 19,079 kidney transplants up to the end of 2018 and 1338 transplants during the last year. The 10-year patient and graft survival rates of the Mansoura experience were 77.8% and 65.5% respectively.[2] The Egyptian society of nephrology and transplantation set the trend for many Arab and Middle East societies. One of the authors, Prof. Bakr was member of the Istanbul declaration steering committee and then of its summit[3] and a member of the KDIGO living donor transplantation working group.[4]

1.2. Algeria

The Algerian Society of Nephrology was established at Beni-Messous Hospital in 1979. The first and second kidney transplants were performed in 1986 and 1987. Up to now, 220 transplants using live donors have been performed in 13 centres. Four transplants using deceased donors were carried out but they all failed. The Algerian kidney foundation was established on 13th April 2015.

1.3. Sudan

The first transplant was performed in 1974. Up to 1989, 30 transplants had been performed. From 2001 to date, 1084 transplants using live related donors were carried out at Ahmed Gasim Centre with ten-year patient and graft survival rates of 67% and 54% respectively. Overall experience exceeds 1600 cases and the acute rejection rate is 15%.

1.4. Iraq

The first renal transplant was performed in June 1973 at Al Rasheed military hospital, by surgeon Alkayal and nephrologist Al-shamaa. The Iraq-Iranian war (1980) and the ensuing sanctions had a negative impact on health services. The first transplant in MOH was carried out in the Medical city teaching hospital in March 1985 by surgeon Rifaat and nephrologist Zaki. Then the government concluded a contract with an Irish team in Ibn Al Bitar hospital, which performed one transplant a week up to 1990. Many hospitals and centres were engaged in transplantation at different times, Karrama (1980), Chazala (40–50 transplant/year) surgical specialties (1991, 261 LDT), Neinava and Erbil (2001), Sulaimaniya (2008), Duhok and Najaf (2009), Nephrology-renal transplant (2009), Basra (2015) and lastly Karbala (2018). As regards private contribution, Al Khayal hospital started its program in 1976 and another five hospitals provided transplantation in the 1980s–1990s. Currently there are seven programs with the central committee in MOH for accepting donors; the overall experience is 5000 transplants with 5-year patient and graft survival rates of 91% and 87%, respectively.

1.5. Morocco

Transplantation experience in Morocco went through four stages. The first stage (1985 to 1990) with the first renal transplantation was in Casablanca in 1985. The patient and graft survival exceeded 27 years. The second stage (1990–1999) included 45 transplants and the 1st private case was in 1997. The third stage (2000–2009) included transplantation at Ibn Rochd University hospital of Casablanca, starting with transplantation in Sheik Zaid hospital in Rabat, and a national registry with 5-year graft and patient survival rates were 95%. The fourth stage (2010–2016) showed the first transplant of a brain from a deceased donor in Casablanca in 2010. The Fes and Marrakesh programs were also initiated. In 2015, 56 transplantations were performed and the first paediatric transplant was carried out one year later.[7]

1.6. Saudi Arabia

Transplantation in Saudi Arabia went through 5 phases. Phase 1 (1970–1979) included a transplant abroad. In phase 2 (1979–1981), a transplant program using live donors was initiated in Riyadh military hospital by a visiting team from the UK. During phase 3 (1981–1984), Euro transplant shipped extended criteria donors (ECD) to KSA. In Riyadh military hospital 64 kidney transplants were performed. The law for transplants using deceased donors was approved in 1982. In phase 4 (1984–1985), the local retrieved DD program was started. During phase 5 (1985 to now), the National Kidney Foundation was established then was transformed to the Saudi Centre of Organ Transplantation in 1993.[8] Currently, 6939 transplants using live donors and 2038 using deceased donors have been performed including de-sensitisation, kidney paired donation and ABO incompatible transplantation.[9] KSA was the first to adopt the brain death principle and deceased donor transplants.

1.7. Yemen

The first transplant was performed in 1998. Transplantation faced numerous problems (non-equipped labs, immunosuppression etc.). The regular program of Al Thawra Modern General Hospital started in 2005 with increased growth and an overall experience of 440 cases. Transplants using deceased donors were approved but the final agreement from the parliament's Supreme Health Committee was delayed because of the war.

1.8. Syria

The first transplant was performed in 1979 by Dr M. Housami; following that, transplants were performed at various academic and non-academic centres. In the eighties, an agreement was made with the Soviet Union to treat one thousand patients for free, including transplantation. A law in 2003 recognised the concept of brain death and permitted transplant using deceased donors. In 2009, the Syrian national centre for organ transplantation was established aiming to initiate a registry (DD program and logistic setup). The war had a disastrous impact on all aspects of life (the health sector in general, and the management of CKD in particular). Transplant centres in Allepo, Homs were closed while the Dam centre continued its activities. Massive internal displacement, including labour force migration, strained healthcare resources in major population centres. Many patients are not sufficiently dialysed due to the ability to maintain or buy new equipment. The MOH issued an order in 2016 to form a national council for organ and tissue transplantation.[3]

1.9. Tunisia

The first transplants using live donors and deceased donors were performed in 1986 and 1988 respectively at Charles Nicole hospital. Then transplantation was also established at the Military hospital (1992), Sfax (1994), Monastir (1995) and Sousse (2007). The law on transplantation and decentralisation was released in 1991, regulating organ procurement and transplantation, while the national centre for the promotion of organ transplantation was established in 1995.[10]

1.10. Jordan

Transplantation started in 1972 with a transplant using a deceased donor. Transplantation rates were 16 cases/million Jordanian citizens. In 2010, a kidney transplantation centre was established at Prince Hamza hospital. In total 200 transplants per year were performed, and around 40 using deceased donors.

1.11. United Arab Emirates

A Federal Law regulating transplantation was issued in 1993. A ministerial decision on the implementation regulation of the law was issued in 2010. The transplantation program revived in Shaikh Khalifa medical city, Abu Dhabi in 2008. The service is provided to UAE citizens free of charge. Up to now, 160 transplants using live related donors and 2 using deceased donors have been performed with a 3-year graft survival rate of 96%.

1.12. Libya

The transplant program was launched in 1989 and revived in 2004. Only transplants using live related donors were available. Basiliximab was used as induction therapy. Steroids, CSA and MPA were used as maintenance therapy.[11]

1.13. Lebanon

The first transplant using a deceased donor was performed in 1990 while the first transplant using a live donor in 1992. Lebanon launched its national organ donation in 1999; this became functional in 2009, leading to a (505%) drop in LURD and a (32–86%) increase in LRD as LD regulation resulted in the stop of commercial donation in 2013.

1.14. Oman

The country initially offered care services for patients transplanted abroad. MOH signed an agreement with Oxford University for transplantations to Omani patients using kidneys from their LRD. Sixty transplants were performed between 1983 and 1988. Some of these patients are alive with functioning grafts up to now. Oman's full transplant program was established in 1988. Before the end of 1988, one LD and 2 DD transplants had been carried out. The MOH issued a decree in 1993 forbidding commercial transactions in transplantation. In 2005, a transplant coordination unit and kidney donor clinic were established to follow up donors.[12]

1.15. Kuwait

The transplantation program was started in 1979 by Abouna at the Hamed Al Essa organ transplant centre. The transplant program went through 3 phases. Phase 1

(1974–1990) included 43 transplants using live donors and 13 using deceased donors. During phase 2 (1991–1993) with the Iraq invasion, centres were closed and the staff left the country. The third phase (1994 to now) showed an increased rate of transplants per year (80–100). Up to the end of 2016, 2500 cases had received transplantation. The desensitisation protocol, including 65 cases up to now, was initiated. The overall outcome was excellent with acute rejection rates of 8–12%. In 2018, new centres were constructed.

1.16. Palestine

The first transplant was performed in 19/12/2003 in Nablus at Al-Arabi Specialised Medical Centre in very difficult circumstances. The second transplant took place in 2010 at the Palestine medical complex of the Kuwaiti hospital. In total, 300 transplants have been performed so far (289 in Ramallah and 11 in Nablus). Donors should be first- or second-degree relatives. No mortalities have been reported up to now. Average hospital stay is around 8 days. Post-transplant success rates are more than 98%.

1.17. Qatar

The first LD transplant was performed in 1986 at Hamad Generalised Hospital and the first DD transplant in 1996. The Doha Accord was issued to avoid commercial transplants, establish a transplant centre of excellence and ensure globally accepted high-quality service.[13] The Qatar Centre for organ transplants (QCOT) was established as a government organisation in October 2011 while the Qatar Organ Donation Centre (HIBA), was launched as a charitable organisation, in August 2012. A new law was issued in 2015.

1.18. Bahrain

The country entered the transplantation field in 1995, performing 57 transplants between 1995 and 1999. Then, transplantation rates decreased and people were forced to seek transplants from Pakistan, Iraq, Iran and Philippines. Transplantation using deceased donors started in 2001. By December 2017, 25 transplants using deceased donors and 100 using live donors had been performed. With the availability of suitable donor and public educational programs, the results became encouraging.

In the end, I hope that in the near future, an Arab transplant committee should be established to supervise organ distribution, set up a regional database, raise funds for less privileged centres and support research.

CONFLICT OF INTEREST

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ΠΕΡΙΛΗΨΗ

Ιστορία της μεταμόσχευσης νεφρού στον αραβικό κόσμο

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Παρουσιάζεται η ιστορία της μεταμόσχευσης νεφρού σε 18 αραβικές χώρες. Στην Αίγυπτο, πρωτοπόρος του προγράμματος μεταμόσχευσης ήταν ο Mansoura, ο οποίος πραγματοποίησε τις δύο πρώτες μεταμοσχεύσεις το 1976. Η εμπειρία της Αιγύπτου υπερβαίνει τις 19.000 μεταμοσχεύσεις, σε 39 κέντρα. Το Πανεπιστήμιο του Καΐρου πραγματοποίησε την πρώτη μεταμόσχευση από μη συγγενή δότη το 1980 και την πρώτη μεταμόσχευση από αποθανόντα δότη το 1992. Στην Αλγερία, οι δύο πρώτες μεταμοσχεύσεις πραγματοποιήθηκαν το 1986 και το 1987. Συνολικά, έχουν πραγματοποιηθεί 220 μεταμοσχεύσεις από ζωντανούς δότες και 4 από αποθανόντες δότες. Στο Σουδάν, το πρώτο

περιστατικό ήταν το 1974, ενώ η συνολική εμπειρία υπερβαίνει τα 1.600 περιστατικά. Στο Ιράκ, το πρώτο περιστατικό ήταν το 1973, με τη συνολική εμπειρία να υπερβαίνει τα 5.000 περιστατικά. Στο Μαρόκο, η μεταμόσχευση ξεκίνησε το 1985. Το 2015, πραγματοποιήθηκαν εκεί 56 μεταμοσχεύσεις. Στη Σαουδική Αραβία, το πρόγραμμα μεταμοσχεύσεων ξεκίνησε το 1979. Συνολικά, έχουν πραγματοποιηθεί 6939 μεταμοσχεύσεις από ζωντανούς δότες και 2038 από αποθανόντες δότες. Στην Υεμένη, η πρώτη μεταμόσχευση πραγματοποιήθηκε το 1998, με το συνολικό αριθμό μεταμοσχεύσεων να υπερβαίνει τα 400 περιστατικά. Στη Συρία, η πρώτη μεταμόσχευση πραγματοποιήθηκε το 1979, ενώ στην Τυνησία μεταμοσχεύσεις με χρήση ζωντανού δότη και αποθανόντα δότη πραγματοποιήθηκαν για πρώτη φορά το 1986 και το 1988 αντίστοιχα. Στην Ιορδανία, η μεταμόσχευση ξεκίνησε το 1972 με χρήση αποθανόντα δότη και ο τρέχων συνολικός αριθμός μεταμοσχεύσεων ανέρχεται σε 4.500. Στα Ηνωμένα Αραβικά Εμιράτα, έχουν πραγματοποιηθεί 160 μεταμοσχεύσεις από ζωντανούς δότες και 2 από αποθανόντες δότες. Στη Λιβύη, το πρόγραμμα μεταμοσχεύσεων ξεκίνησε το 1989 και συνέχισε τη λειτουργία του το 2004. Στον Λίβανο, η πρώτη μεταμόσχευση με χρήση αποθανόντα δότη πραγματοποιήθηκε το 1990, ενώ η πρώτη μεταμόσχευση με χρήση ζωντανού δότη το 1992. Στο Ομάν, μέχρι το 1998 είχαν πραγματοποιηθεί 60 μεταμοσχεύσεις. Στο Κουβέιτ, το πρόγραμμα άρχισε το 1979. Συνολικά, έχουν πραγματοποιηθεί 2.500 μεταμοσχεύσεις. Στην Παλαιστίνη, η πρώτη μεταμόσχευση πραγματοποιήθηκε το 2003 στην Nablus, ενώ η συνολική εμπειρία καλύπτει τα 300 περιστατικά. Στο Κατάρ, η πρώτη μεταμόσχευση με χρήση ζωντανού δότη πραγματοποιήθηκε το 1986 και με χρήση αποθανόντα δότη το 1996. Στο Μπαχρέιν, η πρώτη μεταμόσχευση με χρήση ζωντανού δότη πραγματοποιήθηκε το 1995 και με χρήση αποθανόντα δότη το 2001. Συνολικά, μέχρι το τέλος του 2017, είχαν πραγματοποιηθεί 100 μεταμοσχεύσεις με χρήση ζωντανού δότη και 25 με χρήση αποθανόντα δότη. Ελπίζω ότι στο εγγύς μέλλον θα δημιουργηθεί μία αραβική επιτροπή μεταμοσχεύσεων που θα επιβλέπει τη διανομή οργάνων, θα δημιουργήσει μία τοπική βάση δεδομένων, θα συγκεντρώνει κεφάλαια για λιγότερο προνομιούχα κέντρα και θα υποστηρίζει την έρευνα.

Λέξεις ευρετηρίου: Μεταμοσχεύσεις από αποβιώσαντα δότη, Μεταμοσχεύσεις από ζώντα δότη, Μεταμοσχεύσεις αραβική Χερσόνησο, Μεταμοσχεύσεις βόρεια Αφρική

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ΑΙΜΟΚΑΘΑΡΣΗ/ΜΕΤΑΜΟΣΧΕΥΣΗ

History of nephrology in the Arab world

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ΑΡΧΕΙΑ ΕΛΛΗΝΙΚΗΣ ΙΑΤΡΙΚΗΣ 2020, 37(Συμπλ 2):214 –220

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Ιστορία της Νεφρολογίας στον αραβικό κόσμο

Περίληψη στο τέλος του άρθρου

Nephrology was first recognised as a specialty in 1960, haemodialysis (HD) first used in clinical practice in 1960–1965 and peritoneal dialysis (PD) in 1978. Egypt started dialysis in 1958 with a first dialysis department in 1979. Currently, there are 70,000 HD patients in Egypt. Algeria performed PD, HD for acute cases in 1962 and 1971 respectively. In Sudan, there are 60 dialysis centres, treating 6000 patients; of these 122 are on PD. The first haemodialysis was performed in Iraq in 1964. Morocco started HD in 1978. Saudi Arabia entered the field of HD in 1972; currently there are 184 dialysis units, while PD started in 1980. Dialysis in Yemen began in 1980. The Syrian national dialysis program was launched in 1986. Tunisia used PD for acute cases in 1962 with the first artificial kidney one year later. Nowadays, there are 13 dialysis units. Jordan performed its first dialysis in 1968; today there are 84 HD centres. The United Arab Emirates initiated PD in 1976 and HD in 1977. The first two dialysis units in Libya came in 1971 and 1979. Lebanon used PD for acute cases in the late fifties and started PD in 1994; currently there are 61 HD centres. The Oman Nephrology service started in 1981 and first PD patient was treated in 1983. In Kuwait, dialysis started in 1976 and today there are 9 centres. Qatar introduced PD in 1976 and HD in 1981. Lastly, Bahrain started HD in 1972. Highlighting this history sheds light on Arab experiences, aiming for achievements in the future.

Key words

Nephrology Arab world
Chronic kidney disease
Hemodialysis
Hemodialysis history
Nephrology history

1. INTRODUCTION

Nephrology was first recognised as a specialty in 1960. Haemodialysis (HD) was first used in clinical practice in 1960–1965 and Continuous Ambulatory Peritoneal Dialysis (CAPD) in 1978. Nephrologists in Arab countries entered the field of nephrology at different points in time.

2. EGYPT

Egypt started dialysis in 1963 in Cairo University Hospital. The first independent not academic chronic hemodialysis unit was established in 1979. The service spread to universities, general, military and private hospitals with the establishment of the Egyptian Society of Nephrology in 1965 and the first national congress in 1981. Mohammed Nagy El-Mahallawy was the Founder of Nephrology at Ain-Shams University and the physician behind the first dialysis experience in Egypt. He established what he called a nephro ward in the late fifties. The two first-generation nephrologists were Ismail Abou-Gabal and Mohammed Sadek Sabbour. Abou Gabal was sent to Lund, Sweden where he was trained on the Alwall dialysis machine under its inventor, Nils Alwall himself. Sabbour was directed to Edinburgh, United Kingdom (UK) for obtaining his PhD in clinical nephropathology, Abou-Gabal along with Sabbour and Wahid-El-Saiid, were the first to report, in 1972, the occurrence of nephritis in patients with urinary schistosomiasis, which turned out to signal important discoveries about this parasitic infection by other groups in the following years. In Cairo University, Sayed Taha Abdel-Bar and Anwar El-Mofti had a particular interest in kidney disease and its associated metabolic disorders. By the late 1950s, they foresaw two areas of promising development related to kidneys; (a) the revolutionary understanding of renal physiology as a result of evolving micro-puncture techniques, and (b) the imminent promise of dialysis for the ground-breaking management of acute and chronic renal failure. Hassaballa introduced dialysis in 1963 and renal biopsies in 1968 at Kasr El-Aini. He pioneered the first nephrology unit in the Internal Medicine tower and founded the first dedicated to chronic dialysis ward at Manial University Hospital in 1979. In Alexandria, dialysis services were initiated at the Medical Research Institute (MRI), initially an independent body established in 1957, subsequently attached to the National Research Centre (NRC) and later on affiliated with

Alex University. El Banawy established the first dialysis unit outside the capital in 1966, with Kolff-Travenal machines. By 1970, Aziz Zaki was the leading nephrologist at Alexandria University Medical School. Atef Hozayen introduced haemodialysis (HD) (using a Kiil system) in Alexandria University in 1974. Salah Naga practiced APD (1972) in ICU, pioneered this modality for the rest of his career and established a separate PD unit. El Belbessi started CAPD in 1980. El Kashif, Aggan, El Lakany followed. Mohammed Ghonaim, founder of the Urology Department at Mansoura University, started acute peritoneal dialysis for acute renal failure in 1969. This experience was limited due to the shortage of equipment and some technical difficulties. HD was started the following year, using a Lucas machine and Kiil dialyzers, which were replaced by a Kolff Travenol machine in 1974 with the aid of Mohamed Gaballa. Then Ghonaim appointed two nephrologists, Adel Bakr and Nabil Hassan, who took over. Adel Bakr established the first two clinics of nephrology, created vascular access, established an HD unit main hospital and two annexes, organising daily morning meetings and then became the unit chief. Later, Mohammed Sobh joined the team after returning from Canada and became the unit chief (1981). The Nasser Institute for Research and Treatment opened in 1987, incorporating a large dialysis service under the supervision of Maher Ramzy; Essam Khader joined at the end of the millennium. The Zagazig nephrology school started with Mohammed Zanati performing peritoneal dialysis treatment using customised connections and fluids. In 1977, he started the HD service with Travenol Twin-coil machines. A couple of years later, Essam Lotfy joined the team, followed by Ahmed Adel Hassan for a short while before moving overseas. In the late 1970s, several members of the Internal Medicine Department, namely Essam Amin, Khaled Talaat and Esmat Ezzat, helped develop the Suez Canal University. Assisted by Assem El-Sherif, they started dialysis in Ismaileya in 1980. Banha University joined the club in 1984 with El-Metwally El-Shahawy who established a nephrology unit in 1992. Nabil Zekralla introduced clinical nephrology at the Al-Azhar medical school in 1985, using a Lucas machine that was replaced by a Kolff-Travenol. Zekralla trained excellent second-generation nephrologists, including Ezzat El-Atrebi, Safwat Farag, Hussein Chahine and Tarek Al Baz. Lastly, Egyptian nephrologists maintained the tradition of excellence their grandfathers had established many centuries ago. Egyptian renal Centres indeed existed before some advanced centres in the developed world. Egypt produces high-quality research that keeps it on the top of the African and Arab world. Currently, there are 70,000 HD patients in Egypt.

3. ALGERIA

Algeria performed PD and HD for acute renal failure from 1962 to 1971 in Mustapha University Hospital. The treatment spread from the Reanimation unit of E1 Kettar University Hospital (1971–1973) by PD to HD (four machines) in the same hospital (1973). In 1978, it started treating ESRF and then Badis University started treating ESRF in 1975. The opening of the first unit of nephrology consultation and clinical hospitalisation came in 1977. In 1978, the first chronic haemodialysis and automated peritoneal dialysis unit opened there. In 1979, CAPD started in the same unit and two satellite centres HD (Hospital of Rouiba and Hospital of Kolea). Later, the immuno-histopathological laboratory opened in Beni-Messous Hospital and a research program about diseases responsible for renal insufficiency was launched in the same hospital in 1986. 50 new chronic HD centres opened between 1980 and 1994. Between 1995 and 2003, only one centre was opened. Before 1988, all Algerian nephrologists specialised in France.[1] Today, Algeria has 450 HD centres (280 public, 170 private), 24,000 patients treated by HD, 1,200 patients treated by CAPD, nephrology specialisation is provided in 13 universities, each year 50 new nephrologists obtain a diploma. The prevalence of end-stage renal disease (ESRD) is 100/million inhabitants. Algerian authorities are in charge of paying all bills for dialysis treatment through the Algerian Kidney Foundation since 2015.

4. SUDAN

In Sudan, the reported prevalence of ESRD is 70–140/million inhabitants, with mean of 106. The National Centre for Kidney Diseases and Surgery was established in 1994 to supervise healthcare services offering RRT. 60 dialysis centres were established, 40 of them in Khartoum city; 6,000 patients are on HD. The National Program for PD was established by Prof Abu Aisha (2005), with 122 patients. Prof Hasan Abu Aisha received the ISN pioneer award for the Africa Region (2017). The number of trained nephrologists has now increased to 0.7 per 1 million of population (pmp) compared to 17.5 pmp in the USA.[2]

5. IRAQ

In Iraq, the first HD was performed in 1964 and CAPD followed later. The first artificial kidney device was imported (1964) for possible use in open heart surgery. A Kiil machine was then brought from Germany. Later, Locus machines were purchased for Rasheed military hospital.

The first arteriovenous (AV) fistula was carried out in 1971. Rifat imported a CAPD catheter (Oreopoulos design) from Canada and subsequently introduced CAPD in Iraq. In 1994, a first Ministry of Health (MOH) conference was assisted by international figures from European countries.[1]

6. MOROCCO

In Morocco, HD was introduced in 1978 in Ibn Sina University Hospital in Rabat, PD was used at the Ibn Rochd University Hospital in Casablanca in the early 1980s. Only patients with social security coverage benefited from HD. Later, thanks to benefactors' associations a culture of aid and support for dialysis was established. Several centres opened, designed for disadvantaged patients with no social security coverage.[3] The associations allowed dialysis to take place in Tangies, E1 Jadida, Massakeech and Agadir. In 1996, patient numbers reached 200, with two 5-hour sessions/week each.[4] In 2003, MOH opened 11 centres with the establishment of compulsory health insurance. In 2008, MOH recognised ESRD as a public health issue. At first, the prevalence was 102.09 PMP (2005) and subsequently increased according to the Magredial registry and a Moroccan Society of Nephrology survey.[5]

7. SAUDI ARABIA

Saudi Arabia introduced HD in 1972 with a first dialysis centre in Riyad General Hospital, led by Dr Saeed Rabah with two Travenol machines. A second dialysis unit was created in Jeddah, Bab Shareef Hospital, established by Dr Adan Birkdar (Iraq), after he left the Riyad unit with the first Saudi resident, Dr Faten Shaker. The third unit was established in Medina in 1975 and the fourth in Alzahar Hospital in Makka in 1976. Prof Abuaisha (Sudanese) jointed the King Saud University faculty and helped in operating the dialysis unit at the King Saud Central Hospital. The first fully certified Saudi nephrologist was Dr Tashkandi who joined the King Saud Central Hospital in 1974 and started nephrology and dialysis at the King Faisal Hospital in Taif in 1981 with Traveral, B. Brown and Gambre AK10.[6]

A dialysis unit at the Dammam Central hospital was established in 1975 by Dr Fawzi Awad (Egyptian) with two Travenol machines. It was expanded in 1983 by Dr Ayman Kartar (to 24 AK10 machines) in parallel with his establishment of the Kanoo HD centre in 2001 with 87 state-of-the-art machines. The classic vascular access used a Scribner shunt, patients were sent to Beirut, Cairo, USA, and the UK for AVF creation. Up to when Dr Abdulraheem Miaulana started in Alzaher Hospital in Makka, the dialysate bath was acetate until 1994, where bicarbonate was distributed.[6]

There was an exponential proliferation of units across the country, thanks to many dedicated nephrologists and nurses. The 2010 DOPPS study included 184 dialysis units and 15,000 patients treated by HD or PD and Kingdom of Saudi Arabia (KSA). Due to increasing numbers of patients requiring HD (incidence 187 new patients PMP), MOH formulated a committee to outsource a program to the Diaverum and DaVita companies (2014) to provide dialysis, treating 4,000 patients.[7] On-line haemodiafiltration (HDF) was introduced by Dr Al Meshari in 1998 in Riyad and Dr Al Ghamdi in Jedda one year later. PD was introduced in 1980 by Dr Abu Aisha as IPD and then CAPD. Dr Mitwally and Al Wakeel led the program at the King Saud University. Later, Dr Al-Hwiesh joined Damman University, inventing the three-cuff Saudi PD catheter. Currently, there are two PD units and KSA has the largest number of PD patients in the Middle East.[8]

8. YEMEN

In Yemen, dialysis began in 1980 as a nephrology department was created at Al-Thaowra General Hospital (Sanaa) with 16 beds and two HD machines, increased to 8 machines in 1985. An Urology & Nephrology Centre was opened in 2004 (110 beds). Of these, 40 beds were for nephrology patients and the machines increased to 29. There are 120 new reported ESRD cases per million/year. New dialysis centres were created at the Military Hospital (Sanaa, 1987) then Hudidah (1992), Hajjah and Taiz (1993). After Yemen Unity, HD services were expanded to Aden (1993), Mukalla (1996) and Shabura. Currently, there are 33 centres, 3,797 patients, and 401 machines. PD started in Yemen in 1980 in a small centre at Al-Thawra Hospital. In 1990, eight PD cyclers were available at that centre with a similar number in the new centre. Intermittent Peritoneal Dialysis (IPD) was commonly used; 750 patients were treated with intraperitoneal dialysis (IPD) in 1991, while in 2015, the number reached 1,600. Only 16 patients were treated with CAPD in 1990/1991. This stopped in 1992 due to complications and financial issues.[1]

9. SYRIA

In Syria, until the seventies, the treatment of renal failure was limited (lack of dialysis services). In the mid-seventies, a law was passed, providing free medical services to CRF patients including transplantation. The first

group of specialised nephrologists graduated and were allocated throughout the country in the mid-eighties, and well-equipped HD centres subsequently opened. These steps created the conditions for the establishment of the National Dialysis Program (NDP) in Syria in 1986, which expanded to include both haemodialysis and peritoneal dialysis, using Syrian-made solutions.[1]

10. TUNISIA

In Tunisia, the history of nephrology can be subdivided into three periods: launching of the specialty, development of adequate departments in the regions and development of transplantation. After his appointment as head of the medicine department (ward 10–3) at Charles Nicole Hospital in 1962, Prof H. Ben Ayed introduced PD to treat acute kidney failure. The first artificial kidney was used in 1963, then Drake Willock functioning with a Kiil dialyzer was introduced in 1969; reverse osmosis started in 1971. The available access was the Scribner A-V shunt; then the Cimino-Brescia fistula was introduced. Renal biopsies were carried out initially surgically and then by puncture with a Silverman needle. By the end of 1974, two graduate nephrologists from France (Ben Maiz and El Matri) were recruited in the department. A pathology lab was established (Ben Moussa). An IPD program was set up and then came CAPD in 1983. The input of Ben Abdalla (plasma exchange) and Kheder (hypertension lab) is well-known.

The Military Hospital of Tunis was set up in 1977 by the director of the General Hospital Dr Ben Moussa, under the responsibility of Dr M. Dhahri, who was appointed head of the Anaesthesia Department in 1980. A centre in Sousse (140 km south of Tunis) was founded in 1981. As regards decentralisation, Monastir started acute PD and then HD in 1981 (Prof El May), Sfax started a program in 1982 (Prof Hachicha) and Sousse hosted HD and CAPD programs (2006) (Prof Achour).[9]

11. JORDAN

Jordan performed its first dialysis in 1968 at the main military hospital. The first home dialysis unit was brought in 1969. The first dialysis device model was Travenol and then the REDY sorb system in 1981. The prevalence of HD patients is 627 PMP. In 2015, there were 3,937 dialysis patients, 25 PD patients, 84 dialysis centres and 950 dialysis machines. Jordan, like other developing countries, suffers from a high rate from diseases that mostly lead to kidney failure, such as arterial hypertension (25%), high blood lipids (42%), high levels of obesity (36%), diabetes (43%), and cancer (75:100,000). The dialysis services are provided by MOH, royal medical, private or university hospitals. Hepatitis C-positive patients accounted for 2.5% while HBV infected patients represented 6.4%.[1]

12. UNITED ARAB EMIRATES

In the United Arab Emirates (UAE), the history of nephrology services is linked to the history of the Abu Dhabi renal unit. Dr Avinash Pingle was responsible for setting up the first dialysis unit in the UAE and for introducing nephrology as a specialty. The Central Hospital in Abu Dhabi was the only centre offering such services until 1980 and they received patients not only from the UAE but also from neighbouring countries such as Oman and Bahrain. The first PD program was initiated in 1976 and the first chronic haemodialysis program was established in 1977. The service then extended to 9 emirates of the country. Now there are more than 35 dialysis units, belong to the private governmental sectors.[1]

13. LIBYA

In Libya, the first separate dialysis unit was in Benghazi (Al Hawari Hospital) in 1971. The second dialysis unit was in Tripoli (Tajoura) in 1979.[10] The prevalence of dialysis-treated CKD is 624 PMP, with most (85%) under age of 65, white (87%), and male (58%). The causes of ESRD included DM (26%), chronic glomerulonephritis (21%), hypertensive nephropathy (14%), and congenital/hereditary diseases (12%).[11] Only 4.7% of patients were known to be infected with HCV or HBV before starting dialysis. The seroconversion rate is 7.7% (7.1% for HCV, 0.6% for HBV). The World Health Organization (WHO) assigned Prof Adel Bakr as short-term consultant to Libya in 1997 and 1999 and he advised an action plan to improve healthcare services for renal patients.[12]

14. PALESTINE

In Palestine, in 2016, there were 1,002 patients on HD in the West Bank and 724 patients in Gaza. The prevalence of CKD is 10%, increasing yearly even among young people. The number of newly reported ESKD cases was 117, while the unadjusted incidence rate was 363/million/year.

15. LEBANON

In Lebanon, acute dialysis was launched by Am University Hospital in the late fifties. In 1973, the Lebanese Nephrology Society was established; in 1974, there were

5–6 nephrologists registered while the current number is 124 nephrologists. HD is provided free of charge, with 3,400 patients currently on HD in 61 centres. CAPD was introduced in 1994; the 50 patients of 2004 now reach 180 patients. Nephrology and its related subspecialties have gone a long way. Financing and many essential links are still missing but Lebanese nephrologists hope to take care of them soon.[13]

16. OMAN

In Oman, the nephrology service started in 1981; the first PD patient was treated in 1983 and the second –a child– was initiated on paediatric HD in 1992. The service grew thanks to the efforts of Dr Al-Marhuby. The first nephrology department was established late in the same year at Al Nahda Hospital, including clinical nephrology, HD, IPD and kidney biopsies.[14] MOH (1990) decided to establish dialysis centres in various governorates, with more than 20 such units currently operating. Paediatric HD centres became available in 1992 (Lawati NM). The national registry for CKD and dialysis was initiated by Dr Al Marhuby in 1998. DM emerged as a major non-communicable disease from 1980. Combined diabetic and hypertensive nephropathy represents 70% of aetiologies of ESRD on regular replacement treatment (RRT) while 40% of dialysis patients were diabetic. At present, there are 1,500 dialysis patients.[15]

17. KUWAIT

In Kuwait, dialysis started in 1976 at the Al Amiri Hospital. Dialysis is used in 400 cases/million population. Currently, 2,006 patients are receiving dialysis in nine big dialysis centres, distributed across the country. 88% are treated by HD and 12% receive PD. MOH divided the country to 6 health regions; each has a general hospital providing full adult nephrology services, while paediatric nephrology services are provided in two hospitals only. Regarding the nephrology services, Mubarak Al Kabeer Hospital started dialysis in 1983 with 12 beds for two shifts, increased to 30 beds for 4 shifts, with a new dialysis unit in 2015. The Jaber A. Ahmed Dialysis Centre in Jahra Hospital started in 2000 with 16 beds, increased to 30. A new centre was opened in 2013, including a paediatric dialysis centre and 10 beds for HCV and 4 for HBV infected patients. The Farwaniya Dialysis Centre was established in 2011 with 56 haemodialysis stations and 10 PD beds. The Al Khezam Dialysis Centre in Adan Hospital started in 2009 with a large nephrology program, including teaching and research. The Al Nafisi Dialysis Centre, a satellite centre belonging to Al Sabah Hospital, includes 280 patients (HD, PD). Dialysis access surgeries and kidney biopsies are carried out in all above hospitals, while complicated cases are referred to the Hamed Al Essa Organ Transplant Centre. A new Nephrology and Transplant Centre is being constructed and is to function soon.[1]

18. QATAR

Qatar introduced PD in 1976 at Rumaillah Hospital. In 1981, the first HD unit was created at same hospital (4 machines) with local dialysate preparation. In 1982, the Hamad Medical Corporation started with a subspecialty of nephrology: 40 outpatient clinics/week for nephrology and transplantation. A special low clearance clinic (medical educator, dietitian and social workers) was established. Currently, it provides 250,000 HD sessions per year (2016). The incidence of ESRD was 205/million population in 2015, with diabetes mellitus (DM) as a leading cause representing 48%, HCV positivity down to 10.5%. CAPD started in 1997 and grew rapidly.[17] Acute kidney injury is an important cause of morbidity and mortality (volume depletion, sepsis, and hypotension). Currently, the adult nephrology workforce consists of 16 consultants, 14 specialists and 2 fellows at 8 hospitals in addition to satellite dialysis units.[16]

19. BAHRAIN

Lastly, Bahrain started HD in 1972, when Dr Al Arayed returned from the UK, with only one patient receiving dialysis therapy for one year. The incidence of ESRD in Bahrain is 120 PMP. HD continues to be the major management modality for ESRD patients. In 1981, the dialysis unit included 4 machines, up to 10 in 1988. The new unit started operating in 1992. 390 patients are on dialysis; nearly 30% of them need transplantation. Diabetic nephropathy rates are increasing.[1]

Highlighting this history sheds light on Arab experiences, aiming for achievements in the future.

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ΠΕΡΙΛΗΨΗ

Ιστορία της Νεφρολογίας στον αραβικό κόσμο

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Αρχεία Ελληνικής Ιατρικής 2020, 37(Συμπλ 2):214–220

Η Νεφρολογία αναγνωρίστηκε ως ειδικότητα για πρώτη φορά το 1960. Η αιμοκάθαρση εφαρμόστηκε για πρώτη φορά στην κλινική πρακτική το 1960–1965 και η περιτοναϊκή κάθαρση το 1978. Η Αίγυπτος άρχισε να χρησιμοποιεί αιμοκάθαρση το 1958 δημιουργώντας ένα πρώτο τμήμα αιμοκάθαρσης το 1979. Σήμερα στην Αίγυπτο καταγράφονται 70.000 αιμοκαθαιρόμενοι ασθενείς. Η Αλγερία χρησιμοποίησε για πρώτη φορά περιτοναϊκή κάθαρση και αιμοκάθαρση για οξείες περιπτώσεις το 1962 και το 1971, αντίστοιχα. Στο Σουδάν, μετρώνται 60 κέντρα αιμοκάθαρσης, που παρέχουν θεραπεία σε 6.000 ασθενείς. Από αυτά, στα 122 χρησιμοποιείται περιτοναϊκή κάθαρση. Στο Ιράκ, η πρώτη αιμοκάθαρση πραγματοποιήθηκε το 1964. Στο Μαρόκο, η αιμοκάθαρση άρχισε να χρησιμοποιείται το 1978. Η Σαουδική Αραβία εισήλθε στον τομέα της αιμοκάθαρσης το 1972. Σήμερα διαθέτει 184 μονάδες αιμοκάθαρσης, ενώ το 1980 άρχισε να χρησιμοποιεί και περιτοναϊκή κάθαρση. Στην Υεμένη, η αιμοκάθαρση άρχισε να χρησιμοποιείται το 1980. Το 1986, άρχεται η εφαρμογή του εθνικού προγράμματος αιμοκάθαρσης της Συρίας. Η Τυνησία χρησιμοποίησε για πρώτη φορά περιτοναϊκή κάθαρση για οξείες περιπτώσεις το 1962, και ένα χρόνο αργότερα διέθεσε τον πρώτο τεχνητό νεφρό. Σήμερα, διαθέτει 13 μονάδες αιμοκάθαρσης. Η Ιορδανία πραγματοποίησε την πρώτη αιμοκάθαρση το 1968. Σήμερα διαθέτει 84 κέντρα αιμοκάθαρσης. Τα Ηνωμένα Αραβικά Εμιράτα άρχισαν να χρησιμοποιούν περιτοναϊκή κάθαρση το 1976 και αιμοκάθαρση το 1977. Το 1971 και το 1979 δημιουργήθηκαν οι δύο πρώτες μονάδες αιμοκάθαρσης στην Λιβύη. Ο Λίβανος εφάρμοσε περιτοναϊκή κάθαρση για οξείες περιπτώσεις στα τέλη της δεκαετίας του 1950 και άρχισε τη χρήση περιτοναϊκής κάθαρσης το 1994. Σήμερα διαθέτει 61 κέντρα αιμοκάθαρσης. Η υπηρεσία Νεφρολογίας του Ομάν άρχισε τη λειτουργία της το 1981 και το 1983 υποβλήθηκε σε θεραπεία περιτοναϊκής κάθαρσης ο πρώτος ασθενής. Στο Κουβέιτ, η αιμοκάθαρση άρχισε να εφαρμόζεται το 1976 και σήμερα υφίστανται 9 κέντρα. Το Κατάρ εισήγαγε την περιτοναϊκή κάθαρση το 1976 και την αιμοκάθαρση το 1981. Τέλος, το Μπαχρέιν άρχισε να χρησιμοποιεί αιμοκάθαρση το 1972. Η ανάδειξη αυτής της ιστορίας καθιστά πιο σαφείς τις αραβικές εμπειρίες, αποσκοπώντας σε μελλοντικά επιτεύγματα.

Λέξεις ευρετηρίου: Αίγυπτος, Αιμοκάθαρση, Αραβικός κόσμος, Ιστορία αιμοκάθαρσης, Ιστορία Νεφρολογίας, Χρόνια νεφρική νόσος

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DIALYSIS/TRANSPLANTATION
ΑΙΜΟΚΑΘΑΡΣΗ/ΜΕΤΑΜΟΣΧΕΥΣΗ

Electronic health services in end-stage renal disease. From Galen to the 20th century

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Ηλεκτρονικές υπηρεσίες υγείας σε νεφρολογικές παθήσεις τελικού σταδίου. Από τον Γαληνό στον 20ό αιώνα. Η ελληνική εμπειρία

Περίληψη στο τέλος του άρθρου

Chronic kidney disease (CKD) is a serious public health issue. According to international data, one out of ten individuals suffers from a degree of chronic kidney injury. Unfortunately, there is no official data in Greece, and this is particularly worrying. It is therefore of paramount importance to move from the traditional way of archiving to the use of electronic health records and online applications. The use of electronic health records (EHRs) for document storage and retrieval is increasing in both developed and developing countries, leading to widespread use of EHRs by nephrologists. Moreover, in the last years, electronic and mobile health (telehealth), defined as the comprehensive use of new technologies in the health sector is rapidly evolving and gives promise to the field of nephrology in order to achieve optimal CKD management. Our hospital's Nephrology Department, in collaboration with the Information Technologies Institute of Centre for Research and Technology, with the support of the Hellenic Society of Nephrology, developed the first national online application of patients dialysed via a tunnelled central venous catheter. In December 2018, the application was notified to all dialysis units in order to register their data and to collect all necessary information for management of the disease. Moreover, the Nephrology Department is the first hospital unit in Greece to design and develop an electronic care system to improve chronic kidney disease patients' healthcare management both at inpatient and outpatient level, called e-NeΦros. These applications promote an electronic collaborative environment allowing direct information exchange among physicians, interconnection with patients and ultimately more efficient management of the healthcare system's resources. In conclusion, in CKD, focus should be placed on electronic healthcare actions and information systems with personalised healthcare services and patients should be actively involved in the management of their disease through the electronic healthcare network.

Key words

Chronic kidney disease
Electronic health
Tunneled central venous catheter

1. INTRODUCTION

The concept of data recording and the use of statistical reasoning make its appearance already from ancient years. Emperor Yao had taken a census of the population in China in the year 2238 BC. Governments of ancient Babylonia, Egypt, Greece and Rome all gathered detailed records of population and resources. However, early signs of a rudimental statistical analysis of medical observations emerge during the first century AD in Galen's writings. Among his other major contributions to medicine, Galen laid down many of the principles of scientific investigation and he is considered now as the pioneer of capturing the basic principles of biostatistics.[1]

Centuries later, the word statistics originated in the eighteenth century Germany and described the science of the state, a descriptive and non-quantitative framework of reference and terminology offered by university professors to princes of the numerous German states. In 1960's, along with computing evolution and worldwide information exchange, it became easy to systematically collect and statistically process large quantities of data about specific groups of patients managed in clinical practice, and so the concept of evidence based medicine was born and the first patient registries appeared.[1]

The term registry is defined both as the act of recording or registering and as the record or entry itself. Therefore, "registries" can refer to both programs that collect and

store data and also the records that are created. The term patient registry is focused on health information as opposed to other record sets.[2] E.M. Brooke, in a 1974 publication of the World Health Organization described them as *"a file of documents containing uniform information about individual persons, collected in a systematic and comprehensive way, in order to serve a predetermined purpose"*.[3]

The development of patients' registries the last few decades helped describe the natural history, epidemiology, and burden of a disease; they can capture variations in treatment and outcomes to help evaluate safety, quality and value of patient care. Ultimately, their data may help researchers develop hypotheses about disease mechanisms or treatment approaches and inform healthcare policy and potentially improve quality.[4]

Especially in nephrology, the existence of many registries for End Stage Renal Disease (ESRD) patients has helped in the thorough study of the disease's epidemiology and clinical outcomes in a way that sets an example for other scientific disease registries. European Renal Association – European Dialysis and Transplant Association (ERA – EDTA) Registry was founded in the year 1964 and for many years it was the sole source of information of epidemiology, therapeutic management, complications and outcomes of the disease. Similar registries from the US and other parts of the world appeared later on.

However, in the early 1990's, the great increase in the number of patients and the difficulties of data collection that emerged, became an obstacle for the proper function of the ERA – EDTA Registry and many countries developed their own national or regional registries. So, in 2000, the ERA – EDTA Registry was reorganized, transferred from London to Amsterdam, and data collection started from the already existing registries of the European countries and were presented at the annual Congress in Vienna in 2001.

In the year 1986, in Greece, the Greek Transplantation Coordination and Control Service was founded in order to register epidemiological data and keep the records of Renal Replacement Therapy and Transplant patients. Ten years later, a cooperation of the Greek Transplantation Coordination and Control Service with Hellenic Society of Nephrology resulted in the development of the Hellenic Renal Registry, a national registry which, from 2000, is part or the new ERA – EDTA Registry.[5]

In the era of patient-centred care, high quality registries with complete clinical, humanistic and economic information on patients are essential to help monitor and improve patient outcomes and provide valuable information that can impact healthcare procedures, policy, and ultimately population health. However, although many of the existing renal registries that have been established around the world contain useful data of ESRD patients, less than half provide information accessible to the general public, and few have suitable patient-level data availability and access needed to generate evidence to support improved patient care. There is also a lack of uniformity of type and quality of data collected, laboratory information, medication or therapeutic modality details, and most importantly, they lack of longitudinal data or data for non-dialysis dependent CKD patients. The concept of Electronic Health Records and Electronic Personal Health Records (EHR and EPHR) comes to fill that gap.[4,6]

2. ELECTRONIC HEALTH RECORDS AND ELECTRONIC PERSONAL HEALTH RECORDS

As defined earlier, a registry is an organized system that uses observational study methods to collect uniform data (clinical and other) to evaluate specified outcomes for a population defined by a particular disease, condition, or exposure, and that serves one or more pre-determined scientific, clinical, or policy purposes. While both registries and EHRs use clinical information at the patient level, registries are population focused, purpose driven, and designed to derive information on health outcomes defined before the data are collected and analyzed. On the other hand, EHRs are focused on individuals and are designed to collect, share, and use that information for the benefit of that individual. While in practice there may be some overlap in functionality between EHRs and registries, their roles are distinct, and both are very important to the health care system.[2]

EHRs were first developed in the 1960s as clinical information systems for document storage and retrieval. In the last two decades and with the advancement of technology, they have evolved into a much more sophisticated tool. They include data relating to an individual patients' health such as visit history, test results, medications or treatment plans, and allow electronic communication between individual providers. These data can be used by any health unit the patient visits and centrally by the health service provider. Additionally, the ability of EHRs to store and retrieve data longitudinally can be used for meaningful clinical research.[7]

Use of EHRs for CKD patients could help to improve identification and quality of care delivered to patients. With the use of EHRs for referrals, Veterans Health Affairs (VHA), one of the largest healthcare systems in the United States in early 2000, managed to improve the rates of patients

starting dialysis with a fully functioning arteriovenous fistula rather than a central venous catheter. The pilot project initiated by Kaiser Permanente of Hawaii, a non-profit organisation that used their EHRs documentation and risk stratification, succeeded in having more patients start dialysis as outpatients rather than in an inpatient setting.[7] Finally, the Clevelant Clinic Health System hospitals managed to collect data using their EHRs from 57,276 patients who visited the outpatient clinic from 2005 to 2010, that met the criteria of CKD and formed a CKD registry with the ambition to provide opportunity for outcomes research studies along with improving the care delivered to these patients (CKD screening, surveillance and or management).[6]

One step further, EPHRs are electronic applications that offer individuals more than just access to their health information. They also allow increased patient involvement in their own medical decision-making and promote patient-centred care. Patients with CKD may benefit from electronic PHRs due to their regular follow-up appointments, frequent tests and need for education on disease and life-style topics.[8] A large cohort of 11,352 CKD patients in the United Kingdom showed that up to 75% of patients kept using the EPHR for 1.5 year after their initial sign-up[9] and a small survey from Canada found that the majority of respondents felt that patients should have access to their personal health data while almost three quarters would use an EPHR if it was available.[10]

3. TELEHEALTH

Telehealth is defined by the US Department of Health and Human Services as the use of electronic communication and telecommunications technology to support long-distance clinical healthcare, patient and professional health-related education, and public health administration.[11,12] E-health in general is a broad umbrella term that brings together a number of different modalities, such as mobile health, telehealth, connected health, gaming in healthcare, ubiquitous healthcare ect. and aims to optimise the delivery of healthcare with enhanced health outcomes at individual and population level and also improve provider and patient experience of care at reduced cost.[11,13]

Telehealth applications for patient education and self-management include web-based applications, short message service (SMS) text messaging, mobile health applications, video conferencing, interactive voice response with simple-to-use telephone technology ect.[11]

The internet is ubiquitous in society and many digital educational materials in CKD are now available in various forms. The National Kidney Disease Education Program is the most well established example. This website contains several links to educational topics, with content directed at an elementary school level reading capability targeted for the patient (www.nkdep.nih.gov). Moreover, it goes beyond the provision of static educational content, with the development of social support systems for those affected by kidney disease. For example, as of January 2020, the National Kidney Foundation (NKF) has over 247,000 "likes" on Facebook (www.facebook.com/nationalkidneyfoundation) and 31,200 followers on Twitter (twitter.com/nkf).

One of the most important technological trends nowadays is "mobile computing", a term including various forms of hardware such as smart phones and tablet computers that allow the user to download mobile health applications via the Internet and support self-management practices. Many of these programs allow patients to view their home-recorded data i.e. blood pressure, weight, eating habits and potentially communicate and submit them to their healthcare provider.[11]

Several reports show improved outcomes in patients with chronic disease with the use of this information and communications technology tools for monitoring, training and self-management compared with or as an addition to usual care; however, there are few such applications in CKD.[14] Personal involvement of CKD patients in their healthcare is of great importance in slowing the progression of the disease as much as in reducing adverse safety outcomes and achieving other goals such as medication adherence, lifestyle modification and nutritional adaptation.[8]

4. CUFF TUNNELLED CATHETERS DATABASE INITIATIVE

Although cuff tunnelled catheters (CTC) are considered inferior to arteriovenous fistulas and grafts in all nephrology guidelines, there is a growing prevalence in many developed countries such as Italy, Belgium and Canada, as shown by the DOPPS study.[15] According to 2016 data, in Greece, approximately 3,000 patients (24.7%) underwent haemodialysis via a tunnelled central venous catheter. However, there are no official data regarding other important issues such as who placed the catheter or why the catheter is the first choice, or information about the catheter tip location, its lifetime, its complications, or the morbidity and mortality rates of these patients. This results in a lack of public health strategy regarding this sensitive group of patients.

A collaborative initiative started in June 2018 between our hospital's Nephrology Department and the Informa-

tion Technologies Institute of the Centre for Research and Technology-Hellas with the support of Hellenic Society of Nephrology. It constitutes the first integrated online application for the recording, study and management of patients undergoing dialysis with a permanent central venous catheter. In December 2018, the application was notified to all public and private dialysis units in Greece in order for them to register their data and to collect all necessary information for the management of the disease.

The application consists of a general questionnaire per dialysis unit and a special questionnaire for registering information for each patient, in compliance with the General Data Protection Regulation (GDPR).The general part includes information for all the patients of a unit such as the number of patients with cuff tunnelled catheters, the type of catheter used and catheter placement parameters such as who placed it, the type of complications arising and their management. The special part consists of questions for each patient such as demographics, type of vascular access fistula or catheter, the reasons of choice of this type of access, possible complications regarding the use of the catheter, such as early or late catheter dysfunction or thrombosis and infections, its lifespan and the reason for abandonment. Each unit can have access to these answers, receive analytical reports annually and exchange information with all other dialysis units.

The purpose of this initiative is the creation of a database of all dialysis units in Greece that offers the opportunity of recording, retrieving and exchanging all the necessary information on patients dialysed with cuff tunnelled catheters in order to achieve better clinical management of this sensitive group of chronic patients.

5. THE E-NEΦROS PILOT PROJECT

"G. Papanikolaou" University General Hospital is gradually implementing electronic and mobile health (e/m health) practices. The Nephrology Department is the first hospital unit in Greece to design and develop special digital services to improve chronic kidney disease patients' healthcare management. Since February 2016, it co-operates closely with Greek scientists and Greek technology providers from the Centre for Research and Technology Hellas (CERTH). The department has recently developed an electronic care (e-Care) system called "e-NeΦros". The e-NeΦros platform is an integrated system that includes many e-health tools and automated procedures that will affect CKD management in approximately 30–40% of cases in the beginning, with the prospect of full coverage of patients hospitalised or monitored remotely by the Nephrology Department and aims to gradually digitalise and automate all the department's practices.

6. CONCLUSIONS

As the new electronic era has already entered the health sector and evolves in nephrology too, the use of EHRs for obtaining high-quality data for research projects and improving patient care shows promising results and is expected to rise in the future. Moreover, electronic and mobile health practices and information systems, varying from digital tools and modules for administrative and organisational purposes of a unit, to the most personalised health applications offer a more complete interactive healthcare management and benefit the doctors, the patients and the national healthcare system.

ΠΕΡΙΛΗΨΗ

Ηλεκτρονικές υπηρεσίες υγείας σε νεφρολογικές παθήσεις τελικού σταδίου. Από τον Γαληνό στον 20ό αιώνα. Η ελληνική εμπειρία

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Η Χρόνια Νεφρική Νόσος (ΧΝΝ) θεωρείται σοβαρό πρόβλημα δημόσιας υγείας. Σύμφωνα με διεθνή δεδομένα, ένας στους δέκα ενήλικες πάσχει από κάποιο βαθμό χρόνιας νεφρικής βλάβης. Στην Ελλάδα δεν υπάρχουν επίσημα στοιχεία. Είναι, λοιπόν, αναγκαίο το πέρασμα από τον παραδοσιακό τρόπο αρχειοθέτησης στις διαδικτυακές εφαρμογές υγείας. Τα τελευταία χρόνια, με τη ραγδαία εξέλιξη της τεχνολογίας της Πληροφορικής και των Επικοινωνιών, η χρή-

ση των ηλεκτρονικών ιατρικών φακέλων ασθενών για την καταγραφή και την ανάκτηση πληροφοριών αλλά και η αξιοποίηση μίας νέας μορφής υγείας, της κινητής υγείας (mobile health-telehealth), αυξάνεται τόσο στις ανεπτυγμένες, όσο και τις αναπτυσσόμενες χώρες και δίνει πολλές ελπίδες και στον τομέα της νεφρολογίας για καλύτερη διαχείριση της ΧΝΝ. Το Νεφρολογικό Τμήμα του νοσοκομείου μας μαζί με το Ινστιτούτο Πληροφορικής και Επικοινωνιών του Εθνικού Κέντρου Έρευνας και Τεχνολογικής Ανάπτυξης (ΕΚΕΤΑ) και την Ελληνική Νεφρολογική Εταιρεία ανέπτυξε την πρώτη πανελλήνια διαδικτυακή εφαρμογή ασθενών υπό αιμοκάθαρση μέσω κεντρικού φλεβικού καθετήρα με υποδόριο τούνελ που το Δεκέμβριο του 2018 κοινοποιήθηκε σε όλες τις μονάδες αιμοκάθαρσης. Κάνοντας ένα βήμα παραπάνω, το Νεφρολογικό Τμήμα είναι το πρώτο τμήμα στην Ελλάδα που, με τη βοήθεια επιστημόνων του ΕΚΕΤΑ, ανέπτυξε και σχεδιάζει να χρησιμοποιήσει την ηλεκτρονική πλατφόρμα e-NeΦros, με σκοπό τη βελτίωση της παροχής υπηρεσιών υγείας τόσο σε νοσηλευόμενους όσο και σε εξωτερικούς νεφροπαθείς ασθενείς. Οι εφαρμογές αυτές παρέχουν ένα ηλεκτρονικό συνεργατικό περιβάλλον με ανταλλαγή πληροφοριών μεταξύ ιατρών, δυνατότητα διασύνδεσης με τους ασθενείς και, τελικά, αποτελεσματικότερη διαχείριση των πόρων του συστήματος υγείας. Συμπερασματικά, στη ΧΝΝ πρέπει να δοθεί έμφαση σε δράσεις ηλεκτρονικής υγείας με ταυτόχρονη εξατομίκευση και ο ασθενής θα πρέπει να συμμετέχει ενεργά στη διαχείριση του νοσήματός του.

Λέξεις ευρετηρίου: Ηλεκτρονικές υπηρεσίες υγείας, Στατιστική Υγείας, Κεντρικός φλεβικός καθετήρας caff, Χρόνια νεφρική νόσος

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DIALYSIS/TRANSPLANTATION
ΑΙΜΟΚΑΘΑΡΣΗ/ΜΕΤΑΜΟΣΧΕΥΣΗ

Historical misconceptions in peritoneal dialysis

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ΑΡΧΕΙΑ ΕΛΛΗΝΙΚΗΣ ΙΑΤΡΙΚΗΣ 2020, 37(Συμπλ 2):226–230

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In the long history of medicine, scientific assumptions based on pathophysiological mechanisms, case reports of a number of interesting cases, authority statements and tradition have often been the guides of clinical practice, but have never been scientifically substantiated. As a result, many perceptions in medicine, although wrong, were popular and resistant to change. Some of these appeared in the history of Peritoneal Dialysis (PD). Their understanding changed the course of the method and –perhaps more importantly– the future of its patients. The scepticism surrounding the introduction of continuous ambulatory PD as we know it today and the "flush before fill" system, the supposed worse outcomes in high transporters aiming towards high dialysis doses and the inappropriate twice daily use of icodextrin were some of the misconceptions that were eventually revised. In conclusion, several breakthroughs in the history of PD, at first disapproved, changed the application and future of the method.

Ιστορικές παραναοήσεις
στην περιτοναϊκή κάθαρση

Περίληψη στο τέλος του άρθρου

Key words

CAPD
CCPD
History peritoneal dialysis
IPD
Misconceptions medicine

In the history of medicine, evidence-based practice has only recently gained worldwide acceptance.[1] Before this era, pathophysiologic assumptions, case reports, authority statements and especially tradition had been the guides of clinical practice. Unfortunately, many standards of care were never tested but were promoted based on their longevity. As a result, several conceptions in medicine, though distorted, were popular and resistant to change. Some of these misconceptions appeared in the brief, but exciting history of Peritoneal Dialysis (PD), which together with haemodialysis (HD) represent the two renal replacement therapy modalities currently applied worldwide for the treatment of end-stage renal disease (ESRD). In PD, compared to HD, these misconceptions initially discouraged the global implementation of the method and led to the belief that it was not appropriate for ESRD patients. The understanding of these misconceptions changed the course of the method and the fate of patients.

In its infancy, PD was presented as a therapeutic alternative for ESRD therapy and was prescribed as intermittent PD (IPD) sessions with catheter removal and reinsertion.[2] In 1959, Mae Stewart, a 33-year-old black woman with childbirth complications and glomerulonephritis, was referred to Dr Ruben in San Francisco. With the help of his associates, Ruben applied the method on the patient and after the first PD session, she improved significantly, and her creatinine decreased impressively from 20 to 13 mg/dL. The method was discontinued but, unfortunately, after 7 days without treatment, the patient's condition deteriorated once again, as she suffered from chronic renal failure. She was set on a 48-h weekend in-hospital PD regimen, while on weekdays she stayed at home. The Murphy-Doolan PD catheter was left in place and it was replaced only once during the 7-month period that the patient was on PD. Mae Stewart was the first patient with ESRD maintained on long-term PD without periodic replacement of the PD catheter. Ruben and his associates submitted a paper on this case report to the *New England Journal of Medicine* but the manuscript was rejected.[3,4]

Several years later, in 1975, Moncrief and Popovich in Austin, Texas reviewed the case of a young patient who was started on HD but could not continue due to access thrombosis. The patient refused to move from Austin to Dallas to receive IPD, which was crucial for his survival.

This challenge led Moncrief and Popovich to establish a new form of PD, which would allow complete equilibration of plasma urea with PD fluid solution and eventually maximum urea removal during each dwell. They calculated the volume of the dialysis fluid solution needed to remove the urea generated daily on a 1 g/kg protein diet and thus prescribed five exchanges per day of 2 litres fill volume each for a dwell time of at least 3 hours. They used standard 2-litre glass bottles containing the PD solution, attached a tube and used a Tenckhoff catheter as access. The regimen was called "portable/wearable equilibrium PD technique" and achieved the appropriate laboratory results along with the desirable euvolemia and clinical condition. In 1976, the American Society for Artificial Internal Organs (ASAIO) rejected an abstract by Popovich and Moncrief describing this method, probably due to its "confusing title".[5] Yet, later in 1977, they met Karl Nolph who became interested in the method and started working with the Austin group. They decided to name this new method Continuous Ambulatory PD (CAPD). They studied 9 patients on this method for 136 patient-weeks. The treatment included continuous presence of PD solution in the peritoneal cavity, manual exchanges 4–5 times daily and the PD catheter was capped between exchanges. This "portable" dialysis method allowed the patient to take part in everyday activities. The results, published in the Annals of Internal Medicine, established the use of CAPD.[6] Despite the method's advantages, increased peritonitis rates discouraged the wide implementation of CAPD.

In the late 70s, at the Toronto Western Hospital in Canada, Oreopoulos was the first to widely apply CAPD via a "standard" connection and wearable bags.[7] Yet, peritonitis rates were still high, threatening the method's survival. In 1980, Buoncristiani et al proposed an innovative Y-set technique, which astonishingly reduced peritonitis rates from one episode every 12 months to one episode every 36–40 months.[8] They suggested that after the connections and before draining, fresh dialysate should be washed into the drainage bag flushing away with it any bacteria that could have possibly contaminated the tubing system during the connection. Then, drainage of the dialysate into the bag should take place and the new solution should fill the PD cavity. This technique became widely known as "flush before fill". Despite promising results, scepticism in Canada and USA PD centres regarding the validity of the results delayed the acceptance of this development for at least five years. Once accepted and implemented, these changes reduced the high peritonitis rates and significantly increased the overall use of CAPD around the world.[9]

In the next years, the question raised concerned the delivery of the appropriate dose of dialysis. In 1996, a multicenter Canada-USA PD Study (CANUSA Group) randomised 680 PD patients in 14 centres in Canada and the USA.[10] The results supported a strong, positive association between the level of small, solute clearance with survival. Based on the CANUSA results, the National Kidney Foundation – Dialysis Outcome Quality Initiative (NKF-DOQI) published guidelines in 1997, recommending a weekly Kt/V target of 2.0 for CAPD and 2.1 for Continuous Cycling PD (CCPD).[11] The higher clearance targeted by these guidelines led to an increase in APD cycler use, since the machines allowed higher daily dialysate volume delivery and thus could achieve higher targets. However, in a subsequent re-evaluation of the CANUSA study in 2001, Bargman et al showed that the favourable results in those patients were mainly due to their residual renal function.[12] This suggested that lower weekly Kt/V targets might be appropriate. This was confirmed by another large, prospective study, adequacy of PD in Mexico (ADEMEX), which randomised 965 PD patients to either standard or increased small solute clearance at a 1:1 ratio.[13] They showed that increased doses of peritoneal small molecule clearance delivered by PD were not associated with patient survival or better quality of life. These findings overruled the misconception of the high targets proposed by the NKF-DOQI guidelines.

The CANUSA study, in line with similar studies, suggested that CAPD patients with high membrane permeability had increased mortality, possibly due to fluid overload resulting from low ultrafiltration (UF) volumes. Reanalysis of the CANUSA study showed that renal and peritoneal clearance do not contribute in an analogous manner in solute clearance.[12] This rendered anuric patients, especially those with high peritoneal permeability, as a group difficult to effectively dialyse while on CAPD[14] and a clinical concern about poor outcomes in fast transporters emerged. The European APD Outcomes Study (EAPOS) recruited 177 anuric patients on APD, 58% of which using icodextrin for the long day-dwell. The EAPOS study showed that baseline membrane transport status was not related to ultrafiltration achieved at one year and had no effect on patient survival.[15] The results suggested that by implementing APD especially in combination with icodextrin for the long day-dwell, it is possible to achieve sufficient small solute clearance and UF and this may have a positive impact on the clinical outcome in high transporters.[16] Thus, the concern about poor outcomes for fast transporters on PD was proved again a misconception.

Another overruled misconception was that icodextrin

solutions should be used only once daily. The use of dextrose as the principal osmotic agent in PD solutions was suggested to be associated with peritoneal membrane toxicity and systemic adverse effects.[17] The interest in minimising exposure to glucose introduced an alternative solution based on icodextrin. This glucose polymer was shown to increase UF and at first was recommended for only one exchange per day in high or high-average transporters.[18] Gobin et al were the first to suggest twice-daily icodextrin exchanges in CCPD patients. They showed a significant decrease in patient exposure to glucose after 6 months of treatment. The authors did not observe an increase in UF because of the scheduled dwell of the two icodextrin exchanges (one exchange for 4–5 hours and the other one for 9–10 hours dwell time).[17] Another study by Sav et al demonstrated a significant decrease in body weight and left ventricular mass index in 40 patients CAPD using twice-daily icodextrin.[19] Moreover, in a study from Toronto General Hospital, where 5 CAPD and 4 CCPD patients with poor UF were recruited, the authors reported a significant decrease in body weight in 6 out of 9 patients with UF failure after 6 months of therapy. In addition, a decrease in the mean blood pressure of all patients was observed.[20] In another study, 28 patients with UF failure on CAPD were randomised to receive either one or two icodextrin exchanges per day. Both groups experienced a decrease in serum brain natriuretic peptide, left ventricular mass, heart rate, and cardiothoracic index. In addition, the authors reported an increase in the ejection fraction at 8 weeks in both groups. Yet, the percentage of change of all parameters was enhanced in the patient group on twice-daily icodextrin exchanges.[21] In a retrospective study, 8 PD (5 APD and 3 CAPD) patients with inadequate UF were switched from once daily to twice daily icodextrin exchanges. A significant increase was observed in net UF after 6 months. Moreover, osmolality and residual urinary output remained unchanged throughout the study.[22] These studies established the safety and potential benefits of twice-daily icodextrin use in PD patients, although prescribing more than one icodextrin exchanges is still off-label.

Finally, the use of disinfecting devices with sterilisation properties on the connecting surfaces initially appeared attractive. The implementation of ultraviolet (UV) light, as well as heat sterilisation at the connection site, achieved with either electric resistance or microwaves was appealing. In a large randomised study by Nolph et al, the UV-flash® disinfecting device did not reduce peritonitis rates.[23] A retrospective, multicenter study from Japan showed that the UV-flash® system could be used in CAPD patients with impaired dexterity or vision in order to achieve lower peritonitis rates.[24] Another study tried to evaluate *in vitro* if, by themselves and without the help of disinfecting devices, PD system designs could prevent bacterial contamination into the peritoneum during accidental touch and airborne transmission.[25] This study selected a Y-set and a double-bag system and showed that the "flush before fill" and the fluid path flow designs were those that contributed significantly to the safety and protective action of these PD systems.[25] Many other disinfecting devices were tested, such as the Terumo Flame-Lock System using heating over a flame and ceramic connections,[26] the Fresenius Thermoclave device, which was used with the Safe Lock 5F® connector,[27] the Sterile Connection Device using a heated blade to cut through parallel placed tubing of transfer set and fresh dialysate bag[28] and microwave moist-heating devices.[29] However, despite some good *in vitro* results, these devices never proved patient-friendly, beneficial or practical. They added to the complexity of the method and increased its cost without offering significant germicidal effectiveness. Eventually, and especially after the implementation of disconnecting systems, the use of these devices was abandoned.[30]

In conclusion, despite the short history of PD, several innovations and milestones were at first doubted, rejected by respected contemporary medical journals or even widely adopted without eventually proving their efficacy. Some of these breakthroughs include the importance of a permanent PD catheter, the daily, chronic PD regimen with the 2-liter exchanges, the "flush before fill" system, the appropriate weekly Kt/V targets, the use of APD in high transporters and the twice-daily use of icodextrin. Several misconceptions were overruled and the innovations eventually established in current PD practice changed the application and future of the method. These emphasise that knowledge in medicine is ever-evolving and, as Heraclitus noted, "change is the only constant in life".

ΠΕΡΙΛΗΨΗ

Ιστορικές παρανοήσεις στην περιτοναϊκή κάθαρση

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Στη μακρά ιστορία της Ιατρικής, επιστημονικές παραδοχές με βάση παθοφυσιολογικούς μηχανισμούς, δημοσιεύσεις που αφορούσαν σε ολιγάριθμα ενδιαφέροντα περιστατικά, τη γνώμη των ειδικών αλλά κυρίως η παράδοση αποτελούσαν συχνά οδηγό της κλινικής πρακτικής, χωρίς όμως να έχουν ποτέ τεκμηριωθεί επιστημονικά. Ως αποτέλεσμα αρκετές αντιλήψεις στην Ιατρική ήταν λανθασμένες, αλλά δημοφιλείς και ανθεκτικές στην αλλαγή. Ορισμένες από αυτές τις παρανοήσεις εμφανίστηκαν στην ιστορία της περιτοναϊκής κάθαρσης, μιας εκ των δύο μεθόδων υποκατάστασης της νεφρικής λειτουργίας. Η κατανόησή τους άλλαξε την πορεία της μεθόδου αλλά και –ίσως σημαντικότερο– το μέλλον των ασθενών της.

Λέξεις ευρετηρίου: CAPD, CCPD, IPD, Ιστορία περιτοναϊκής κάθαρσης, Παρανοήσεις στην Ιατρική

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DIALYSIS/TRANSPLANTATION
ΑΙΜΟΚΑΘΑΡΣΗ/ΜΕΤΑΜΟΣΧΕΥΣΗ

The history of haemodialysis in Turkey

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ΑΡΧΕΙΑ ΕΛΛΗΝΙΚΗΣ ΙΑΤΡΙΚΗΣ 2020, 37(Συμπλ 2):231–236

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Η ιστορία της αιμοκάθαρσης στην Τουρκία

Περίληψη στο τέλος του άρθρου

Key words

History of haemodialysis Turkey
Home dialysis Turkey
Renal Registry Turkey

The review of the historical process of haemodialysis (HD) application in Turkey from the beginning to the present. It can easily be seen that the founders on Nephrology made great sacrifices that these days have not been easily reached. The establishment of dialysis centres was also time- consuming and difficult. The first application was made in 1962 at the Ankara University Faculty of Medicine. This was followed in 1965 by the Cerrahpaşa Medical Faculty. Dialysis recording systems started in 1989. Today, there are about 884 HD centres in Turkey, two-thirds of which are private and one-third public. The fees of these patients are covered by the government and no extra payment is required. These centres are spread all over Turkey and there is no patient who has died due to lack of HD treatment. Patients are taken from and to their homes free and meals are provided by HD centres. Procedures and regulations related to HD are thoroughly arranged. All centres are supervised twice a year. A certificate program has been implemented since 2000 and authorised staff has been trained and given five-year certificates. Recent data shows that in Turkey there are about 63,349 patients and 17,322 devices. The annual mortality rate is 15%. The number of patients who use home HD has exceeded 800, placing Turkey in third position in Europe.

1. HISTORY OF HAEMODIALYSIS IN TURKEY

The first studies and views on dialysis in the world emerged in 1854, when Thomas Graham, a Scottish chemist from Glasgow University first described dialysis. The first studies on artificial kidneys were made in 1912 by Abel, Rowtree and Turnel. In 1942, it was administered by Kolff in a patient with acute renal failure. The artificial kidney, which had not been used in chronic cases until 1960, was used in irreversible kidney failure cases with the development of the closed cannula (Scribner et al, 1965). However, the actual solution was achieved with the arteriovenous fistula performed for first time by Brescia and Cimino.[1]

Our first encounter with the term haemodialysis (HD) was when a plane crashed at Ankara Ulus Square in 1963. The lack of dialysis was then realised and the term "acute renal failure" first appeared on the agenda. Nephrology was not a separate discipline yet and kidney diseases were treated in the context of Internal Medicine. Due to the accident, the media focused on dialysis and the World Health Organization donated three haemodialysis machines for the treatment of those injured.[1]

Turkish Nephrology took a great leap in 2000. Progress started in the 1950s, increased in the 1960s and gained momentum in the 1970s. In the beginning, it developed slowly with the efforts of individualists, progressed with the establishment of haemodialysis centres in the 1980s, and reached world standards in the 1990s. Its course is parallel to the historical scientific developments occurring throughout the world, but it faces difficulties in dialysis practice such as the necessity of providing most materials and tools from abroad and the inadequacy of dialysis for society. The lack of trained personnel caused delays in these practices.[1–4] The history of Turkish Nephrology started in the 1950s, with the book "Internal Renal Diseases" by C. Sökmen, Professor of Ankara University Faculty of Medicine, which saw a second edition in 1961.[5,6] Following this book, peritoneal lavage was performed in 1958 at Cebeci Hospital of the Ankara University Faculty of Medicine,[7] acute haemodialysis with Kolff's artificial kidney device in 1962, acute peritoneal dialysis in 1963 and a percutaneous renal biopsy in 1964.[8]

According to Professor E. Ertuğ, at the end of 1961, a closed system (tank type), positive pressure HD device developed by Kolff and manufactured by Travenol was imported by the Ankara Medical Faculty and applied to a patient for the first time in June 1962.[1]

Following this, it is understood from "Internal Renal Diseases" by C. Sökmen, that the next HD studies were

performed at the Istanbul University Cerrahpaşa Faculty of Medicine. Professor K. Önen was introduced to the HD machine in 1956, when it was shown to him by the renowned nephrologist and thinker Professor J. Hamburger at the Necker Hospital in Paris. In 1962, at Los Angeles County General Hospital, he learned to use the oldest Travenol-type machine in the renal unit and its application in patients. He states that there was a total of 7–8 HD machines in Los Angeles, all used for the treatment of acute renal failure. When Professor Kemal Önen returned to the Istanbul University Faculty of Medicine "Treatment Clinic and Pharmacology" chair in 1964, he started HD in patients with acute renal failure for the first time in 1965 by purchasing a Travenol 100l tank and a Sigmamotor pumped HD device. Since 1966, this practice has continued as needed[1,3] (fig. 1). A positive pressure HD device was used for the first time in June 1962 at Ankara University School of Medicine.[1,2] Research shows that at the end of 1961, a tank-type HD machine was imported and first used in the treatment of a patient at the Ankara University Faculty of Medicine in June 1962. There were no posts, nor professional staff allocated to conduct dialysis at that time.[1,10,11]

Later applications in Turkey were made at Istanbul University Cerrahpaşa Faculty of Medicine by Kemal Önen (1965), Istanbul University Çapa Faculty of Medicine by Muhsin Özen (1969), Sağlık Bilimleri University Gülhane Faculty of Medicine by Müştak Özüer (1972), Hacettepe University Faculty of Medicine Paediatrics by Ümit Saatçi (1974), Atatürk University by Ayla San (18.07.1975) and Uludağ University by Aydoğan Öbek and Mustafa Yurtkuran (28.11.1975)[12] (fig. 2, tab. 1).

Figure 1. First used haemodialysis (HD) machine, 1962 (device).[9]

2. FIRST APPLICATIONS OF HAEMODIALYSIS

- 1962 Ankara University Faculty of Medicine (E. Ertuğrul and his team)
- 1965 Istanbul University Cerrahpaşa Faculty of Medicine (K. Önen)
- 1969 Istanbul University Çapa Faculty of Medicine (M. Özen)
- 1970s Ege University Faculty of Medicine (S. Yeğinboy, A. Cura)
- 1970 The first company in the field of haemodialysis, Tibsan A.Ş. (Ş. Soyuyüce)
- 1972 Gülhane Military Medical Faculty (M. Özüer)
- 1974 Hacettepe University Faculty of Medicine (Ü. Saatçi, A. Gürçay, Ş. Çağlar)

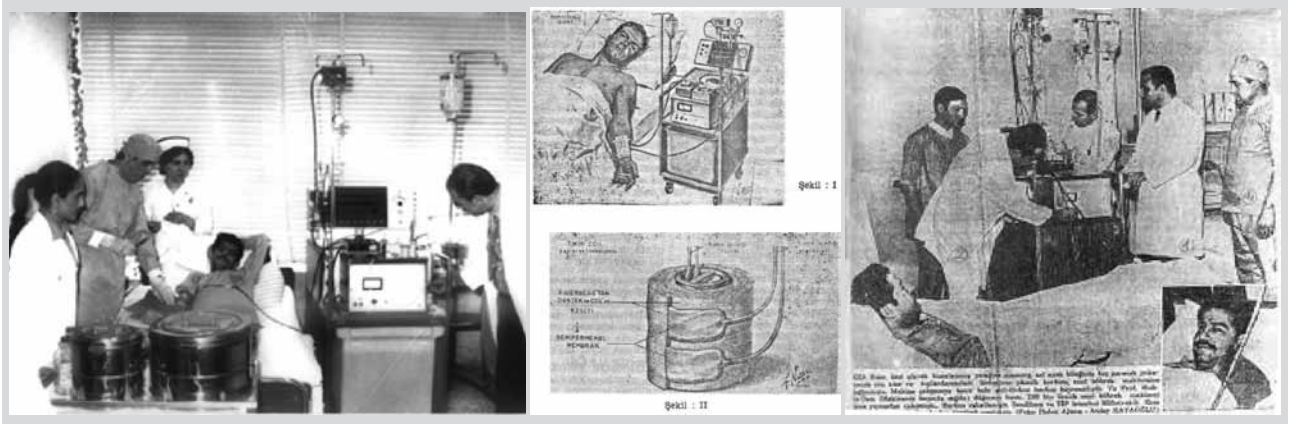


Figure 2. The first dialysis device and coil dialyser.[10]

Table 1. Haemodialysis centres and device types available in 1980 in Turkey.[11]

	Travenol		Fresenius Canister	Rhoidal 75	Gambro	Seatle
	RSP	Clear				
Adana						
Medical Faculty	5	–	–	–	–	–
Ankara						
A.Ü. Medical Faculty	3	4	–	1	2	1
Gülhane Medical Faculty	4	–	–	–	–	–
Güven Hospital	3	–	2	–	–	–
Hacettepe Medical Faculty	13	–	–	–	–	–
Trafik Hospital	3	–	–	–	–	–
Yüksek İhtisas Hospital	5	–	–	–	–	–
Bursa						
Medical Faculty	7	–	–	–	–	–
Erzurum						
Medical Faculty	1	–	–	–	–	–
Istanbul						
Beyoğlu First Aid Hospital	–	–	1	–	–	–
İ.Ü. Çapa Medical Faculty	6	2	–	–	–	–
İ.Ü. Cerrahpaşa Medical Faculty	4	–	–	–	–	–
Haydarpaşa Numune Hospital	5	–	–	–	–	–
Samatya SSK Hospital	9	–	–	–	–	–
İzmir						
Ege Medical Faculty	5	–	–	–	–	–
Tepecik SSK Medical Faculty	5	–	–	–	–	–
Trafik Hospital	–	–	–	2	–	–
Kayseri						
Gevher Nesibe Medical Faculty	3	–	–	–	–	–
Home Dialysis in Develi	1	–	–	–	–	–
Samsun						
Medical Faculty	1	–	–	–	–	–
Total	83	6	3	3	2	1

- 1974 Haemodialysis in infant patients first applied at Hacettepe (Ü. Saatçi)
- 1975 Atatürk University Faculty of Medicine (A. San)
- 1975 Uludağ University Faculty of Medicine. (A. Öbek, M. Yurtkuran)
- 1975 Yüksek İhtisas Hst. [The Turkish High Specializing Hospital] (S. Çetin and his team)
- 1976 First private dialysis centre (M. Özüer)
- 1976 Çukurova University (C. Kobal)
- 1978 Istanbul Training Hospital [SSK] (M. Erman, F. Karakullukçu, F. Kutlar)
- 1979 Ankara Training Hospital [SSK] (S. Şen)
- 1980 Dr Behçet Uz Children's Hospital, is the first haemodialysis centre in Turkey to serve children among state hospitals (G. İnan, M. Bak)
- 1991 The first company to produce haemodialysis bicarbonate solution (Ren-Med)
- 1996 First Haemodialysis Material Production in Turkey (Tıpsan A.Ş., SA-SAN)

3. DIALYSIS RECORDING SYSTEMS[13]

- HD recording systems started in Istanbul in 1989 by the Society of Turkish Nephrology. From 1990 onwards, it developed to today's modern status. The Ministry's of Health comprehensive national dialysis and transplantation recording system was introduced in 1996.

The number of HD Centers in our country historical development has steadily increased. The number of centers in Turkey between 1980 and 1985 was 19. The number of patients was between 600 and 700. There were 256 centres in 1998 and 472 centres in 2003. In 2004, there were 518 centres and 29,775 patients. In 2005, there were 577 centres and 33,241 patients. In 2012, there were 48,900 haemodialysis patients (including paediatric cases). Regarding the number of devices, the Ministry of Health had 4,483, the private sector 9,877 and universities 1,276.[18]

4. CURRENT STATUS OF HAEMODIALYSIS IN TURKEY

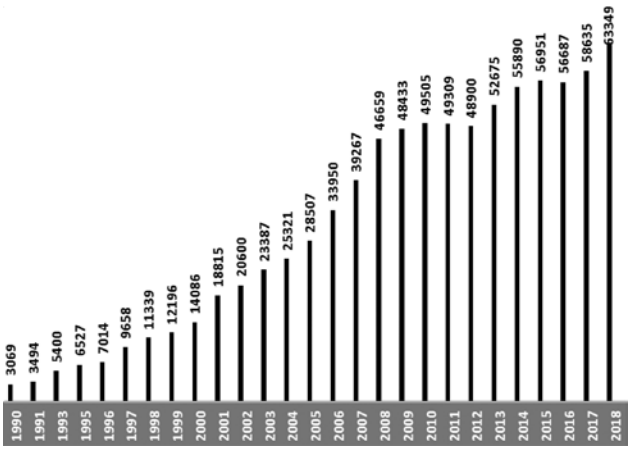
Recent data show that there are about 63,349 patients in Turkey and 17,322 devices. The annual mortality rate is 15%; there were about 882 HD centres in 2018,[14] two-thirds of which private and one-third public. The fees of these patients are covered by the government and no extra payment is required. These centres are spread all over Turkey.[15] Patients are taken from and to their homes free and meals are provided by HD centres.[16]

However, inadequate numbers of trained personnel reduce the quality of the dialysis process. The focus should be not on opening dialysis centres but on providing better health services to our patients by quality dialysis while safeguarding the national economy against unnecessary expenses.

According to the Ministry of Health, as of 2019, there are 884 HD centres in Turkey. All dialysis centres are inspected twice a year by the health directorates. Since 2000, a dialysis certificate program has been implemented and physicians and nurses other than nephrologists who will work in dialysis have been trained in dialysis training centres and certified, with certificates subject to recertification after 5 years.[16]

In the last 10 years, approximately 30 dialysis technician schools have been established in vocational colleges within universities and so far 13,500 technicians have graduated. 3,500 new dialysis technicians graduate each year[17] (tab. 2).

Table 2. Number of haemodialysis patients in Turkey.[18]



5. MINISTRY OF HEALTH HAEMODIALYSIS DATA 2018 IN TURKEY

See table 3.

6. DISTRIBUTION OF HD PATIENTS ACCORDING TO HD TYPE AS OF THE END OF 2018

Standard HD in centre; n (57.649), % (95.06), haemodiafiltration; n (1.733), % (2.86), home HD; n (555), % (0.92), haemofiltration; n (15), % (0.02), unknown type; n (691), % (1.14), total; n (60.643), % (100.00).[19]

6.1. Home haemodialysis

Home haemodialysis (HD) for the treatment of end-stage renal disease was first developed in the early 1960.[20] In Turkey, home HD started for the first time in 2006, with 4 patients in İzmir. After four years of trouble-free treatment of these patients, home HD was defined in Dialysis Centres Regulation 18, published in the Official Gazette of 18.06.2010 under number 27615, and has since been

Table 3. Ministry of Health. Haemodialysis data 2018 for Turkey.[19]

Type of institution	Number of institutions	Number of patients	Number of machines
Ministry of Health	502	19.858	5.953
University	55	4.584	1.162
Private	325	38.907	10.207
Total	882	63.349	17.322

reimbursed by the Social Security Institution. In the following years, haemodialysis at home became widespread throughout Turkey. In early April 2018, there were approximately 380 private and 75 public sector home HD patients in Turkey. In the end of 2016, in terms of the number of home haemodialysis patients, Turkey, third in Europe after the UK and Germany,[16] rose to eighth in the world. Planning and financing a healthy home haemodialysis program is possible through close cooperation between clinicians, health authorities, the social security institution and the private sector. In order to spread home HD, which seems profitable for all stakeholders, its awareness should be increased, service should be made available in all cities, red tape should be minimised and procedures should be reduced.[15]

CONCLUSIONS

Turkish Nephrology has witnessed great developments since its beginnings. Major steps have been taken in HD and nowadays, all types of HD are used, including all the latest scientific developments. Home HD has also gained ground. As of 1 March 2019, the Dialysis Centres Regulation was renewed.

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ΠΕΡΙΛΗΨΗ

Η ιστορία της αιμοκάθαρσης στην Τουρκία

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Αρχεία Ελληνικής Ιατρικής 2020, 37(Συμπλ 2):231–236

Η ανασκόπηση της ιστορικής διαδικασίας εφαρμογής της αιμοκάθαρσης (HD) στην Τουρκία από την αρχή μέχρι σήμερα. Μπορεί εύκολα να φανεί ότι οι ιδρυτές της Νεφρολογίας έκαναν μεγάλες θυσίες που δεν επιτυγχάνονται εύκολα σήμερα. Η ίδρυση κέντρων αιμοκάθαρσης ήταν επίσης χρονοβόρα και δύσκολη. Η πρώτη εφαρμογή έγινε το 1962 στην Ιατρική Σχολή του Πανεπιστημίου της Άγκυρας. Αυτή ακολούθησε το 1965 η Ιατρική Σχολή του Πανεπιστημίου Cerrahpaşa. Τα συστήματα καταγραφής αιμοκάθαρσης ξεκίνησαν το 1989. Σήμερα, υπάρχουν περίπου 884 κέντρα αιμοκάθαρσης στην Τουρκία, τα δύο τρίτα των οποίων είναι ιδιωτικά και το ένα τρίτο δημόσια. Το κόστος νοσηλείας αυτών των ασθενών καλύπτεται από την κυβέρνηση και δεν απαιτείται επί πλέον πληρωμή. Τα κέντρα αυτά είναι διεσπαρμένα σε ολόκληρη την Τουρκία και δεν υπάρχει ασθενής που πέθανε εξ αιτίας της δυνατότητας για αιμοκάθαρση. Οι ασθενείς μεταφέρονται από και προς τα σπίτια τους δωρεάν και παρέχονται γεύματα από τα κέντρα αιμοκάθαρσης. Οι διαδικασίες και οι κανονισμοί που σχετίζονται με την αιμοκάθαρση είναι καλά οργανωμένοι. Όλα τα κέντρα εποπτεύονται δύο φορές τον χρόνο. Από το 2000 εφαρμόστηκε πρόγραμμα πιστοποιητικών και το εξουσιοδοτημένο προσωπικό έχει εκπαιδευτεί και έχει λάβει πιστοποιητικά πενταετούς διάρκειας. Πρόσφατα στοιχεία δείχνουν ότι στην Τουρκία υπάρχουν περίπου 63.349 ασθενείς και 17.322 συσκευές. Το ετήσιο ποσοστό θνησιμότητας είναι 15%. Ο αριθμός των ασθενών που κάνουν κατ' οίκον αιμοκάθαρση ξεπέρασε τους 800, τοποθετώντας την Τουρκία στην τρίτη θέση στην Ευρώπη.

Λέξεις ευρετηρίου: Ιστορία της αιμοκάθαρσης Τουρκία, Κατ' οίκον αιμοκάθαρση Τουρκία, Νεφρολογικό αρχείο

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DIALYSIS/TRANSPLANTATION
ΑΙΜΟΚΑΘΑΡΣΗ/ΜΕΤΑΜΟΣΧΕΥΣΗ

The history of peritoneal dialysis in Turkey

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ΑΡΧΕΙΑ ΕΛΛΗΝΙΚΗΣ ΙΑΤΡΙΚΗΣ 2020, 37(Συμπλ 2):237–241

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Η ιστορία της περιτοναϊκής κάθαρσης στην Τουρκία

Περίληψη στο τέλος του άρθρου

Peritoneal Dialysis (PD) in Turkey was first applied in 1950s by Kemal Önen in Istanbul Haseki Treatment Clinics. In Ankara, it was first applied by Nihat Sipahi at the Ankara University Faculty of Medicine in 1958. In modern sense, PD applications started in Istanbul University, Faculty of Medicine Treatment Clinic in 1965. In Ankara, it was first applied at Hacettepe University, Faculty of Medicine by Şeref Zileli in 1969. CAPD was first applied at Istanbul University Faculty of Medicine in 1981. The recording system started in 1994 by the coordination of the Turkish Society of Nephrology and Ministry of Health. 2018 reports show that there are 139 PD centers and 3192 patients in Turkey.

Key words

Continuous ambulatory peritoneal dialysis (CAPD)
First applications
History of peritoneal dialysis
Peritoneal dialysis (PD) to day
Turkey

1. INTRODUCTION

J. Kolff developed the first functioning artificial kidney for the treatment of patients with uraemia in Holland in 1940. Frank Seligman and Jacob Fine put peritoneal dialysis **(**PD) into practice in 1946 with peritoneal irrigation. In 1950, Odell conducted a literature review of 101 patients and these procedures were reviewed.[1–4]

In Turkey, Kemal Önen first applied PD with Celal Öker and Tahsis Artunkal on two patients with septic abortion and acute renal failure (ARF) by placing two catheters in the peritoneal cavity on both sides, filling from one side and draining from the other side with Ringer's solution in the early 1950s.[5–7] The first publication on the history of PD in Turkey was by K. Önen et al 1968[8] (figures 1, 2).

In modern sense, Uğur Ülkü first applied PD at the Istanbul University Faculty of Medicine Treatment Clinic in 1965. The first domestic commercial PD solutions were produced in 1965–1966. Ali Gürçay applied PD with peritoneal catheters which he brought to Turkey from the USA in acute renal failure cases in Erzurum, a city in eastern Turkey in 1971.[6–10]

In 1964, the first acute peritoneal dialysis applications started by Necdet Koçak and Ercüment Özdağ. Between 1968 and 1970, chronic renal failure patients received intermittent PD. After 1973, it became routine to apply chronic intermittent PD on patients. In 1979, with the use of Tenckhoff catheter, patients themselves began to apply chronic intermittent PD. Necdet Koçak and his team applied bottle dialysis on the 18 patients using Tenckhoff catheter by waiting for 6–8 hours in the abdomen, as Popovich

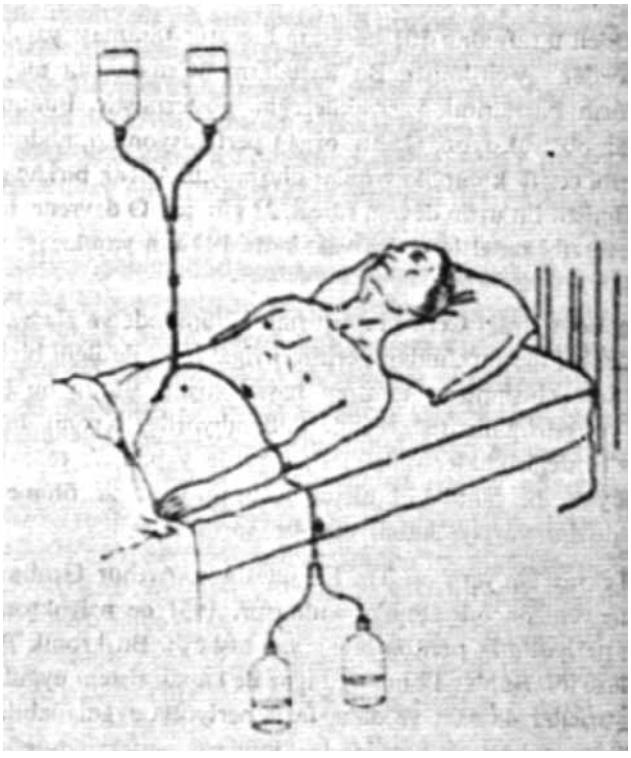


Figure 1. Modification of Maxwell's practice was first applied from Grollman's method in Turkey.[9]

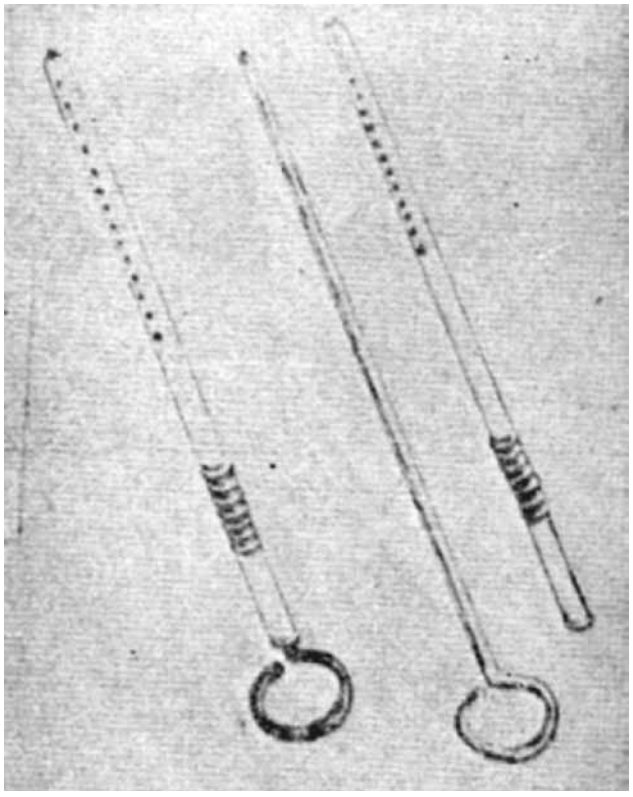


Figure 2. Weston and Robert's chuck catheter first used in Turkey.[9]

Figure 3. An outpatient on peritoneal dialysis (PD) at Erzurum Atatürk University (1980).

and Moncrief described. Bottle dialysis was applied on two patients at Akdeniz University, Faculty of Medicine in 1982, but it was not published.[10–12] Ambulatory PD in the modern sense started in 1985 with plastic vacuum bags and Braun connection sets and Tenckhoff-type silastic permanent catheters. The first article on Continuous Ambulatory Peritoneal Dialysis (CAPD) was published in Ankara Medical Bulletin.[9–12]

After Ayla San was appointed to establish the Faculty of Medicine and Department of Nephrology in Atatürk University in 1973, she first applied hemodialysis and later PD to outpatients. She started CAPD application at the Atatürk University Faculty of Medicine, Erzurum in 1992[9] (fig. 3).

At the same time, Semra Bozfakioğlu started CAPD at Istanbul University in 1994.

Automatic PD (APD) applications have also been implemented.[8,10] CAPD bags were produced by Eczacibaşi Company. The Turkish Multicentre Peritoneal Dialysis Study Group contributed to the regulations for it's clinical use (1998).[13] Research has progressed greatly in Turkey since 2008 and about 316 scientific publications on PD have emerged.[14–16]

2. PERITONEAL DIALYSIS TYPES APPLIED TODAY[9]

2.1. Acute Peritoneal Dialysis

In this classical technique, a temporary catheter is used.

2.2. Chronic Intermittent Peritoneal Dialysis (IPD)

Dean's prosthesis and Gotloib's device or continuous peritoneal catheter (Tenckhoff) used as catheters.

2.3. Continuous Ambulatory Peritoneal Dialysis (CAPD)

Permanent peritoneal catheter used.

2.4. Automated Prolonged Dwell Peritoneal Dialysis (PDPD) and Continuous Cyclic PD (CCPD)

This is essentially another form of CAPD. The difference is that the solutions are changed automatically at night.

2.5. Continuous Equilibration Peritoneal Dialysis (CEPD)

It is similar to CAPD except that the patients are not

ambulatory. CEPD was applied to five hypercatabolic and seven non-hypercatabolic patients with ARF or exacerbation of CRF.

All of these PD types can be applied in Turkey.

3. RESULTS

3.1. Worldwide Firsts in peritoneal dialysis[17]

- 1923: Ganter (University of Wurzburg)
- 1924: USA and Germany Intermittent PD
- 1976: Popovich et al. First CAPD experience
- 1978: Oreopoulos et al. CAPD with plastic bags (Toronto Western Hospital Technical).

3.2. Peritoneal Dialysis in Turkey[18]

- Late 1950s: ARF patients were treated through bottle dialysis
- 1968: Chronic Renal Failure (CRF) patients were treated with bottles
- 1980s: A small number of CRF patients were treated with CAPD with imported bags
- 1989: The first CAPD was applied at the Paediatric Department of the Ankara Medical Faculty (N. Tümer, M. Ekim)
- Since 1994: CRF patients were treated with CAPD, with bags produced in Turkey.

3.3. First practices in acute peritoneal dialysis[19]

- Early 1950s: Treatment Clinic at Istanbul Haseki Hospital (C. Öker, T. Artunkal)
- 1958: Ankara University Medical Faculty (N. Sipahi)
- 1969: Hacettepe University Medical Faculty (Ş. Zileli)
- 1967: Ege University Medical Faculty (S. Yeğinboy, A. Cura)
- 1971: Atatürk University Medical Faculty (A. Gürçay)
- 1978: Istanbul Social Security Institution Training Hospital (F. Karakullukçu)
- First Domestic Peritoneal Dialysis Solution Production, produced by Eczacibaşi (1994)

3.4. First applications in continuous ambulatory peritoneal dialysis[19]

- 1981: Istanbul University Medical Faculty (N. Koçak et al)
- 1982: Works initiated on two patients at Akdeniz University Medical Faculty, but they were not published
- 1982–1983: Atatürk University, Medical Faculty practice on two patients (A. San)
- First thesis on CAPD (1983, A. San)
- 1984: Ankara University Medical Faculty (B. Erbay, O. Karatan)
- 1985: CAPD results of Istanbul Samatya Istanbul Social Security Institution Training Hospital as presented at the congress held in Erzurum (F. Karakullukçu).

4. DISCUSSION

4.1. According to the Turkish Society's of Nephrology (TSN) 2018 Report[20]

- A decline in the number of patients undergoing PD after the peak in 2008 is noteworthy. There is a clear downtrend, which is continuing for a decade.
- According to USRDS data, although hemodialysis (HD) is the most common dialysis type worldwide, in Turkey PD is widely used.
- The aetiology of decreasing PD rates seems to be multifactorial. There is no significant increase in new recruited patients (2017: 876/2018: 886). Moreover, the drop-out rate is high (total deaths or modality switches: 1,007). Renal transplantation was performed on 157 patients (5.0% of all PD patients).
- Inadequate dialysis and PD-related infections seem to be the most important factors for switching to HD, followed by mechanical complications and ultrafiltration failure.
- The most common non-infectious complications in PD patients are obesity and hernias.
- It is noteworthy that PD patients are younger than HD patients.
- The ratio of patients with hypoalbuminaemia is higher in PD than in HD.
- Cardiovascular diseases are the most common death causes among PD patients, followed by cerebrovascular diseases and infections.
- The number of patients (including paediatric patients) who started PD for the first time in 2018 is 886 (CAPD: 669 and APD: 217) (tables 1–4).

Table 1. Distribution of prevalent peritoneal dialysis (PD) patients according to peritoneal membrane permeability at the end of 2018 (according to data obtained from 32 centres).[20]

	n	%
Low	85	9,06
Low-average	332	35,40
High-average	365	38,91
High	156	16,63
Total	938	100,00

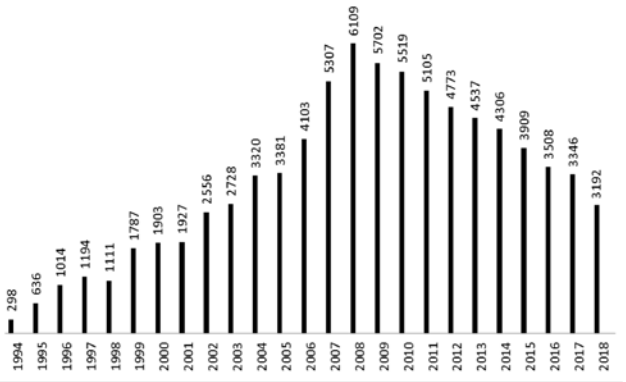
Table 2. Distribution of causes of transfer to hemodialysis (HD) in prevalent peritoneal dialysis (PD) patients in 2018.[20]

	n	%
Inadequate dialysis	148	30,33
PD-related infection	93	19,06
Mechanical complications	88	18,03
Ultrafiltration failure	77	15,78
Patient preference	43	8,81
Psychosocial causes	22	4,51
Other	17	3,48
Total	488	100,00

Table 3. Number of peritoneal dialysis (PD) centres at the end of 2018 in Turkey.[20]

	n	%
Ministry of Health	74	53,24
University	48	34,53
Private	17	12,23
Total	139	100,00

Table 4. Number of peritoneal dialysis patients in Turkey.[20,21]



5. CONCLUSIONS

The 2018 Joint Report of the Ministry of Health and the Turkish Society of Nephrology shows that, in Turkey, there are 139 PD centres and 2,139 patients, 1,053 on CAPD and 3,192 on APD.

With the contribution scientific research and experience, PD, which started 50 years ago in Turkey, has reached world standards.

ΠΕΡΙΛΗΨΗ

Η ιστορία της περιτοναϊκής κάθαρσης στην Τουρκία

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Αρχεία Ελληνικής Ιατρικής 2020, 37(Συμπλ 2):237–241

Η περιτοναϊκή αιμοκάθαρση (PD) στην Τουρκία εφαρμόστηκε για πρώτη φορά τη δεκαετία του 1950 από τον Kemal Önen στην κλινική θεραπείας Haseki της Κωνσταντινούπολης. Στην Άγκυρα, εφαρμόστηκε για πρώτη φορά το 1958 από τον Nihat Sipahi στη Σχολή Ιατρικής του Πανεπιστημίου της Άγκυρας. Στη σύγχρονη εποχή, οι εφαρμογές περιτοναϊκής αιμοκάθαρσης ξεκίνησαν στο Πανεπιστήμιο της Κωνσταντινούπολης, το 1965, στη Σχολή Ιατρικής. Στην Άγκυρα, εφαρμόστηκε για πρώτη φορά το 1969 στο Πανεπιστήμιο Hacettepe στην Ιατρική Σχολή από τον Şeref Zileli. Η συνεχής περιπατητική περιτοναϊκή κάθαρση (CAPD) εφαρμόστηκε για πρώτη φορά το 1981 στο Πανεπιστήμιο της Κωνσταντινούπολης στην Ιατρική Σχολή. Το σύστημα καταγραφής ξεκίνησε το 1994 με συντονισμό της Τουρκικής Νεφρολογικής Εταιρείας και του Υπουργείου Υγείας. Οι εκθέσεις του 2018 δείχνουν ότι υπάρχουν 139 κέντρα περιτοναϊκής αιμοκάθαρσης και 3.192 ασθενείς στην Τουρκία.

Λέξεις ευρετηρίου: Ιστορία περιτοναϊκής κάθαρσης, Περιτοναϊκή κάθαρση (PD) σήμερα, Πρώτες εφαρμογές, Συνεχής περιπατητική περιτοναϊκή κάθαρση (CAPD), Τουρκία

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ISLAMIC MEDICINE
ΙΣΛΑΜΙΚΗ ΙΑΤΡΙΚΗ

What did al-Rāzī (Rhazes) quote from Philagrius of Epirus on kidney diseases in *Kitāb al-Ḥāwī fī al-Ṭibb* (*Liber Continens*)?

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ΑΡΧΕΙΑ ΕΛΛΗΝΙΚΗΣ ΙΑΤΡΙΚΗΣ 2020, 37(Συμπλ 2):242–249

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OBJECTIVE ***Kitāb al-Ḥāwī fī al-Ṭibb/Liber Continens*** **of Rhazes is a significant work because it presents valuable quotations from the works of Greek, Indian and Arabic authors. These quotations also render Rhazes' work important for the history of medicine because it provides us with information about writings that have not survived. Philagrius of Epirus, who practiced medicine in Thessaloniki during the third or fourth century, is one of the most prominent and important writers included in Rhazes' work. The purpose of this study is to present quotations from Philagrius from *Continens* on kidney diseases and introduce and register them to the culture, literature and history of medicine in the English language.** METHOD **The Arabic and Latin editions of the 10th book of *Continens* were used in this study. Twelve quotations related to urogenital diseases from Philagrius were identified in both in Arabic and Latin texts. Consequently, these fragments are compared to each other, translated into English, and discussed in the light of literature on the history of medicine.** RESULTS AND CONCLUSIONS **These quotations relate to kidney pains, kidney stones, diabetes, and genital diseases. Philagrius' writings had also been adopted in the Islamic world through their translations into Arabic. Considering that Philagrius' works have not survived today, it is important that quotations from his works are found in Rhazes' *Continens;* as some of these relate to nephrology.**

Τι παρέθεσε ο al-Rāzī (Rhazes) από τον Φιλάγριο τον Ηπειρώτη σχετικά με τις ασθένειες των νεφρών στο *Kitāb al-Ḥāwī fī al-Ṭibb (Liber Continens);*

Περίληψη στο τέλος του άρθρου

Key words

Liber Continens
Medical practice in Medieval Thessaloniki
Philagrius of Epirus
Rhazes
Urinary system diseases

1. INTRODUCTION

Abū Bakr Muḥammad b. Zakariyyā al-Rāzī (865–925 AD) is one of the most notable clinicians of all time. Known as Rhazes in the West, he is reported to have written approximately 200 or more books, half of which on medicine.[1,2] Although *Kitāb al-Ḥāwī fī al-Ṭibb/Liber Continens* is a posthumous treatise, it is one of his most important works, completed thanks to the vizier of Buwayhid ruler Rukn al-Dawla (r. 935–976), namely Ibn al-ʿAmīd (d. 970), who bought the unfinished notes of Rhazes from his sister Khadīja and had his students compile them for him.[2–4] This book contains many quotations from various works of previous and contemporary writers, including the names of these writers and their works. *Continens* was translated into Latin by Farraguth in Sicily in 1279 and was published in Brescia in 1486.[4,5] This is an important book for the history of medicine because it contains quotations from substantial authors' works, most of which have not survived today.[5] Consequently, and as a result of these quotations, we are now able to gain a greater insight regarding these works and their contents. A prominent writer included in Rhazes' work is Philagrius of Epirus.

Philagrius, the brother of the physician Posidonius, is a Greek physician and writer who was born in Epirus and practiced medicine in Thessaloniki during the third or fourth century. Although Philagrius followed the Galenic doctrine, he was considered an eclectic who also focused on the Pneumatists' views.[6–8] According to Suda,[9] a 10th-century Byzantine encyclopaedic lexicon, Philagrius compiled medical books including 70 monographs, various composite works whose numbers are comparable to the monographs written, and commentaries on Hippocrates. None of his complete works is preserved or found today. However, certain fragments have been preserved following his death in works of other authors in either Greek (or in their translations) or Arabic.[10] Philagrius was considered a distinguished surgeon and gynaecologist[6] and was also

famous for providing accurate diagnosis and treatment for many spleen diseases.[6,8] The fragments from his writings on internal diseases are found in the works of Aetius and Oribasius.[6] Sezgin[10] states that the Islamic world recognises Philagrius directly from his writings or from the works of Oribasius of Pergamum, Alexander of Tralles, and Paul of Aegina. Sezgin[10] also informs us that according to Ibn al-Nadīm, Abū'l-Ḥasan al-Ḥarrānī (d. 980 AD) had translated some of Philagrius' books into Arabic. Furthermore, and according to Ibn Abī Uṣaybiʿa, in the 11th century, ʿAlī b. Riḍwān, an Egyptian physician, has compiled several significant parts from Philagrius' work on healthy and delicious beverages. The majority of the fragments related to Philagrius' works, translated into Arabic, have also been preserved in Rhazes' *Continens*.[10] The purpose of this study is to present Philagrius' quotations on kidney diseases in *Continens* and to register them in the culture, literature and history of medicine in the English language.

2. MATERIAL AND METHODS

The Arabic and Latin editions of *Kitāb al-Ḥāwī*[11]/*Liber Continens*[12] were used in this study. Topics related to urogenital system diseases are included in the tenth section of *Continens: "*fī amrāḍ al-kulā wa majārī al-bawl wa ghayrihā[11]/ de dispositionibus renum et vesice et aliqualiter veretri tractans continet tractatus tres (In Latin edition, 1509, Book 23)".[12] First of all, 12 quotations from Philagrius were identified in both Arabic and Latin texts, and were subsequently compared to each other before being translated into English (tab. 1) as presented in the results section. It is shown that these quotations relate to kidney pains, kidney stones, diabetes, and genital diseases.

3. RESULTS

Quotation 1 concerns the symptoms and signs of kid-

Table 1. Quotations from Philagrius in both Arabic and Latin editions of *Kitāb al-Hāwī/Liber Continens*.[11,12]

Rhazes – *Liber Continens*	**Abū Bakr Muḥammad b. Zakariyyā al-Rāzī – *Kitāb al-Ḥāwī fī al-Ṭibb*** ***أبو بكر محمد بن زكريا الرازي ـــ كتاب الحاوي في الطب***
"Filogorius: Accidit laborantibus dolore renum dolor in dorso et ancha et lumbis cum ponderositate: an forte accidit sincopis et deterius erit si urina eius fuerit arenosa aut sanguinea an forte accidet ei cum ea febris vertigo et frequentatio vomitus."[12]	«فليغريوس: يعرض لأوجاع الكلى وجع في الظهر والورك والقطن والثقل، وربما عرض غشي وأسر، ويكون بوله رملياً أو دموياً، وربما عرض له معه حمى ودوار وتتابع القيء.»[11,p.49]
"Filogorius de secundo capitulo de lapidibus dixit: lapides qui generantur citrini et albi non indigent minutione sed laxatione cum scamonea ad substantiam colere: et regimine cum nutrimentis: ut non generetur flegma: et proprie in eis quibus generatur flegma etiam trahitur superfluitas ad membra alia per fricationem, calefactionem et similia, si negocium fuerit leve."[12]	«من رسالة فليغريوس في الحصى؛ قال: لون الحصى الذي يتولد أصفر أبيض لا يحتاج إلى الفصد بل إلى الإسهال بالسقمونيا لئقل الصفراء، والقصد في الأغذية لئلا يتولد البلغم، وقد تستحجر الفضلة إلى أعضاء أخر بالدلك والكماد ونحوه إذا كان الأمر مهولاً.»[11,p.130]
"Filogorius dixit in libro eius ad Georgium de lapidibus: illum qui mingit harenam noli minuere: sed laxa eum de colera ru(bea) et nigra: mediocriter attenuando nutrimentum eius: ita tamen quod sit fri(gi)dum cum hoc."[12]	«فليغريوس في كتابه إلى جريج في الحصى: من بال حصاة فلا تقصده لكن اسهله صفراء ومره يمشي وسطاً ولطف غذاءه ويكون مع ذلك بارداً.»[11,p.137]
"Filogorius dixit. Debet etiam evitare satietates nauseativas: quoniam ipse sunt origo huius passionis. Etiam da ei in potu de decoctione nigelle et asse fe. Ad mundificandum vesicam de lapidibus quae in ea sunt."[12]	«فليغريوس؛ قال: ليحذروا اللحم فإنه أصل تولد هذه العلة واسقهم طبيخ الشونيز والحلتيت فإن هذه تنقي المثانة مما فيها من الحصاة.»[11,p.138]
"Hoc est medicamen mirabile quod descripsit pro Filogorio. Dixit: frangit lapidem et prohibet quod non generetur lapis: et mitigat dolorem renum de apostemate calido aut alio: quoniam mirabile est ad hoc: et convenit lapidi renum valde: quando uva als urina nigrescit, Accipe olam fictilem novam: et lava eam cum aqua ebullita in ea: et postea eam desiccando de ipsa aqua: macta byrcum etatis quattuor annorum: ac de mediocri sanguine: RY in ipsa ola: dimittendo ipsum in ea dum ligetur: deinde incide ipsum in partibus parvis in ola ponendo super eum pannum rarum: et dimittendo ipsum sub celo in sole et luna similiter dum desiccetur valde caute ne inveniat eum aqua pluvialis: aut aliquo humectatio: aut aliud contrarium: unde habita perfecta desiccatione in eo: tere aliquam partem cum modica parte spice in tantum inquantum bonus sit odor ipsius. Dando de eo in potu aureo pondera ii. cum vino dulci: et hoc debet fieri in tempore quietis doloris: et mirabilis erit effectus eius."[12]	«دواء عجيب لفليغريوس؛ قال: يفت الحصى ويمنع من تولدها ويسكن وجع الكلى من ورم حار أو غيره وهو عجيب في ذلك، ويصلح لحجارة الكلى جداً: إذا ابتدأ العنب يسود فخذ قدر فخار جديدة فصب فيها ماء وغله ثم صب عنها وجففها واذبح تيساً له أربع سنين، وخذ من الدم الأوسط فأودعه القدر واتركه إلى أن ينعقد ثم قطعه صغاراً صغاراً في القدر واجعل عليه خرقة مهلهلة واتركه تحت السماء في الشمس والقمر جميعاً حتى يجف جداً، واحذر أن تصيبه ندوة مطر أو غيره، فإذا استحكم جفافه فاسحق منه شيئاً مع قليل سنبل بقدر ما قطعت رائحته به واسق منه ملعقة بشراب حلو، تفعل ذلك في أبان سكون الوجع، فإنك تعجب من فعله.»[11,p.152]

Table 1. (continued) Quotations from Philagrius in both Arabic and Latin editions of *Kitāb al-Hāwī/Liber Continens*.[11,12]

Rhazes – *Liber Continens*	**Abū Bakr Muḥammad b. Zakariyyā al-Rāzī – *Kitāb al-Ḥāwī fī al-Ṭibb*** ***أبو بكر محمد بن زكريا الرازي ــ كتاب الحاوي في الطب***
De fissura pro lapide: dixit quidam antiqui scindunt pro lapide renum de parte posteriori in lumbis: et in hoc erit fallacia: imo derisio: quoniam fissura vesice salvantur plures: videlicet quorum carnes sunt humide. Etiam illi quibus non accidit apostema: et ipsorum vulnera putredinem faciunt de levi salvantur. unde qui patiuntur apostema difficilem habebunt sanationem: quoniam in iuvenibus accidit apostema calidus penes fissuras: et in senioribus non adherent vulnera: sed in pueris non accidet apostema: et ipsorum vulnera consolidabunt. Ideo in eis ipsa passio erit levior. Lapis magnus de levi detinetur: et difficilis erit egressio eius. Sed parvus econverso: et rotundus facilem habet exitum. Quod si ipse fuerit asper: laborans eo potentior erit süper fissuras: et aliud praeter ipsam: quoniam consuevit pati dolores, et si fuerit levis: econverso. Ad faciendum mingere expedit quod fiat urinatio: si ibi non fuerit apostema: nec dolor vehemens non quod apostema factum fuerit ex lapide: aut ex aliqua coagulatione sanguinis: quoniam bona erit ad mitigandum dolorem si remotum fuerit utrumque de meatu. Quod si difficile fuerit valde: et non poterit cum ingenio instrumentum urinationis operari: expedit quod fissura fiat inter sellam ani et testiculos modo parvo: et ponatur cannula in ea ad emittendum cum ea antequam urinam. Quoniam melius erit quod homo vivat cum ea antequam alio modo moriatur.[12]	«في شق الحصى؛ قال: وقد كان قوم من القدماء يشقون عن حصى الكلى خلف القطن وفي ذلك خطر. فأما شق المثانة فيسلم فيه الأكثر، فالذين لحومهم رطبة ومن لم يعرض لهم ورم وقاحت منهم جراحاتهم فإنهم يتخلصون بسهولة، فإما من ورم فأعسر، والشباب يعرض لهم منه ورم حار عند الشق، والمشايخ، لا يلتحم جرحهم، والكهول لا يعرض لهم ورم ويلتحم جتحهم فلذلك هو أسلم فيهم، والحجر العظيم يسهل بطه ويعسر إحراجه والصغير بالعكس والمتوسط يسهل خروجه، وإذا كانت الحصى خشنة كان صاحبها على الشق أقوى من غيره ولأنه قد اعتاد احتمال الوجع، وإذا كانت لينة فبالضد. في التبويل: يجب أن يستعمل التبويل أذا لم يكن هناك ورم ولا وجع شديد إلا أن يكون الورم عن حجر أو علق دم فإنه حينئذ يسكن الورم إذا نحيت هذين عن المجرى، ومتى عسر الأمر جداً ولم يمكن الاحتمال بالمبولة فيجب أن يشق فيما بين الشرج والخصي شقاً صغيراً واجعل فيه أنبوباً ليخرج به البول فإن عيش هكذا خير من أن يموت.»[11,p.153]
De complemento et perfectione Filogorius dixit utendum est calefactione pectinis cum balneo: pila: et oleo: et ponatur super pectinem spongia plena aqua calida: et comprimenda est: et fricanda potenter: nisi cum ea fuerit dolor vehemens: unde penes istud comprimere debes cum temperie: etiam fricare: et post hoc impone in veretro de sambucino.[12]	«من الكامل والتمام؛ فليغريوس قال: استعمل تكميد العانة والحمام والأبزن والدهن وتوضع على العانة إسفنجة بماء حار وتغمزه وتدلكه بقوة إلا أن يكون معه وجع شديد فعند ذلك تغمزه برفق وكذلك يدلك وبعده يصب في الإحليل زنبق.»[11,p.183]
"De epistola Filogorii: de diabete dixit: semper tuum propositum sit ad mitigandum sitim in primo cum potu aquae rosae aut succi rosae in tempore ipsarum in quantitate unc xviii. Et patiens esse debet in aere frigido valde: et loco occulto: et humido valde: utendo emplastris frigidis: et nutrimentis frigidis: dum inde mitigetur sitis: et mitigata siti procede cum clysteribus laxativis et lenificatione ventris. Dixit: provoca somnum ei cum omni ingenio. Unde precipe quod curetur post mitigationem laxationis cum pillulis aloe post clysteria: et cum logodione: postea utatur vomitu: et emplastro sinapis. Licet non inveniatur in hac causa."[12]	«من رسالة فليغريوس؛ في ذيابيطس: اقصد في الأول لتسكين العطش بأن تسقيه ماء الورد أو عصير الورد في أبانه اسقه قدر قوطولين، ولتكن في هواء بارد أو موضع كنين رطب جداً، وضمده بالأضمدة الباردة واغذه بها حتى يسكن عطشه، وإذا سكن فعليك بالحقن المسهلة وتليين البطن. قال: وأجلب له النوم بكل حيلة. قال: ومتى أزمن السهر والتخم والسكر وشرب الماء البارد وبرد الجسد كله وضعف الكبد ولم يأت في ذلك بعلة مقنعة، وأمر أن يعالج بعد سكون الإسهال بحب الصبر بعد الحقن وبلوغاذيا بعده، واستعمال القيء وضماد الخردل ولم يحد ذلك ولا جاله بسبب.»[11,p.195]
"De libro Filogorii de dyabete dixit: hic morbus fit ex debilitate epatis: et frigiditate totius corporis: ex satietate nauseativa: aut insomnietate et potu aquae frigidae: verum tamen cum eo acci[di]t sitis valida nimis."	«في ذيابيطا من كتاب فليغريوس؛ قال: هذا الداء يكون من ضعف الكبد وبرد الجسم كله من تخمه أو سهر وشرب الماء البارد، ويعرض معه عطش قوي جداً. قال: فعليك بتسكين العطش، وقد ذكرنا ما ذكر لذلك في باب تسكين العطش، فإذا سكن العطش فاحقنه بالحقن المسهلة اللينة مرات ثم أسهله بحب الصبر يكون كالحمص إحدى عشرة حبة فإنه يسهل إسهالاً جيداً ثم دعه ثلاثاً ثم عاوده ثم استعمل القيء بعد الطعام بالفجل والمهاجم الحارة على جميع الجسم والكماد والدخن ولا سيما أطراف البدن، واستعمل الأدوية المحمرة ثم أرحه أياماً، واستعمل الركوب باعتدال والدلك خاصة في أطراف الجسم والحمام ويشرب الشراب اليسير فإنه يبرئه برءاً تاماً.»[11,pp.207,208]
"De libro Filogorii de dyabete dixit: stude ad mitigandum sitim sicut diximus tibi in capitulo mitigationis sitis: et mitigata ipsa siti clystere fiat cum rebus laxativis et lenitivis pluries: deinde laxanda eum cum pillulis aloe confectis ad modum cicerum in numero xi. Quoniam laxabunt efficaciter: deinde dimitte eum per triduum: reiterando postea curam: et utendo vomitu facto post cibum cum radice: etiam ventosis calidis positis super totum corpus. Etiam calefactione facta cum millio praecipue super extremitates corporis: etiam medicinis rubificantibus: deinde quiescat per dies: et utatur equitatione cum temperie: et fricatione praecipue facta in extremitatibus corporis: etiam balneo: et potu vini modice: quoniam inde sanabitur perfecte."[12]	«فليغريوس؛ ينفع من زبله بغير إرادة: القعود في المياه القابضة والضمادات بثقلها [والأغذية القابضة] والحقن ودلك الصلب دائماً والرياضة والقعود في ماء الشب.»[11,p.208]
"Filogorius dixit: confert illi cuius urina egreditur non voluntarie sessio in aquis stipticis: etiam emplastra fieri debent ei cum substantia stipticarum rerum et rebus metipsis: utendum est nutrimentis stipticis clysteribus: fricatione spinalis, exercitio, sessione in aqua aluminis."[12]	«فليغريوس: الذين يخرج منهم منيهم بلا إرادة يهزلون جداً ويضعفون ويموتون إذا دام بهم ذلك، وعلاجهم الجلوس في مياه قابضة، واطل الظهر والعانة بشوكران وادلك الجسم دائماً وأغذية قابضة وألزمهم الرياضة والتعب وترك الدعة والأطعمة الحلوة الدسمة ويتجوعوا كثيراً فإنه نافع لهم جداً.»[11,p.275]
"Filogorius dixit quod illi quibus fluit sperma non voluntarie extenuantur valde: et debilitatur: et moriuntur si durabile fuerit hoc."[12]	
"Filogorius dixit quod illi quibus fluit sperma non voluntarie curantur per sessionem in aquis stipticis: et illinitionem dorsi et pectinis cum iusquiamo: fricationem corporis frequenter: per nutrimenta stiptica: usus exercitii et laboris: dimisso otio: per cibaria dulcia et unctuosa: famem abundanter; quoniam hec conferunt eis valde."[12]	

Table 1. (continued) Quotations from Philagrius in both Arabic and Latin editions of *Kitāb al-Hāwī/Liber Continens*.[11,12]

Rhazes – *Liber Continens*	**Abū Bakr Muḥammad b. Zakariyyā al-Rāzī – *Kitāb al-Ḥāwī fī al-Ṭibb*** **أبو بكر محمد بن زكريا الرازي ــ *كتاب الحاوي في الطب***
"Filogorius dixit: curari debet qui durat per longum tempus et non perveniet ad virilitatem: cum exercitio membrorum inferiorum: fricatione inguinis et anche: et illinitione veretri et pectinis eius cum medicinis punctivis: sicut cum pipere euforbio et cum potu vini odoriferi cum cibo de fructibus pini magni et satirion et cum visu personarum pulcherrimarum absque ulla proximitate facta cum eis dum perveniet ad potentem virilitatem."[12]	«فليغريوس: يعالج العنين برياضة الأعضاء السفلى ودلكها ودلك الأربية والفخذ واطل عانته وذكره بأدوية لذاعة قوية كالفلفل والفربيون، واسقهم شراباً ريحانياً وأطعمهم حب الصنوبر الكبار وخصي الثعلب، ويديم النظر إلى ذوات الجمال ولا يقربهن حتى تشتد غلمة.»[11,pp.323-324]

ney pains, which may represent a probable inflammatory kidney disease:

Philagrius: kidney pains cause pain in the back, the hip [Lat.ancha], and the low-back [with a feeling of] ponderosity. It may also cause syncope and retention of urine if urine is arenaceous and sanguineous, it may also cause fever and vertigo and vomiting followed in succession [Lat. frequent vomiting].[11,12]

Quotation 2 is from Philagrius' booklet on kidney stones and mentions the therapeutic treatment followed against these yellow-white stones. Most probably, and according to the principles of humoral pathology, these stones were thought to be caused by excessive bile and phlegm. Hence, it is recommended to purge the bile and to prevent the phlegm as opposed to implementing venesection:

In his booklet (Lat. in the second chapter) on [kidney] stones Philagrius said that: yellow-white stones do not require venesection but instead laxation of the excessive yellow bile with scammony and regime with nourishments in order to prevent the production of phlegm. If this situation deteriorates, the superfluous phlegm is drawn away to other members by means of friction, fomentation and the like.[11,12]

Quotation 3 is taken from his book, *Kitāb ilā Jurayj/Liber ad Georgium*, and provides valuable information regarding kidney stone treatment. In this quotation, Philagrius believes that the development of kidney stones is not caused by excessive blood, but is instead facilitated by bile. Therefore, Philagrius does not recommend bloodletting to cure this condition, but purgation of the bile [by means of diarrhoea].

On kidney stones, Philagrius said in his book, Ad Georgium: do not let blood from him who passes water together with stones, but purge him of the yellow bile. Continue his nourishment to be soft and moderately purgative, thus it becomes cold with it. [Lat. purge him of the red and black bile by moderately lessening his nourishment, in such a manner that it becomes cold with it.].[11,12]

Quotation 4 suggests that kidney stones are mainly caused by meat consumption, and hence Philagrius underlines the necessity of abstaining from eating meat:

Philagrius said that: it is necessary to avoid meat (Lat. to avoid satiety which induces nausea), because it is the main cause of this disease. You should give him to drink a decoction of black cumin and fenugreek, because [this decoction] cleanses the bladder from the stones in it.[11,12]

Quotation 5 relates to the admirable medicament of Philagrius, which breaks the stone into pieces, prevents its recurrence, and mitigates the kidney pain caused by hot swelling and other reasons. The advent of this medicament will be discussed separately in the discussion section.

This is Philagrius' admirable medicament. He said that it breaks the stone into pieces and it prevents its generation and it mitigates kidney pain [caused] from hot swelling and others. Since it is admirable for this purpose, it is very convenient for kidney stones. When the grapes begin to turn black, take a new earthenware cooking-pot, put water in it and boil. Then pour it out and desiccate the pot. Slaughter a four year-old male goat, take his midstream blood, put it in the pot and leave until it coagulates. Then cut it into small pieces in the pot and place a piece of cloth with a loose texture over it. Leave it in open air both under the sun and moon until it dries thoroughly. Avoid rain or anything moistened falling on it. When it is desiccated, pound a piece of it with such an amount of hyacinth as to remove its malodour. Make him drink a spoonful [Lat. 2 aureus] together with sweet wine. You should perform this when pain stops and you will admire its effect.[11,12]

Quotation 6 provides information on surgical procedures to treat kidney stones. The incision of the kidney stone from the posterior part of the lumbar region is not recommended. However, bladder incision is reported to be a significantly safer procedure. More specifically, forced urination by puncturing the bladder between the anus and the testicles is one of the recommendations:

On incision of the stone: he said that the ancients incised

the kidney stone from the posterior part of the lumbar region. There is a risk [Lat. fallacy, and indeed absurdity] in this [procedure]. More people are saved by incision of the bladder, especially those whose flesh is humid and those to whom the swelling does not befall, and those whose wounds suppurate, are easily saved. If the patient has swelling, it becomes difficult [Lat. for those who bear from swelling, the sanation will be difficult]; hot swelling occurs in young people during incision and the wounds do not heal in elders, but in mature aged persons [Lat. children (puer)] swelling does not occur and their wounds heal. Therefore, they are more secured among them [Lat. this disease is easier for them.] A big stone is incised easily but removed difficultly. The opposite occurs in small stones while medium [Lat. rotund] ones are removed easily. If the stone is hard, those suffering from it are stronger than others during the incision, because they are accustomed to enduring pain. But if the stone is soft, it is the opposite. On urination: urination should be used if there is no swelling and vehement pain, except in cases of swelling caused by a stone or blood coagulation, because if both of them are removed from the path, it mitigates the pain. When the situation is very difficult and urine provocation is not possible [Lat. it is not possible to use the urination instrument], a small incision is necessary between the anus and the testicles. And then put a cannula through which the urine flows. Living is better than death.[11,12]

Quotation 7 provides information regarding the treatment of urinary retentions:

In De complemento et perfectione Philagrius said: apply fomentation to the pubes along with bathing, sitz-bathing and oil. Put a sponge full of hot water on the pubes and compress it and rub it strongly unless severe pain occurs. In that case compress it gently and also rub it. Then pour lily [water] into the urethra.[11,12]

Quotation 8 mentions Philagrius' treatment methods on diabetes:

From Philagrius' booklet on diabetes: aim to mitigate patient's thirst first by making him drink rose water or rose juice, at that time make him drink two quṭūl [Lat. 18 uncia] of it. The patient should be in very cold air, and in a secluded and very humid place. Use cold bandages and cold nutriments until his thirst is mitigated. When it is mitigated, you should proceed with laxative clysters and relax the bowels. He said: provoke him to sleep using every effort. He also said: [when the insomnia, indigestion, inebriation become chronic and he drinks cold water and his entire body becomes cold, the liver becomes weak and the abovementioned treatments are not sufficient for the disease (This sentence does not appear in the Latin, but only in the Arabic text)], order him to treat himself with aloe pills, clysters, and compound purgative pills following mitigation of the diarrhoea, then use vomiting and a mustard bandage. Neither this is alone nor the cause of it is found.[11,12]

Quotation 9 clarifies the aetiology of diabetes and recommends several treatment methods:

From Philagrius' book on diabetes: he said that this disease occurs because of liver weakness, coldness of the entire body, indigestion [Lat. nauseative satiety] or insomnia, and by drinking cold water. Excessive thirst occurs with this disease. He said: you should mitigate the thirst following the method we mentioned in the chapter on thirst mitigation. When thirst is mitigated, inject a relaxing and softening clyster often. Then instigate bowel movement with eleven chickpea-shaped aloe pills because they cause diarrhea effectively. Then let him go for three days, then reiterate the treatment; then make him vomit using radish after the meal and hot cupping over the whole body, and apply fomentation and fumigation especially to the extremities of the body, and use rubefacient medicaments. Consequently, let him rest for several days. Make the patient ride [a horse] in moderation, and especially rub his body extremities; bathe him, and let him drink modicum wine, because the patient will regain his health perfectly.[11,12]

Quotation 10 provides treatment recommendations for urinary incontinence:

Philagrius [said]: it is useful for him who has urinary incontinence to sit in styptic waters and use bandages with their dregs [Lat. bandages with styptic substances and their dregs should be used] and styptic nutriments, clysters and to rub the backbone continuously and to exercise and to sit in waters with alum.[11,12]

Quotation 11 concerns involuntarily flow of sperm (probably gonorrhoea). It is reported that this disease will lead to death if it lasts long. Several recommendations are provided to treat this condition:

Philagrius: those whose sperms flow involuntarily become weakened and very lean. If the disease endures, the patients will die. [In Latin text: Philagrius said that: those whose sperms flow involuntarily] their treatment involves sitting in styptic waters and anointing the back and pubes with hemlock [Lat. with henbane] and frequently rubbing their bodies and [providing] styptic nourishments and using exercise and labour and abandoning leisure and sweet fat foods and letting them go hungry are needed, because these are very useful for it.[11,12]

Quotation 12 concerns impotence; several treatment methods are recommended:

Philagrius [said]: impotence is cured by exercising the inferior members, by rubbing them and the groins and thighs; by anointing the penis and pubes with pungent medicaments

like pepper and spurge/euphorbium, by making the patient drink odoriferous wine and eat big pine nuts, and satyrion; the patient should continue to look at the most beautiful persons without any intimacy until his lust becomes stronger [Lat. until he reaches potency].[11,12]

4. DISCUSSION

Philagrius is an important physician, surgeon and writer who influenced subsequent writers with his writings. Although his works are not saved today, several quotations from them have been preserved in the works of many notable writers. For instance, his accounts on urogenital system diseases are included in *Tetrabiblion* of Aetius of Amida (6th century AD):[13] "Cap. 4. De calculosis renibus: Archigenis and Philagrius", "Cap. 8 Diaeta eorum quibus renes e lapide laborant, reliqui vero totius corporis habitus gracilis est: Philagrii", "Cap. 24. De seminis in somnis profluvio: Philagrii."

Philagrius' admirable medicament, mentioned by Rhazes in *Continens*, is a very interesting example. Aetius of Amida[13] mentions Philagrius and provides us with information about this medicament under the title "*de hircino sanguine*". We also encounter this medicament in *Epitome* of Paul of Aegina (625–690 AD),[14] and in Islamic geography, in *al-Taṣrīf* of al-Zahrāwī (936–1013 AD),[15] in *Kitāb al-Qānūn fī al-Ṭibb* of Avicenna (980–1037 AD),[16,17] in *Kitāb al-Mukhtārāt fī al-Ṭibb* of Ibn Hubal al-Baghdādī (1122–1213 AD),[18] in *al-Mūjaz fī al-Ṭibb* of Ibn al-Nafīs (1210–1288 AD)[19] – this medicament was called "yad-Allah/God's hand" by him and its Turkish translation (in the 16th century AD),[20] in *Anmūzaj al-Tibb* of Emir Çelebi (d. 1638 AD),[21] and in *Tadbīr al-Mawlūd* of Shaʿbān Shifāʾī (d. 1705 AD).[22] A very interesting point related to this drug is that no other writer except Rhazes in the Islamic world mentions Philagrius' name. In addition, it is very interesting that this drug is quoted so many times. Hence, we can assume that it was either as effective as suggested by these quotations or it had been proposed because it seemed to be a very interesting drug, considering the difficulty to make it.

The surgical method called lithotomy is discussed in detail in *De Re Medica* of Celsus (1st century BC – 1st century AD).[23] It is also encountered in the quotations in *Continens* of Rhazes that Antyllus (2nd century AD) provides very detailed information about the surgical removal of bladder stones.[11,12] Aretaeus of Cappadocia (1st–2nd century AD)[24] does not provide any details in his work but recommends surgery for persistent bladder stones that do not pass. Aetius of Amida[13] in his *Tetrabiblion* quotes from Philagrius' account on surgery. Information similar to those written by Philagrius is also found in the *Epitome* of Paul of Aegina.[25] According to Adams,[25] Serapion's (8th century AD) book also contains information on bladder incision and describes the insertion of a cannula for emergency urination in addition to lithotomy.

Diabetes, which is considered today an endocrine disorder, was considered a kidney disease at that time, termed urine diarrhoea by Rufus of Ephesus (late 1st – early 2nd centuries AD),[26] Rhazes' quotations from Archigenes on diabetes include similar terminology to that of Rufus.[27] Philagrius seems to have adopted the terminology of Aretaeus of Cappadocia.[24]

As presented in the results section, it is seen that the principles of the humoral model are used both in the description and treatment of these diseases such as purging the bile, reducing the phlegm and bloodletting, etc. The notion "*contraria contrariis curantur*"[28] –the opposite is cured by the opposite–- is encountered in diabetes and urinary incontinence treatment.

CONCLUSIONS

Philagrius' works have not survived today. However, his writings acted as a guide and a valuable source for subsequent physicians. It is evident that Philagrius' writings had also been adopted in the Islamic world because they were translated into Arabic. Therefore, it is important that quotations from his works are found in Rhazes' significant work *Continens*, and some of these quotations relate to nephrology.

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Τι παρέθεσε ο al-Rāzī (Rhazes) από τον Φιλάγριο τον Ηπειρώτη σχετικά με τις ασθένειες των νεφρών στο Kitāb al-Ḥāwī fī al-Ṭibb (Liber Continens);

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ΣΚΟΠΟΣ Το *Kitāb al-Ḥāwī fī al-Ṭibb/Liber Continens* (Περιεκτικό Βιβλίο της Ιατρικής) του Ραζή αποτελεί σημαντικό έργο, καθώς παρουσιάζει πολύτιμα αποσπάσματα από έργα Ελλήνων, Ινδών και Αράβων συγγραφέων. Τα αποσπάσματα αυτά καθιστούν επίσης το έργο του Ραζή σημαντικό για την Ιστορία της Ιατρικής καθώς μας παρέχει πληροφορίες σχετικά με γραπτά που δεν έχουν επιζήσει. Ο Φιλάγριος της Ηπείρου, ο οποίος ασκούσε ιατρική στη Θεσσαλονίκη κατά τον τρίτο ή τέταρτο αιώνα, αποτελεί έναν από τους πιο αξιόλογους και σημαντικούς συγγραφείς που περιλαμβάνονται στο έργο του Ραζή. Σκοπός της παρούσας μελέτης είναι να παρουσιάσει αποσπάσματα του Φιλάγριου από το *Περιεκτικό Βιβλίο της Ιατρικής* που αναφέρονται στις ασθένειες των νεφρών και να τα μεταφέρει και να τα καταγράψει στον πολιτισμό, τη λογοτεχνία και την Ιστορία της Ιατρικής στην αγγλική γλώσσα. **ΥΛΙΚΟ-ΜΕΘΟΔΟΣ** Στην παρούσα μελέτη χρησιμοποιήθηκαν οι εκδόσεις στην αραβική και λατινική γλώσσα του 10ου βιβλίου του *Περιεκτικού Βιβλίου της Ιατρικής*. Εντοπίστηκαν δώδεκα αποσπάσματα του Φιλάγριου που σχετίζονται με ουρογεννητικές ασθένειες, τόσο στα αραβικά όσο και στα λατινικά κείμενα. Εν συνεχεία, πραγματοποιήθηκε σύγκριση μεταξύ των αποσπασμάτων αυτών, μεταφράστηκαν στην αγγλική γλώσσα και εξετάστηκαν υπό το φως της βιβλιογραφίας για την Ιστορία της Ιατρικής. **ΑΠΟΤΕΛΕΣΜΑΤΑ ΚΑΙ ΣΥΜΠΕΡΑΣΜΑΤΑ** Τα αποσπάσματα αυτά αναφέρονται στο νεφρικό άλγος, τις πέτρες στα νεφρά, τον διαβήτη και τις ασθένειες των γεννητικών οργάνων. Τα γραπτά του Φιλάγριου είχαν υιοθετηθεί και στον ισλαμικό κόσμο, μέσω των μεταφράσεών τους στην αραβική γλώσσα. Λαμβάνοντας υπ' όψη ότι τα έργα του Φιλάγριου δεν έχουν επιβιώσει σήμερα, είναι σημαντικό ότι αποσπάσματα από τα έργα του εντοπίζονται στο *Περιεκτικό Βιβλίο της Ιατρικής* του Ραζή καθώς ορισμένα από αυτά αφορούν στη Νεφρολογία.

Λέξεις ευρετηρίου: Η άσκηση της Ιατρικής στη Βυζαντινή Θεσσαλονίκη, Liber Continens, Παθήσεις του ουροποιητικού συστήματος, Rhazes, Φιλάγριος ο Ηπειρώτης

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ΙΣΛΑΜΙΚΗ ΙΑΤΡΙΚΗ

A study on chapters related to nephrology in *Qıṭaʿātu neqāve fī tercemeti kelimāti Boerhāve* by Ṣubḥī-zāde ʿAbd al-ʿAzīz Efendi in the eighteenth century

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ΑΡΧΕΙΑ ΕΛΛΗΝΙΚΗΣ ΙΑΤΡΙΚΗΣ 2020, 37(Συμπλ 2):250–256

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OBJECTIVE: **Ṣubḥī-zāde ʿAbd al-ʿAzīz Efendi (1735–1783), a chief physician, translated the famous Dutch physician Hermann Boerhaave's (1668–1738) *Aphorisms*, known as *Aphorismi de cognoscendis et curandis morbis in usum doctrinae domesticae digesti*, into Turkish as *Qıṭaʿātu neqāve fī tercemeti kelimāti Boerhāve* (1769). Turkish medical historians have found this work important because it is one of the "first complete translations of European medicine" for Ottoman medicine. This study aims to identify and evaluate the topics related to nephrology in *Qıṭaʿātu neqāve fī tercemeti kelimāti Boerhāve*.** METHOD: **In this study, manuscripts of *Qıṭaʿātu neqāve fī tercemeti kelimāti Boerhāve* registered in Süleymaniye Manuscript Library, Esad Efendi Collection, nr. 2462 and Beyazıt State Library, Veliyüddin Efendi Collection, nr. 2484 were examined. First, sections on nephrological diseases were identified, and then Turkish texts written in Arabic letters were transliterated into the contemporary Turkish alphabet. English translations of Boerhaave's *Aphorisms* were used for comparison.** RESULTS: **The subjects related to nephrology in this work are examined under the headings of "kidney pain" and "urolithiasis". The section on "pain of the kidneys" or "nephritis" consists of 14 aphorisms (993–1006), explaining the causes, signs, symptoms, and treatments of nephritis. The section on "urolithiasis" contains 26 aphorisms (1414–1439), elaborating the causes, signs, symptoms, treatments, and interventional methods, e.g., lithotomy, for kidney and bladder stones.** CONCLUSIONS: ***Qıṭaʿātu neqāve fī tercemeti kelimāti Boerhāve* on the approach of European medicine to nephrological diseases was almost immediately transferred to Ottoman medical literature. In this book, Latin and Greek medical terms, such as nephritis, pelvis, ureter, calculus, and a surgical intervention called lithotomy by Europeans, are probably used for the first time in Ottoman medical literature.**

Σπουδή των κεφαλαίων με νεφρολογικό ενδιαφέρον στο *Qıṭaʿātu neqāve fī tercemeti kelimāti Boerhāve* γραμμένο από τον Ṣubḥī-zāde ʿAbd al-ʿAzīz Efendi στον 18ο αιώνα

Περίληψη στο τέλος του άρθρου

Key words

Aphorisms
Boerhaave
Nephrological problems
Qıṭaʿātu neqāve fī tercemeti kelimāti Boerhāve
Ṣubḥī-zāde ʿAbd al-ʿAzīz

1. INTRODUCTION

During the period known as *Understanding and Translating Western Medicine* (1730–1827) in the Ottoman Empire, some physicians who knew a foreign language, such as ʿOmar Shifāʾī (d. 1742), ʿAlī Munshī (d. 1733), and ʿAbbās Vesīm (d. 1760), tried to follow European medicine by translating some Western works into Turkish. One of these physicians was Ṣubḥī-zāde ʿAbd al-ʿAzīz Efendi (1735–1783), who translated *Aphorisms*, a seminal work of the famous Dutch physician Hermann Boerhaave, into Turkish.[1–3]

Hermann Boerhaave (1668–1738), who used the knowledge and concepts of iatrochemists and iatrophysicists, was a pioneer physician in Europe in the eighteenth century. He studied medicine at the University of Leiden. In 1701, he was elected chair of theoretical medicine and soon became an eminent clinician in Europe. His concept of medicine was entirely Hippocratic, the main purpose of which is to cure the patient. Boerhaave, who was Hippocratic in teaching and writing, made valuable observations and treatment rules as short aphorisms.[4] Gerard van Swieten (1700–1772) and Anton de Haen (1704–1776), the leaders of the Old Vienna School, and Hieronymus David Gaubius (1705–1780), Albrecht von Haller (1708–1777), John Prin-

gle (1707–1782), and William Cullen (1710–1790) were his famous pupils.[5] His works *Institutiones Medicae* (1708) and *Aphorisms* (1709) were translated into many languages and published several times.[4,5]

The Ottoman chief physician Ṣubḥī-zāde ʿAbd al-ʿAzīz Efendi, who was the son of Meḥemmed Ṣubḥī Efendi, the *vaqʿa-nuvīs* (historian), graduated from the madrasa and became a *müderris* (professor) at a young age. He was appointed as court physician[6,7] and was one of the early physicians who studied medicine in Vienna.[8] He worked as a chief physician between February and December 1776.[6,7] He was appointed the qādī of Üsküdār (the judge of Scutari) by the end of 1782[7] and was then deported to Istanköy (Cos) in January 1783, where he passed away in September 1783 at the age of 48.[6] He was a poet and musician.He knew Arabic, Persian, Latin, Italian, and French.[7,9,10]

Ṣubḥī-zāde ʿAbd al-ʿAzīz Efendi's work *Qıṭaʿātu neqāve fī tercemeti kelimāti Boerhāve (excellent verses in the translation of Boerhaave's words)* is the Turkish translation of Boerhaave's *Aphorismi de Cognoscendis et Curandis Morbis in Usum Doctrinae Domesticae Digesti*.[2,3,6,7] In the preface of his work, Ṣubḥī-zāde states that a copy of the book, written in 1135 AH/1722–1723 AD by Boerhaave (likely printing date of his copy), who was famous among European physicians, was brought to Istanbul in 1180 AH/1766–1767 AD. During the reign of Sultan Muṣṭafā III, the physicians who knew Latin suggested that the Turkish translation of this book would benefit the general public. Thereupon, Ṣubḥī-zāde, one of the court physicians, was appointed by the Sultan to translate the book into Turkish. He used the interpretations of Gerard van Swieten, Boerhaave's student.[3,11,12] Herbert, the Austrian embassy's translator, assisted Ṣubḥī-zāde with the translation.[10,13] The work was completed on Muḥarram 10, 1183 AH/May 16, 1769 AD.[3,11,12]

Emine Atabek[10] reports that Ṣubḥī-zāde translated "aphorism" into Turkish as "kelime," meaning "word" or "sentence," and named the work "kelimāt," meaning "words" or "sentences", because it consists of 1495 aphorisms or words or sentences. Şehsuvaroğlu et al[9] explain that the original work contains 1495 "faṣl", meaning "chapter", or "qıṭʿa", meaning "verse", and the word "qıṭaʿāt" in the title of the work represents this as a plural. The work was found in the first half of the twentieth century and introduced to Europe by Ord. Prof. Dr. Akil Muhtar Özden (1877–1949), who later on received a medal from the Dutch State.[9,10]

This study aims to identify and evaluate the topics related to nephrology in *Qıṭaʿātu neqāve fī tercemeti kelimāti Boerhāve* and its importance in relation to the history of Turkish medicine.

2. MATERIAL AND METHOD

Manuscripts of *Qıṭaʿātu neqāve fī tercemeti kelimāti Boerhāve* registered in Istanbul's Süleymaniye Manuscripts Library, Esad Efendi Collection, nr. 2462[11] and Beyazıt State Library, Veliyüddin Efendi Collection, nr. 2484[12] were examined.

Hermanno Boerhaave. *Aphorismi de Cognoscendis et Curandis Morbis in Usum Doctrinae Domesticae Digesti* (1737),[14] *Boerhaave's Aphorisms: Concerning the Knowledge and Cure of Diseases With Useful Observations and Explanations* by J. Delacoste M.D. (London, 1715),[15] and *The Commentaries Upon the Aphorisms of Dr Herman Boerhaave Concerning the Knowledge and Cure of Several Diseases Affecting Human Bodies* by Gerard Van Swieten M.D. (Vol. X, London, 1765 and Vol. XVI, London, 1773)[16,17] were used for comparison.

First, the sections on nephrological diseases were identified, and then the Turkish texts written in Arabic letters were transliterated into the contemporary Turkish alphabet and compared with the English translations of Boerhaave's *Aphorisms*.

3. RESULTS

The subjects related to nephrology in *Qıṭaʿātu neqāve fī tercemeti kelimāti Boerhāve* are examined under the headings of "Maqāleʾ rabiʿa - Bāb ḥādī ʿaşar vecaʿ kilyeteyn beyānındadur/The fourth section - The eleventh chapter declares kidney pain" and "Maqāleʾ sādise - Bāb thāmin ḥaṣāt beyānındadur/The sixth section - The eighth chapter declares the stone".

3.1. Nephritis

The section on "kidneys pain" or "nephritis" or "inflammation of the kidneys" consists of 14 aphorisms (993–1006), explaining the causes, signs, symptoms, and treatments of nephritis.

Ṣubḥī-zāde ʿAbd al-ʿAzīz Efendi says that when there is an inflammation in the kidneys, called nephritis in Europe and *vecāʿ külā* in our [Turkish] terminology, the following symptoms occur: a burning, pungent, acute, and inflammatory pain of the places where the kidneys are, an acute continual fever, scarcity and frequency of urine, numbness, or pain of the leg on the affected side, painful groin and testicle on the same side, iliac pain, nausea, and continual hiccups.[11,12]

There are four causes that contribute to nephritis. The

first includes inflammatory causes, such as blows and bumps, wounds, abscesses, swellings of the kidneys and the adjacent parts, having to lie on the affected side, being forced to lift an object, and the occlusion of the arteries of the kidneys due to stones. The second cause constitutes everything that prevents passing the urine attracted by the kidneys to *viʿāʾ bevliyye*, called pelvis by the Europeans, and then into the bladder in two ways, called *berābīkh* in our terminology and ureter in Europe. The third cause concerns all the reasons for sending coarse pieces of blood to the urinary tracts of the kidney (e.g., during intense running and riding). The final cause points to the continuous contraction of the urinary tract.[11,12]

When a great phlegmon occurs in the urinary tracts that encircle the kidneys, the urine is often trapped, or sometimes a very little, transparent and thin urine can pass, which is one of the worst signs. Furthermore, when the aforementioned phlegmon occurs, it often irritates the adjacent nerves, causing a contraction in the stomach, mesentery, intestines, and ureters, followed by hiccups, nausea, vomiting, diarrhoea, ileus, hard urination, numbness in the legs, and low back pain.[11,12]

Sometimes nephritis is resolved by the help of nature or avoided by maturing and discharging, which nature accomplishes in two ways: first, by a great quantity of red and thick urine before the 7th or 14th day and, second, by nosebleed at the outset of the disease.[11,12]

Non-natural/human-made treatment is limited in four ways: (a) the treatment of inflammation; (b) the preparation and frequent use of emollient decoctions for inflammation; (c) the preparation of clysters, fomentations, and baths of the same kind; and (d) the continuation of a moist, soft diet, and rest while avoiding the heat of the bed, especially when lying on the back. If the pain and contractions exacerbate, opiates become appropriate, and if vomiting occurs, warm water mixed with honey is suitable. This method is also beneficial for nephritis resulting from the obstruction of stones in the kidneys and the urinary tract.[11,12]

If the causes of the nephritis are severe and the inflammation is neither resolved nor cured, and if it exceeds the 7th day, it is feared that it may turn into an abscess. The occurrence of an abscess can be inferred through the calming of the pain, an increase in throbbing, repeated stinging, and heaviness and numbness in the affected place. The signs and symptoms of an abscess include severe throbbing and inflammation and the prolongation of the affected site, to which pus-like, stinky, salty, and putrefied urine can be added. When an abscess is diagnosed, maturing and softening medicines should be immediately administered, and once purulent urine emerges, diuretics (e.g., whey of new milk or mineral water) and balsamic should be prescribed.[11,12]

If suppuration continues, the cavities of the kidneys will be eaten up and become dreggy in the form of a useless bag; this characteristic fragmentation will also spread to all organs. If the inflammation causes scirrhus, then flaccidity and numbness or palsy or lameness of the affected leg will follow, which cannot be cured. However, if a small portion of the inflamed matter is coagulated and trapped in some of the smallest secretory ducts of the kidney, it forms a basis on which the sandy portions of the leaking urine gradually adhere to one another, forming a solid body (i.e., stone), which will be explained in the stone section, if Allah wills. Furthermore, this inflammation sometimes causes gangrene; its symptoms include the sudden abatement of pain without any cause, cold sweating, a weak and intermittent pulse, hiccups, urinary retention or black urine if not retained, with streaks in it resembling hair, stinking with blackish pieces of flesh, and a sudden and entire loss of strength.[11,12]

Nephritis has diverse types and causes, and apart from those that arise from the stone, the rest require almost the same treatment.[11,12] Nonetheless, no disagreement exists over the treatment methods, and often one treatment is appropriate for the others. The occurrence of nephritis with fever is usually caused by the urinary excretion of the fever substance when cooked, which is immobilized in the kidneys due to its thickness and density, resulting in phlegmon form. Urinary retention is also caused by diseases of the kidneys and ureters.[11,12]

3.2. Urolithiasis

The section on "urolithiasis" or "the stone" contains 26 aphorisms (1414–1439), explaining on causes, signs, symptoms, treatments, and some interventional methods (e.g., lithotomy) concerning bladder stones.

Ṣubḥī-zāde ʿAbd al-ʿAzīz Efendi says that an insolvable object in the human body leads to the formation of a layer that surrounds and adjoins the said object, which will gradually gather another layer to turn into a stone. In the kidneys, especially at the end of the renal arteries, if the supply of blood dries up, a petrified substance similar to sand appears, known as *calculus* in European terminology and *ḥaṣāt* in our terminology. The original petrified material is always red, with layers that are red, white, and black. These colours are indicative of the degree of insolvability. This situation is familiar for those who know the art of chemistry (i.e., iatrochemists).[12]

The formation of the stone chokes the kidneys, obstructs their ways, and consumes their flesh. As a result, dregs come out of the bladder in the form of flesh and pieces of skin. The whole kidney gradually begins to decay. The urine becomes bloody, purulent, and fetid. Occasionally, inflammation also occurs, especially in the adjacent decayed parts. The symptoms of a kidney stone include the feeling of obtuse pain in the aforementioned location, urination of blood when the patient takes a walk on the stone ground or becomes tired by a carriage and other means, and sometimes the discharge of small objects such as sand, stones, pieces of flesh, and yarn-like materials.[12]

When the stone departs from its place and reaches the *viāʾ bevliyye*, known as *pelvis* by the Europeans, it prevents the flow of the urine and causes an inflammatory pain from there to the bladder through two ways, called *berābīkh* in our terminology and ureter in Europe. When the stone crosses the two ways and reaches the bladder, it either goes out or stays in the bladder and begins to grow. When the stone reaches the bladder, it causes inflammation accompanied by itching, ulcerations, purulent urination, stranguries, obstruction of the urethra, no urination except in supine position, and hectic fever and consumption. Sometimes the stone enters the urethra and stays there. The symptoms of bladder stones include pain during, before, and after urination, urination with driblets, white urine with a mucous, thick, heavy sediment in a great quantity, itching at the glans penis, and tenesmus while passing water. The bladder stone is also felt by introducing a finger into the anus or by probing with catheter.[12]

Physicians can treat kidney stones by (a) lessening the petrified matter, (b) expelling it, or (c) reducing it to a state that will cause minimal damage to the kidneys. Kidney stones can be lessened by moist, soft, and moderately salty food and beverages and by medicines helping the vital powers. Kidney stones can be expelled by relaxing the vessels with baths, clysters, and oleaginous liniments and making the passages slippery with moistening emollients and soft, gentle oily medicines; diuretics can be used to drive the stones on by a gentle motion, and opiates can be used to mitigate pain. Kidney stones can be reduced to a safe state by preventing inflammation by bloodletting and applying appropriate remedies, such as anodyne emulsions and oleaginous, saponaceous, and glutinous medicines to deal with rough stones. Some caution is required as that claimed to be a specific dissolver for stones is not true and has not been tested yet. Hence, the author [Hermann Boerhaave] warns against the arbitrary use of objects introduced as the true medication for stones. As noted earlier, given the limited time available to understand the origin of the stone and seek a solution through experience, especially to understand what is required with respect to the location of the stone, it is not appropriate to arbitrarily prescribe an object to the sufferer.[12]

When the stone has reached the pelvis, then clysters, fomentations, and phlebotomy can be effective. When the stone falls through the ureters into the bladder, then it is essential to immediately expel it by oleaginous baths, clysters, and the injection of oil lest the stone staying behind grow larger and cause greater detriment.[12]

When the stone leaves the kidneys and enters the bladder in two ways, known as *berābīkh*, relief in kidney inflammation symptoms and ureteral pain is observed. As a result, before it grows and becomes noxious, it is necessary to immediately expel it by oleaginous baths, clysters, and injections while externally applying appropriate oils.[12]

If the stone enters the urethra and obstructs the pathway (this is only known after being investigated by a gold probe), it is necessary to remove it by oily injections, fomentations, baths, suction, gentle pressure, or opening the penis or the perineum using a special tool. If the stone is too large to be extracted by the aforementioned means, the operation known by Europeans as lithotomy becomes essential. Lithotomy is most effective when it is attempted with the most appropriate route [*Apparatus magnus*], although the safety of the patient may be compromised. Sometimes the stone is easily extracted by dilating the urethra without cutting it. However, when the stone is deep in the neck of the bladder and prevents the passage of urine, it is convenient to push back the stone into the bladder by inserting a catheter into the urethra.[12]

4. DISCUSSION

In the seventeenth century, Sāliḥ b. Naṣr-allah (d. 1669) introduced a new medical system (i.e., iatrochemistry), of which Paracelsus (1493–1541) made alchemy the basis, to the physicians of the Ottoman Empire by his work called *Tibb Cedīd al-Kimyāvī*. This new system influenced Ottoman physicians such as ʿOmar Shifāʾī (d. 1742) and ʿAlī Munshī of Bursa (d. 1733) in the eighteenth century.[18] ʿAlī Munshī of Bursa translated Hadrian Mynsichts's, or Adrian Mintsicht's, (1603–1638) *Thesaurus et Armamentarium Medico-Chymicum* (*Qrabādīn Tercemesi* or *Qrabādīn Mirāb*), Michael Ettmüller's (1644–1683) *Epitometius Medicina Institutiones Chymian Rationalem* (*Qurāḍat al-Kimyā*), and Rhazes' (865–925) *Kitāb al-Tajārib* (*The Book of Experiences*) into Turkish.[19]

During the reign of Sultan Muṣṭafā III (r. 1757–1774), Muṣṭafā Efendi of Tokat translated Ibn Sīnā's *al-Qānūn fī al-*

Ṭibb into Turkish from Arabic for the first time (1761–1766). Although *Qānūn* was extensively used by physicians, it was not translated until the eighteenth century.[18] At the same time, Ṣubḥī-zāde translated *Aphorisms* of the Dutch physician Hermann Boerhaave into Turkish from Latin (1769).[19] These translations illustrate that this era was a period of transition when both classical and contemporary medical works were translated into Turkish.

Turkish medical historians have ranked *Qıṭaʿātu neqāve fi tercemeti kelimāti Boerhāve* as a seminal work because it is the first complete translation of a European medical book for the Ottoman medicine.[6,7,13] Ṣubḥī-zāde ʿAbd al-ʿAzīz Efendi also used many Latin terms in this work. It is also important because it contains William Harvey's (1578–1657) explicit descriptions of blood circulation in 1628, which would be introduced to the Ottoman medical world more than a century later.[18]

The chapters on nephrology examined in this study show that Ṣubḥī-zāde kept some Latin terms intact in his Turkish translation (tab. 1), for example:

Faṣl 993. When an inflammation occurs in the kidneys, the Europeans call it nephritis, which is called vecāʿ külā in our terminology, its symptoms are…[12]

Faṣl 1417. When the stone departs from its place and reaches the viāʾ bevliyye, which the Europeans call the pelvis...[12]

Faṣl 1435. If the stone is too large to be extracted by this method, the operation called lithotomy by Europeans becomes necessary.[12]

He also used many Turkish/Arabic medical terms for Latin in his translation (tab. 2). Ṣubḥī-zāde made a few changes in his translation of the aphorisms, for instance:

Faṣl 1434. If the stone enters the urethra and obstructs the

Table 1. Some Latin terms preserved in the Turkish translation of Boerhaave's *Aphorisms*.[12]

Turkish terms in *Qıṭaʿāt*		Latin terms in *Qıṭaʿāt*		Latin terms in *Aphorismi*	English terms in *Aphorisms*
وجع کلی	Vecaʿ külā	نفریطس	Nefrītis	Nephritis	Nephritis
وعاء بولیّه	Viʿāʾ bevliyye	پلویس	Pelvīs	Pelvis	Pelvis
برابیخ	Berābīkh	اوورتر	Uvreter	Ureteres	Ureters
حصاة	Ḥaṣāt	قالقولوس	Qālqūlūs	Calculus	Stone
		غنغرنیا	Ghanghranyā	Gangræna	Gangrene
		لیطوطومیا	Līṭōṭōmiyā	Lithotomia	Lithotomy
		ایلاوس	Īlāvus	Ileus	Iliac passion
		سقیروس	Seqīrūs	Schirrus	Schirrus

Table 2. Some Turkish medical terms and their Latin and English equivalents in Boerhaave's *Aphorisms*.[12]

Turkish terms in *Qıṭaʿāt*		Latin terms in *Aphorismi*	English terms in *Aphorisms*
فلغمونی	Felghamūnī	Inflammation	Inflammation
حماء حادة دائمی	Ḥummāʾ ḥāddeʾ dāʾimī	Febre acuta continua	Acute continual fever
بول	Bevl	Urina	Urine
کلی	Külā	Rene	Kidneys
معده	Miʿde	Stomachum	Stomach
ماساریقا	Māsārīqā	Mesenterium	Mesentery
امعا	Emʿā	Intestina	Intestines
فواق	Fuvāq	Unde ructus	Belchings
غثیان	Ghaseyān	Nausea	Nauseousness/sickness
قیء	Qayʾ	Vomitus	Vomiting
خدر ساقین	Khader sāqeyn	Crurum stupor	Numbness of the thighs and legs
تشنج	Teshennüc	Convulsionis	Convulsions
حقنه لر	Ḥuqneler	Clysmata	Clysters
کمادات	Kimādāt	Fomenta	Fomentations

pathway – this is only known after being investigated with a [gold] probe…*[12]

*Faṣl 1438. [In women,]** the stone is extracted by dilating the urethra without cutting it.*[12]

He also added some comments where appropriate. For instance, in *Faṣl 1428*, Ṣubḥī-zāde translated Boerhaave's aphorism into Turkish under "tenbīh" or "warning" and then tried to explain it to the reader:

"1434. For as to any true dissolver or specific for the stone, none as yet deserves any credit."[15]

"Sect. MCCCCXXVIII. For no certain dependance can be placed on the specific Lithontriptics hitherto discovered."[17]

"Faṣl 1428. It should be known that what is claimed as being a specific dissolver for the stone is not true and has not yet been tested. Hence, the author warns against the arbitrary use of objects introduced as the true medication for the stone. As noted earlier, given the limited time available to understand the origin of the stone and seek a solution through experience, especially to understand what is required with respect to the location of the stone, it is not appropriate to arbitrarily prescribe an object to the sufferer."[12]

Atabek[10] states that it is not possible to compare the numbers of Turkish "kelimāt" with the numbers of "aphorisms" in Latin since the order of chapters is not followed in the Turkish translation. However, the aphorisms on kidney pain and stones and their numbers are consistent with Boerhaave's *Aphorisms* in the same way that are the numbers in his book and Latin[20] and English editions of Gerard van Swieten's commentaries.[16,17]

We may conclude that *Qıṭaʿātu neqāve fī tercemeti kelimāti Boerhāve* on the approach of European medicine to nephrological diseases in the eighteenth century was almost immediately transferred to the Ottoman medical literature. In this book, Latin and Greek medical terms such as nephritis, pelvis, ureter, calculus, and a surgical intervention called lithotomy by the Europeans are probably used for the first time in the Ottoman medical literature.

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ΠΕΡΙΛΗΨΗ

Σπουδή των κεφαλαίων με νεφρολογικό ενδιαφέρον στο *Qıṭaʿātu neqāve fī tercemeti kelimāti Boerhāve* γραμμένο από τον Ṣubḥī-zāde ʿAbd al-ʿAzīz Efendi στον 18ο αιώνα

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ΣΚΟΠΟΣ: Ο Ṣubḥī-zāde ʿAbd al-ʿAzīz Efendi (1735–1783), επικεφαλής ιατρός, μετέφρασε τους *Αφορισμούς* του διάσημου Ολλανδού ιατρού Hermann Boerhaave (1668–1738), γνωστοί ως *Aphorismi de cognoscendis et curandis morbis in usum doctrinae domesticae digesti*, στα Τουρκικά ως *Qıṭaʿātu neqāve fī tercemeti kelimāti Boerhāve* (1769). Οι Τούρκοι ιστορικοί της Ιατρικής βρήκαν αυτό το έργο σημαντικό επειδή είναι μια από τις «πρώτες ολοκληρωμένες μεταφράσεις της ευρωπαϊκής Ιατρικής» για την οθωμανική Ιατρική. Σκοπός της μελέτης αυτής είναι να εντοπίσει και να αξιολογήσει τα θέματα που σχετίζονται με τη Νεφρολογία στο *Qıṭaʿātu neqāve fī tercemeti kelimāti Boerhāve*. Υλικό-Μέθοδος: Σε αυτή τη μελέτη, εξετάστηκαν τα χειρόγραφα του *Qıṭaʿātu neqāve fī tercemeti kelimāti Boerhāve* που βρίσκονται στη Βιβλιοθήκη Χειρογράφων Süleymaniye, Συλλογή Esad Efendi, αρ. 2462 και στην Κρατική Βιβλιοθήκη Beyazıt, Συλλογή Veliyüddin Efendi, αρ. 2484. Αρχικά, εντοπίστηκαν τα τμήματα που αφορούν στις νεφρολογικές παθήσεις και στη συνέχεια τουρκικά κείμενα γραμμένα με αραβικά γράμματα μεταγράφηκαν στο σύγχρονο τουρκικό αλφάβητο. Χρησιμοποιήθηκαν αγγλικές μεταφράσεις των *Αφορισμών* του Boerhaave προς σύγκριση. Αποτελέσματα: Τα θέματα που σχετίζονται με τη Νεφρολογία εξετάζονται υπό τις επικεφαλίδες «νεφρικό άλγος» και «ουρολιθίαση». Το τμή-

* "Included by Ṣubḥī-zāde.
** Excluded by Ṣubḥī-zāde.

μα σχετικά με το «νεφρικό άλγος» ή τη «νεφρίτιδα» αποτελείται από 14 αφορισμούς (993–1006), που εξηγούν τα αίτια, τις ενδείξεις, τα συμπτώματα και τις θεραπείες της νεφρίτιδας. Το τμήμα σχετικά με την «ουρολιθίαση» περιέχει 26 αφορισμούς (1414–1439), που μελετούν τα αίτια, τις ενδείξεις, τα συμπτώματα, τις θεραπείες και τις επεμβατικές μεθόδους, π.χ. τη λιθοτομία, για τις πέτρες στα νεφρά και στην ουροδόχο κύστη. Συμπεράσματα: *To Qıṭaʿātu neqāve fī tercemeti kelimāti Boerhāve* αναφορικά με την προσέγγιση της ευρωπαϊκής Ιατρικής στις νεφρολογικές παθήσεις μεταφέρθηκε σχεδόν αμέσως στην οθωμανική ιατρική βιβλιογραφία. Σε αυτό το βιβλίο, λατινικοί και ελληνικοί ιατρικοί όροι όπως η νεφρίτιδα, η πύελος, οι λίθοι και ο ουρητήρας, καθώς και μια χειρουργική επέμβαση που ονομάζεται από τους Ευρωπαίους λιθοτομία, χρησιμοποιούνται πιθανώς για πρώτη φορά στην οθωμανική ιατρική βιβλιογραφία.

Λέξεις ευρετηρίου: Αφορισμοί, Boerhaave, Νεφρολογικά προβλήματα, Qıṭaʿātu neqāve fī tercemeti kelimāti Boerhāve, Ṣubḥī-zāde ʿAbd al-ʿAzīz

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ΙΣΛΑΜΙΚΗ ΙΑΤΡΙΚΗ

Shaʿbān Shifāʾī of Ayash and his observations and suggestions for nephrological problems in children

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ΑΡΧΕΙΑ ΕΛΛΗΝΙΚΗΣ ΙΑΤΡΙΚΗΣ 2020, 37(Συμπλ 2):257–262

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Ο Shaʿbān Shifāʾī του Ayash και οι παρατηρήσεις και προτάσεις του για τα νεφρολογικά προβλήματα σε παιδιά

Περίληψη στο τέλος του άρθρου

OBJECTIVE: ***Tadbīr al-Mawlūd* written in 1701 by Shaʿbān Shifāʾī of Ayash is considered as the first book written extensively on child health and diseases in the classical period of Ottoman medicine. The present study aimed to determine and evaluate the topics related to nephrological problems in children written in this book.** METHOD: **For this study, a copy of the manuscript of *Tadbīr al-Mawlūd* from Shaʿbān Shifāʾī of Ayash's own handwriting was retrieved from İstanbul Süleymaniye Manuscript Library, Mihrişah Sultan Collection, nr. 344. Firstly, the nephrological sections of the manuscript were identified and Arabic texts were transliterated into contemporary Turkish alphabets.** RESULTS: **The subjects related to nephrology in the *Tadbīr al-Mawlūd* were discussed under the main heading of "Diseases of kidneys and bladder" with three subheadings: "Urinary tract stones in children", "Urinary retention–voiding difficulties in children", and "Bedwetting." The causes and treatment options of kidney and bladder stones, urinary retention and voiding problems, and lastly the causes and treatment of enuresis in children have been discussed. It was noticed that Shaʿbān Shifāʾī of Ayash benefited from the works of Ibn Sīnā and Ibn al-Nafīs, who were prominent physicians during the Middle Ages. It can be deducted that the principles of humoral paradigm, which is an accepted medical understanding of that period, was valid in explaining the aetiology of nephrological diseases and their treatment.** CONCLUSIONS: **These documents are important in terms of being the first written work about the approach to paediatric nephrological diseases and urological problems in children, written in the Ottoman period.**

Key words

Bedwetting Ottoman medicine
Children's nephrological problems in Ottoman texts
Shaʿbān Shifāʾī of Ayash
Tadbīr al-Mawlūd

1. INTRODUCTION

Shaʿbān Shifāʾī b. Ahmet was from Ayash; Shifāʾī was his nickname. He arrived to Istanbul at a young age and studied medicine at the Süleymaniye Madrasa. His teacher was Hayatizade Büyük Muṣṭafā Feyḍi Efendi. In 1671, he served as the chief physician of the palace during the reign of Sultan Mehemmed IV and also worked in Süleymaniye Hospital. He was a versatile man, who was interested in history, poetry, and medicine. He died in Ayash in 1705.[1–3]

Shaʿbān Shifāʾī wrote some valuable works in medicine and history, e.g., *Tadbīr al-Mawlūd* and *Shifa'iyye fi al-Tibb* or *Risala-i Shifa'iyye*. The latter consisted of three parts: minerals, animal originated poisons, and their properties.[1–3]

Tadbīr al-Mawlūd is considered as the first book written extensively on child health and diseases in the classical period of Ottoman medicine.[1–3] The present study aimed to determine and evaluate the topics related to nephrological problems in children written in aforementioned book.

2. MATERIAL AND METHODS

For this study, the copy of manuscript of *Tadbīr al-Mawlūd* from Shaʿbān Shifāʾī of Ayash's handwriting (autograph) was retrieved in İstanbul Süleymaniye Manuscript Library, Mihrişah Sultan Collection, nr. 344,[4] and reviewed. Firstly, the book sections related to nephrology were determined and subsequently the Turkish text written in Arabic letters was transliterated into the contemporary Turkish alphabets.

3. RESULTS

We observed that the subjects related to nephrology

were discussed under the main heading "Diseases of kidneys and bladder" and its three subheadings: "Urinary tract stones in children", "Urinary retention-voiding difficulties in children" and "Bedwetting". These sections discuss causes and treatment options for kidney and bladder stones, urinary retention and voiding difficulties, and lastly the causes and treatment of enuresis in children.

3.1. Diseases of the kidneys and bladder

In this section, it is noted that: "Various diseases, each of which is written and described in medical books, even affect the kidneys and bladder". Conditions in which calculi are formed and voiding dysfunction in children are explained in this section.[4]

3.1.1. Urinary tract stones in children. Shaʿbān Shifāʾī of Ayash states in the book that small stones appear in the human body in five distinct places according to the former physicians: kidneys, bladder, intestines, liver, and lungs, but they also tend to develop in the stomach. However, in children, urinary tract stones occur primarily in the bladder, whereas in young adults, middle-aged, and elderly people, they occur in the kidneys.[4]

Furthermore, he states that there are two principal reasons that cause stone formation. First is material cause, i.e., formation of sticky, thick phlegm, pus (from ulcerated wound), or thickened blood. The second cause (efficient cause) is heat. Heat diminishes moisture, and density of that substance increases. If this condition lasts for longer, stones appear as seen in children working in the hammam.[4]

The characteristics of stones are different in young and old individuals because of the lower or excessive amounts of accumulating substances. The location of stones can be identified by the respective symptoms.[4]

He notes that this condition is commonly observed in children who consume excessive food and move a lot when their stomachs are full. This causes the formation of dense humors due to insufficient digestion; however, this can also be attributed to hereditary factors.[3]

In addition, he notes that wherever stones occur, treatment is difficult (particularly in case of bladder stones). It may be necessary to remove some of the bladder stones by shattering them with a sharp-headed tool. However, the principal treatment method in treating stones is to dissolve the substances causing stone formation by some drugs and subsequently remove them from the body by vomiting or diarrhoea. Interestingly, he recommends use of a fixer (such as plum or *prunus*) to prolong the effect of calculi-dissolving drug used together with diuretics, and stresses that each drug functions on its own.[4]

He emphasizes that the drugs used in bladder stones should be stronger because the bladder is further away from the kidney. Regarding that topic, he cites the treatment knowledge from *al-Mūjaz fī al-Ṭibb* text written by Ibn al-Nafīs (1210–1288 AD) selected from the *al-Qānūn fī al-Ṭibb* by Ibn Sīnā (980-1037 AD). More specifically, he mentions the drugs against urinary tract stones recommended by Ibn Sīnā as well as Ibn al-Nafīs (tab. 1).[4] He explains two drugs in detail that could be very useful. The first drug was named as "the hand of God" probably because of its effectiveness. A 4-year old goat should be sacrificed at the time a speckle of darker colour starts appearing on the skin of ripening grapes. After pouring the first blood, the middle blood is taken to a container and it is stored after fully drying in sun. This when given with radish or celery juices was suggested to be very effective in removing kidney and bladder stones.[4]

The second drug he mentions is the meat, either raw or cooked, of a "special kind of sparrow," which should be consumed after salting. He explains the features of this bird (*Motacilla flava*) in detail. Its name is "Ṭarāghūlīdayṭūs" in Greek (Aṭrāghulīayṭūs in *al-Mūjaz*), "Ṣafrāghiyūn" in Latin (Ṣafrāghūn in *al-Mūjaz*), and "Kuyruk sallayan" in Turkish.

Table 1. Drugs that break calculi (Lithontriptics) as quoted from *al-Mūjaz fī al-Ṭibb* by Ibn al-Nafīs.[4]

Turkish	English
Herbal medicines	
Altun otı	The fern hart's-tongue
Baldırı qara	The maiden-hair fern
Ḥarshaf	The artichoke
Ḥasak	The plant caltrop
Qusṭ	Arabian costus
Belesānuñ chubughı	The wood of the balsam tree
Belesānuñ ḥabbı	The berries of the balsam tree
Belesānuñ yaghı	Balm
Yanmısh laḥana yapraghı	Burnt leaf of cabbage
Animal medicines	
ʿAqrebüñ yanmısh küli	Ash of the scorpion
ʿAqrebüñ yaghı	Oil of the scorpion
Serchenüñ küli	Ash of sparrow
Ṭavshan küli	Ash of the hare
Yumurṭa qabughınuñ küli	Ash of eggshell

He states that its colour is slightly yellow, and it is very commonly found around Ankara.[4]

3.1.2. Urinary retention: voiding difficulties in children. He states that there may be several reasons that facilitate urinary retention and/or voiding difficulties. These reasons include renal and bladder insufficiencies, swelling of the bladder neck and urethra, or diseases of other organs. Sometimes there is blood clotting, pus, or accumulation of flatus (from the body) that do not dissolve easily on urine flow paths. When the temperament of bladder is cold, has a thick/strong body and distorted shape (described as bent), urinary retention may occur if the abdominal muscles are not used. Sometimes, it can also be caused by alternating hot and cold conditions or trauma. However, all these causes can be distinguished from each other by their symptoms. Occasionally, flesh formation in the urinary tract prevents normal urine flow. Provided that this obstruction is identified by the respective symptoms, it may be controlled through the insertion of a catheter into the penis. He describes the catheter in detail and highlights that this should be performed by an experienced person.[4]

Furthermore, Shaʿbān Shifāʾī emphasizes that the underlying causes of retention or difficulty in urination should first be thoroughly investigated. If the reason for this obstruction is pus/thick humor, it can be treated by medicines (strong diuretics) that remove the obstruction and eliminating the causative substances (tab. 2).[4] For breastfed children, he recommends that their mother should consume cooked radish or black chickpeas, to eliminate this problem.[4]

He mentions that laxatives and diuretics are important in the treatment process, and drugs used in the treatment of kidney and bladder stones are also effective in this condition as stated by Ibn Sīnā. Because urinary retention may be caused by blocking of the urinary tract by substances such as blood and pus, the drugs (particularly the radish and its leaves) will eliminate these substances.[4]

Table 2. Strong diuretics and medicines for urinary retention-voiding difficulties.[4]

Turkish	English
Herbal medicines	
Dūqū	Seed of wild carrot
Fuṭrasāliyūn	Rock-parsley
Qusṭ	Arabian costus
Sīsāliyūs	Assafoetida
Turpuñ cirmi ve yapraghı	Body and leaf of radish
Egir	The sweet flag; or orris
Animal medicines	
Gelincik methānesi	Bladder of the weasel
Ṭatlı ṣu yengecinüñ küli	Ash of the cray-fish

In case of severe bladder outlet obstruction, he recommends the insertion of a catheter through the penis as described by previous physicians.[3] If the catheter is not helpful and the problem is located above the urethra, he recommends other herbal treatments and sitting baths; he warns that urinary retention in children is very painful and it should be resolved within an hour.[4]

He mentions that some ointments and oils can be applied to the groin and sitting bath can be prepared from the certain plants to relieve the pain. These include chamomile oil, goose oil, or substances that have the ability to relax the tissues, and plants with pain-relieving properties such as tall grass.[3]

Although he mentions putting a layer of saffron on the penis or sending a louse (*Pediculus corporis*/*Pediculus capitis*) through the urethra (to facilitate urination), as explained in *al-Mūjaz*, he emphasizes his own prescription, claimed to show effect within an hour. This prescription includes radish extract, ten dirhams of butter, and five dirhams of plant sugar.[4]

3.1.3. Bedwetting. Shaʿbān Shifāʾī of Ayash says that the main reason for bedwetting is the relaxation of the muscles surrounding the outlet of the bladder. Because of the high humidity in their temperament, they have extremely deep sleep pattern; hence, their bladder is weak. When the urine flows at night, the bladder is unable to control or prevent the driving force of urine, and the child may urinate in bed without waking up. Some of these children see a place to pee while sleeping, and pee as if they are awake. Therefore, Shaʿbān Shifāʾī recommends that these children should avoid eating and drinking excessively prior to sleep and they should urinate before bedtime. He suggests that children peeing while dreaming is an issue that can be rebuked, or children may control themselves during sleep thinking that they have polluted the respected places like mosques and cemeteries. Hence, he mentions various herbal (Frankincense, the root of alpinia galangal, the inner bark of the nut-gall oak, flowers of the wild pomegranate, etc.) and animal products (pigeon droppings, rabbit kidney) in detail that may control enuresis. He says that urine output regulating methods, and enema are profoundly beneficial.[4]

He highlights that senior physicians recommend no treatment because this condition eventually improves during puberty.[4]

4. DISCUSSION

Tadbīr al-Mawlūd (written in 1701) is an important book because it presents and registers early written work and approaches regarding paediatric diseases and nephrological problems in the classical period of Ottoman Medicine.[1–3]

Shaʿbān Shifāʾī of Ayash identified and underlined three essential issues related to the urinary system problems in children and he provided detailed information, particularly on the means with which they can be treated. Although he refers to the works of Ibn Sīnā and Ibn al-Nafīs, he has also provided recommendations that are based on his own observations, particularly for children with voiding difficulties.

When investigating urinary tract stones in this book, it becomes evident that he has not provided many details on the causes and particularly the symptoms of urolithiasis in children. Instead, he roughly emphasizes the presence and development of different types of stones. Although the incidence of bladder stones in children has been gradually decreasing, and it is now primarily related to low socioeconomic levels,[5] his observation of distinguishing the locations of these stones according to the respective age groups was valid at that time.

His explanation of the stone formation is consistent with the Aristotle's Theory of Causality because he mentions that "four causes together bring a complete view of the object under consideration": its formal cause, material cause, efficient cause, and the final cause.[6] In this case, Shaʿbān Shifāʾī of Ayash states that material cause was sticky thick phlegm or pus, or perhaps thickened blood, whereas efficient cause was heat.

His recommendation to breastfeeding mothers to prevent voiding problems in infancy is interesting. Although he does not address the reasons that propel the manifestation of voiding problems in this age group, it has been long known that crystalluria/microcalculi/ stones may cause voiding difficulties in infants. Epidemiological data have demonstrated that stone formation during the first few days or weeks of after birth may be related to the frequent intake of carbohydrates leading to a relative dietary phosphates deficiency and the formation of insoluble urinary salts.[7] Considering that breast milk content may facilitate crystalluria and or stone formation in infants, his recommendations (cooked radish or black chickpea, which are rich in minerals) may be of utmost importance.

His note regarding the increased incidence of stones in children with excessive food consumption is interestingly consistent with current knowledge because the majority of studies underline the high incidence of developing stones in obese children. One of these recent studies demonstrated that overweight and obese children with urolithiasis have decreased urine citrate, phosphate, and magnesium levels and increased incidence of hypercalciuria compared with children with normal body mass indexes.[8]

It is hard to comment on the definition provided under the subheading of "voiding difficulties" that "if the temperament of bladder is cold, has a thick body and too much bent, urinary retention may occur if the abdominal muscles are not used." It may be attributed to a neuropathic bladder. However, we are unaware of whether he meant *too many contractions* or *impaired function of bladder* while describing "bent."

He also mentions a rare reason of urinary obstruction, i.e., "the flesh formation in the urinary tract." However, it is unclear whether this refers to the posterior urethral valve or to a mass.

Although Shaʿbān Shifāʾī of Ayash mainly highlights the previous prominent authors' recommendations on urinary tract diseases, he also shares his own experiences in this book. His own method, claimed to show effect within an hour for voiding difficulties, is interesting and it includes extract of radish, butter, and plant sugar. A recent study demonstrated anti-inflammatory and antitumor activities of 4-Methylthio-butanyl derivatives obtained from the seeds of *Raphanus sativus*.[9] The healing effect, which was observed within one hour, is probably connected to the anti-inflammatory effects of the drug under investigation. However, it seems difficult to fully explain his empirical observations based on recent scientific data.

The role of deep sleep in enuresis is well known.[10] Although his recommendations to avoid eating and drinking too much prior to sleeping and to urinate before bedtime are valid, his other suggestions such as "rebuke and/or felt guilty" are far from acceptable now. Instead, positive motivation may have a prominent effect on the subsequent treatment.

It is important to mention the genetic basis of enuresis because it is inherited in the majority of cases, despite the fact that there is a wide spectrum between genotype and phenotype.[2] In the light of current knowledge, enuresis has not been accepted as a psychiatric disorder; hence, somatic factors such as vasopressin deficiency, nocturnal detrusor overactivity and high arousal thresholds can play a crucial role in the pathogenesis of this condition.[11]

His emphasizes that "therapies regulating the urine output, and enema are undoubtedly beneficial" for bedwetting children, which is likely to be consistent with today's

knowledge and treatment processes regarding bladder-bowel dysfunction.

Since monosymptomatic nocturnal enuresis improves spontaneously with age and, consequently, no treatment is needed in most cases, his note that "senior physicians recommend no treatment because this condition eventually improves in puberty" is consistent with current knowledge.

5. CONCLUSIONS

Shaʿbān Shifā'ī of Ayash benefited from the works of Ibn Sīnā and Ibn al-Nafīs, who are considered to be prominent physicians during the Middle Ages. It can be deducted that the principles of humoral theory, which was an accepted medical understanding of that period, was valid in explaining the aetiology of nephrological diseases and their underlying treatment processes. Although most of the recommendations are rational, the effectiveness of some of these methods is difficult to explain with current knowledge. These documents are important in terms of being the first written works on paediatric diseases and nephrological problems and treatment approaches in children during the Ottoman period.

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ΠΕΡΙΛΗΨΗ

Ο Shaʿbān Shifā'ī του Ayash και οι παρατηρήσεις και προτάσεις του για τα νεφρολογικά προβλήματα σε παιδιά

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ΣΚΟΠΟΣ: *Το Tadbīr al-Mawlūd* που γράφτηκε το 1701 από τον Shaʿbān Shifā'ī του Ayash θεωρείται το πρώτο βιβλίο που εξετάζει εκτενώς την υγεία και τις ασθένειες των παιδιών κατά την κλασική περίοδο της οθωμανικής ιατρικής. Η παρούσα μελέτη στοχεύει να προσδιορίσει και να αξιολογήσει τα θέματα που σχετίζονται με τα νεφρολογικά προβλήματα στα παιδιά που παρουσιάζονται σε αυτό το βιβλίο. **ΥΛΙΚΟ-ΜΕΘΟΔΟΣ:** Για αυτή τη μελέτη, ανακτήθηκε από τη Βιβλιοθήκη Χειρογράφων İstanbul Süleymaniye, Συλλογή Mihrişah Sultan, αρ. 344 ένα αντίγραφο του χειρόγραφου του Tadbīr al-Mawlūd, γραμμένο από τον Sha'bān Shifā'ī του Ayash. Αρχικά, εντοπίστηκαν τα τμήματα του χειρόγραφου με νεφρολογικό ενδιαφέρον και τα αραβικά κείμενα μεταγράφηκαν στο σύγχρονο τουρκικό αλφάβητο. Αποτελέσματα: Τα θέματα που σχετίζονται με τη νεφρολογία στο *Tadbīr al-Mawlūd* εξετάζονται υπό τον κύριο τίτλο «Ασθένειες των νεφρών και της ουροδόχου κύστης», σε τρία υποκεφάλαια: «Λίθοι του ουροποιητικού συστήματος σε παιδιά», «Κατακράτηση ούρων-δυσκολίες στη διούρηση», και «Νυκτερινή Ενούρηση». Εξετάστηκαν οι αιτίες και οι επιλογές θεραπείας των λίθων της νεφρικής και της ουροδόχου κύστης, και, τέλος, οι αιτίες και η θεραπεία της ενούρησης στα παιδιά. Διαπιστώθηκε ότι ο Sha'bān Shifā'ī του Ayash επωφελήθηκε από τα έργα των Ibn Sīna και Ibn al-Nafīs, που ήταν διακεκριμένοι ιατροί κατά τη διάρκεια του Μεσαίωνα. Συνάγεται ότι οι αρχές του χυμικού μοντέλου, που ήταν η αποδεκτή ιατρική γνώση αυτής της περιόδου, εξηγούσαν έγκυρα την αιτιολογία των νεφρολογικών ασθενειών και την υποκείμενη θεραπεία τους. **ΣΥΜΠΕΡΑΣΜΑΤΑ:** Αυτά τα έγγραφα είναι σημαντικά διότι είναι το πρώτο γραπτό έργο σχετικά με την προσέγγιση των παιδιατρικών νεφρολογικών ασθενειών και των ουρολογικών προβλημάτων στα παιδιά, που γράφτηκε στην οθωμανική περίοδο.

Λέξεις ευρετηρίου: Νεφρολογικά προβλήματα παιδιών αραβική Ιατρική, Νυκτερινή ενούρηση αραβική Ιατρική, Shaʿbān Shifā'ī του Ayash, Tadbīr al-Mawlūd

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MIRACULOUS HEALING
ΘΑΥΜΑΤΟΥΡΓΙΚΗ ΘΕΡΑΠΕΙΑ

Saint hieromartyr Therapon Bishop of ancient Kition, Cyprus, Healer of kidney pains

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ΑΡΧΕΙΑ ΕΛΛΗΝΙΚΗΣ ΙΑΤΡΙΚΗΣ 2020, 37(Συμπλ 2):263–266

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Περίληψη στο τέλος του άρθρου

Hieromartyr Therapon Bishop of ancient Kition, Cyprus (3–4th century AD), born in the East, lived an ascetic life. Later he moved to the island of Cyprus, where he served as a Bishop. He died a martyric death, probably during the persecution under Diocletian (284–305 AD). The saint's relics, initially kept in Cyprus, were transferred to Constantinople to be protected during the second Arab invasion (653 AD). They were placed in a temple in honour of the Icon of Maria "Eleousa" ["the Merciful"]. In 806 AD, the saint's relics were transferred again, this time to a temple built in his honour. During the relics' transfer, myrrh flowed and miracles were reported. Since then, it has been popular belief that the seriously ill are healed through Saint Therapon's prayers. He is considered the protector of children suffering from fever and the healer of kidney pains. Miraculous healing of kidney pains is reported in a monument in Larnaka, believed to be the saint's grave. Healing of kidney pain is accomplished by rubbing the patient's waist on the monument of the saint. Therapon's role as a healer Saint in the Eastern Orthodox Church is explained by his miracles but also simply by his name – Therapon in Greek means server and healer. He is considered a healer of kidney pains, mainly on the island of Cyprus. Another recognised patron saint of kidney sufferers is the Saint virgin and martyr Marina of Antiochia in Pisidia (255–270 AD).

Key words

Bishop of Kition
Healer
Hieromartyr
Renal
Saint Therapon

1. INTRODUCTION

Saint Hieromartyr Therapon, Bishop of ancient Kition in Cyprus, is a Saint of the Eastern Orthodox Church. He lived before the 7th century, most probably between the 3rd and 4th century AD and died a martyric death. Apart from Cyprus, Saint Hieromartyr Therapon is worshipped in many other Eastern Orthodox Church communities. However, there is no detailed description of his life.

The main source of information about the Saint's life and miracles is a single text, entitled –freely translated– as "Encomium of the miracles of Saint Hieromartyr Therapon". It has the form of a laudatio and was meant to honour the Saint. It was probably presented to a congregation and various versions are found in certain codices,[1,2] namely, the codex Laurentianus plut. 9,14 (11th century), the Codex Messanensis 29 (12th century), the Codex Monacensis Graece gr. 366 (State Library of Bayern, 10–11th century) and the codex of Patmos 257 (11th–12th century).[3] Some researchers ascribe this encomium to Saint Andreas of Crete the Jerusalemite (660–740 AD), while others dispute this assumption on an argued historiographical basis.[2] All these manuscripts include only a short description and encomium of the saint's life, followed by a more detailed encomiastic description of all the miracles linked to him.[1,2]

Many in the Eastern Orthodox Church believe that the seriously ill are healed through Saint Therapon's prayers. He is also considered the protector saint of children suffering from fever and a healer of kidney pains. Miraculous healing of kidney pains is reported in a monument in Larnaka,

believed to be the saint's grave. This belief that he is a healer of kidney pains was the main reason for the present work.

1.1. The Saint's life

The Saint's encomium, from the codex Laurentianus plut. 9,14 (11th century), was printed for the first time in the Acta sanctorum Maii (1688, pp 682–692).[4] The biographical information is very scarce and is added as an introduction (AASS Maii, page 281) to the main text (AASS Maii, pages 282–292), which concerns the miracles. This text passage (page 281) clearly states that the sources about the Saint's biography were probably worn out and therefore missing, due to the long time that had passed since his death.[4] This fact is also attested in the book by L. Deubner (1900) entitled "De incubatione capita quattuor. Accedit Laudatio in miracula Sancti Hieromartyris Therapontis e codice Messanensi denuo edita", which cited the codex Laurentianus and a version of the Codex Messanensis 29 (12th century) as well.[1]

According to these sources, the Saint lived before the 7th century, most probably between the 3rd and 4th century AD. He was born in the East (Syria or Mesopotamia), where he lived in a monastery. He became famous in the East for his ascetic life. He later moved to the island of Cyprus, where he served as a Bishop of Kition. He finally died a martyric death,[4] most probably at the time of the persecution under Diocletian (284–305 AD). The fact that his martyric death took place in a paganistic environment is supported by many reports about this, found in the ecclesiastical hymnography devoted to Saint Therapon.[5] The Saint's fight against idolatry is explicitly reported in the hymns of Joseph the hymnographer.[5]

1.2. Miracles, miraculous healing

After his death, the Saint was buried near Larnaca (ancient Kition). He was worshipped in Larnaca and his relics were kept there, in his church until the second Arab invasion in Cyprus. Many miracles are reported at the location of his grave. It was believed that the seriously ill were healed through the prayers of Saint Therapon.[6] Today only remnants of this Byzantine Church are preserved near Larnaca (fig. 1).[6] In order to be protected from the second Arab invasion (653 AD), his relics were transferred to Constantinople. The Saint was said to have appeared in a dream of the guardian of his grave, advising him to ship his relics away, to protect them from the imminent Arab invasion.

As the ship sailed to Constantinople, myrrh began to flow from the relics, and those on-board were miraculously saved during a storm by praying to Saint Therapon. In Constantinople, the relics were placed in a church built in honour of the Icon the Mother of God of "Maria Eleousa" ["Maria the Merciful"]. In 806 AD, the saint's relics were transferred again, this time to a temple built in honour of Saint Hieromartyr Therapon. Myrrh flowed from the relics and miracles were reported.

Figure 1. The remnants of a Byzantine underground small Church, which are saved near Larnaca.

Many miracles of Saint Therapon are described in the encomium, a compendium of miracles. This is possibly the work of Saint Andrew of Crete (660–740 AD), although this is disputed by many researchers.[1,6] Collections of miraculous healing in Byzantine bibliography bear obvious resemblance to collections of clinical cases in the medical works of antiquity, for example those of Hippocrates.[7]

In all, 15 miracles are described in 28 narrative sections. Most of these took place in the church of "Maria Eleousa"; one of these sections concerns the miraculous healing of kidney disease.[1,6] Miraculous healing of kidney pains was re-

ported in a monument in Larnaka, believed to be the saint's initial grave. Healing of kidney pain was accomplished by rubbing the patient's waist on the monument of the saint.[6]

Today, Saint Hieromartyr Therapon is worshipped in many communities of the Eastern Orthodox Church, such as Athens, Thessaloniki, Lesvos, Crete and Cyprus. In Cyprus, there are two churches in the Saint's honour, one in Larnaca and an older one in Anglisides, a village near Larnaca. The oldest icon of the Saint in Cyprus (fig. 2) is found in the church in Anglisides, built by the village inhabitants in 1733.[6]

2. CONCLUSIONS

In Greek hagiography and patrology, many Saints are named patrons of various body organs, organ ailments and diseases. The central role of Hieromartyr Therapon in the Eastern Orthodox Church, as a healer Saint, is explained by his miracles but also simply by his name – Therapon in Greek means server and healer. He is considered a healer of kidney pains, mainly on the island of Cyprus. Another recognised patron saint of kidney sufferers is the Saint virgin and martyr Marina of Antiochia in Pisidia (255–270 AD).[7]

Figure 2. The miraculous 18th century icon of Saint Therapon kept in the homonymous Church (built in 1733) in the village Anglisides near Larnaca in Cyprus.

ΠΕΡΙΛΗΨΗ

Άγιος Ιερομάρτυς Θεράπων, Επίσκοπος αρχαίου Κιτίου, Κύπρος: Θεραπευτής των πόνων στους νεφρούς

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Ο Ιερομάρτυς Θεράπων, Επίσκοπος Κιτίου της Κύπρου (3–4ος αιώνας μ.Χ.) γεννήθηκε στην Ανατολή και έζησε ασκητική ζωή. Αργότερα μετέβη στο νησί της Κύπρου, όπου υπηρέτησε ως επίσκοπος. Πέθανε μαρτυρικά, πιθανώς κατά τη δίωξη του Διοκλητιανού (284–305 μ.Χ.). Τα λείψανα του αγίου, που φυλάσσονταν αρχικά στην Κύπρο, μεταφέρθηκαν στην Κωνσταντινούπολη για να προστατευτούν κατά τη δεύτερη αραβική εισβολή (653 μ.Χ.). Τοποθετήθηκαν σε ναό ο οποίος είχε χτιστεί προς τιμήν της εικόνας της Παναγίας της «Ελεούσας». Το 806 μ.Χ., τα λείψανα του αγίου μεταφέρθηκαν ξανά, αυτή τη φορά σε ναό που χτίστηκε προς τιμήν του. Κατά τη μεταφορά των λειψάνων, έρεε μύρο και έγιναν αναφορές για θαύματα. Έκτοτε, επικράτησε η πεποίθηση ότι οι σοβαρά άρρωστοι θεραπεύονται μέσω των προσευχών του Αγίου Θεράποντα. Θεωρείται προστάτης των παιδιών που πάσχουν από πυρετό και ότι θεραπεύει τους πόνους στους νεφρούς. Σε ένα μνημείο στη Λάρνακα, που πιστεύεται ότι βρίσκεται ο τάφος του αγίου, γίνεται αναφορά για θεραπεία των πόνων στους νεφρούς. Η θεραπεία του πόνου των νεφρών επιτυγχάνεται τρίβοντας τη μέση του ασθενούς στο μνημείο του αγίου. Ο ρόλος του Θεράποντα ως θεραπευτή Άγιου στην Ανατολική Ορθόδοξη Εκκλησία εξηγείται από τα θαύματα του, αλλά και απλώς από το όνομά του - Θεράπων σημαίνει υπηρέτης και θεραπευτής. Θεωρείται θεραπευτής των πόνων των νεφρών, κυρίως στην Κύπρο. Ένας άλλος γνωστός προστάτης των νεφρών είναι η Αγία παρθενομάρτυς Μαρίνα της Αντιόχειας Πισιδίας (255–270 μ.Χ.).

Λέξεις ευρετηρίου: Άγιος Θεράπων, Επίσκοπος Κιτίου, Θεράπων, Ιερομάρτυς, Νεφρός

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MIRACULOUS HEALING
ΘΑΥΜΑΤΟΥΡΓΙΚΗ ΘΕΡΑΠΕΙΑ

Miraculous renal healing in the church of the Life-Giving Spring in Constantinople
Compendium (1812) from the original by Nikiphoros Kallistos Xanthopoulos (1256–1335)

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ΑΡΧΕΙΑ ΕΛΛΗΝΙΚΗΣ ΙΑΤΡΙΚΗΣ 2020, 37(Συμπλ 2):267–270

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Nikiphoros Kallistos Xanthopoulos (1256–1335) was a priest in Hagia Sofia and a scholar considered as the last Greek ecclesiastical historian. Apart from "Ecclesiasticae Historiae", dedicated to the emperor Andronikos-II Palaeologos (1282–1328), he wrote poems, liturgical hymns and "synaxaria" of the Orthodox Church. His book of the miracles in the church of the Life-Giving Spring in Constantinople was published in a compendium translation in vulgar Greek (1812). Initiated by the ex-Bishop of Stages (Meteora) Paisios (1784–1808), this translation aimed to offer contemporary Greeks a book more comprehensible and thus more beneficial than the original. Our aim was to analyse the forms of miraculous healing applied and the renal ailments healed in this compendium. Miraculous healings (54 among 63 miracles) included prayers, visions and the spring-water. Drinking was applied in 43, washes in 11 and mud compresses in 8 cases. Renal ailments were present in 11 cases: bladder stones with dysuria, hematuria, pyuria or urine retention in 9 and hydrops in 2. Emperor Justinian (527-565) was healed from an obstructive bladder stone. Help was sought after doctors' treatments failed. In two cases, water drinking was applied despite medical advice and side effects of drug-therapy were healed in two other. In the compendium edition of the book of Nikiphoros Kallistos Xanthopoulos on the miracles of the Life-Giving Spring in Constantinople, healing of renal disorders was very frequent (20%). This publication implies a close relationship of Greek scholars, during the Hellenic Enlightenment (1750–1821), with Palaeologian Byzantine Humanism.

Θαυματουργικές θεραπείες νεφρικών παθήσεων στην εκκλησία της Ζωοδόχου Πηγής στην Κωνσταντινούπολη. Εγκόλπιο (1812) από το πλήρες κείμενο του Νικηφόρου-Κάλλιστου Ξανθόπουλου (1256–1335)

Περίληψη στο τέλος του άρθρου

Key words

Life-Giving Spring
Miraculous renal healing
Nikiphoros Kallistos Xanthopoulos
Zoothohos Pege

1. INTRODUCTION

Nikiphoros Kallistos Xanthopoulos (1256–1335) was a native of Constantinople. He lived during the reign of the Byzantine emperor Andronikos-II Palaeologos (1282–1328). He was a priest of the Great Church, Hagia Sophia, and later in life became a monk. He was a scholar, trained in the florid, rhetorical style of the Paleologian Renaissance historiography, which flourished in the 13th and 14th centuries.[1] He taught rhetoric and theology and was considered the last Greek ecclesiastical historian.

Andronikos II was born in Nicaea and was proclaimed co-emperor in 1261, when his father Michael VIII Paleologos recovered Constantinople from the Latin Empire and transformed the Empire of Nicaea into a restored Byzantine Empire. Andronicos II (fig. 1), who was crowned sole emperor in 1282, managed, during his reign, to mitigate the problems in the west using diplomacy. However, the Empire faced great economic difficulties and the Turks conquered most of its Western Anatolian territories. Andronikos II also repudiated his father's unpopular Church union with the Vatican but managed to resolve the related schism within the Orthodox clergy only in 1310.[2]

Nikiphoros Xanthopoulos has written many books. His 18-volume "Ecclesiasticae Historiae" was dedicated to emperor Andronikos-II Palaeologos. He also wrote poems, liturgical hymns and "synaxaria" of the Eastern Orthodox Church. The volume and thematic variety of his work was

Figure 1. Andronikos II Palaiologos, Byzantine emperor (1282–1328). From the History of George Pachymeres, cod. Monac. gr. 442, fol. 6v, Bayerische Staatsbibliothek, Munich.

impressive.[3] However, it has not yet been published in printed form because it was prohibited by the Pope and the Vatican due to dogmatic differences in the 16th century.[4]

His book about the miracles in the church of the Life -Giving Spring in Constantinople was published in a compendium translation in vulgar Greek (1812, fig. 2). Initiated by the ex-Bishop of Stages (Meteora) Paisios (1784–1808), this translation aimed to offer contemporary Greeks a book more comprehensible and thus more beneficial than the original.

The aim of the study presented was to analyse the forms of miraculous healing applied and the renal ailments healed in this compendium.

2. RESULTS

The compendium edition of Nikiphoros Kallistos Xanthopoulos' book on the miracles of the Life -Giving Spring in Constantinople included 54 miraculous healings among the 63 miracles described. Healing was accomplished with the help of prayers or visions and also, in most cases, by using the spring-water. Drinking was applied in 43, washes in 11 and mud compresses in 8 cases.

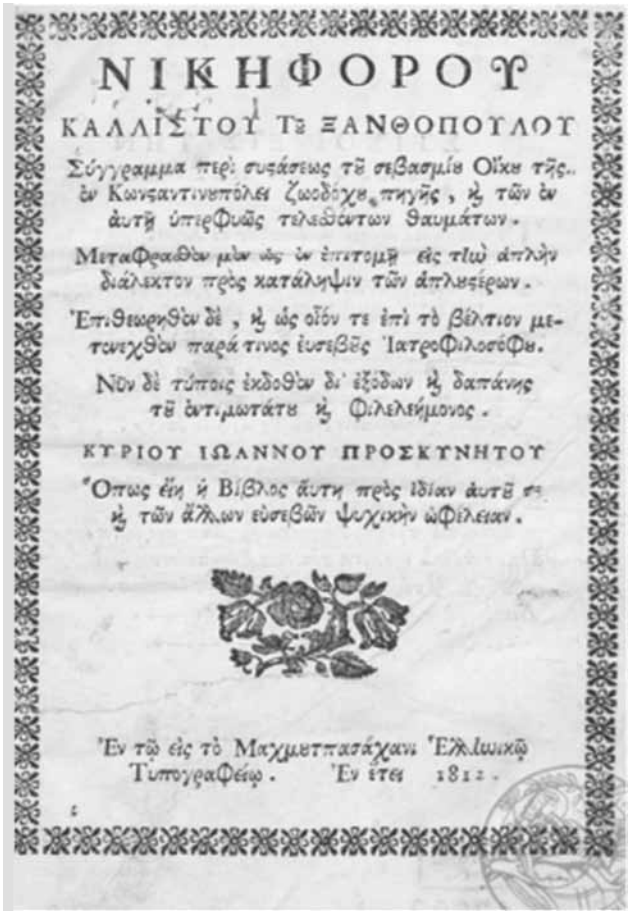
ΝΙΚΗΦΟΡΟΥ
ΚΑΛΛΙΣΤΟΥ Τῦ ΞΑΝΘΟΠΟΥΛΟΥ
Σύγγραμμα περὶ συστάσεως τῦ σεβασμίου Οἴκου τῆς..
ἐν Κωνσταντινουπόλει ζωοδόχου πηγῆς, καὶ τῶν ἐν
αὐτῇ ὑπερφυῶς τελεσθέντων θαυμάτων.
Μεταφρασθὲν μὲν ὡς ἐν ἐπιτομῇ εἰς τὴν ἁπλῆν
διάλεκτον πρὸς κατάληψιν τῶν ἁπλουστέρων.
Ἐπιθεωρηθὲν δὲ, καὶ ὡς οἷόν τε ἐπὶ τὸ βέλτιον με-
τενεχθὲν παρά τινος εὐσεβοῦς Ἰατροφιλοσόφου.
Νῦν δὲ τύποις ἐκδοθὲν δι' ἐξόδων καὶ δαπάνης
τῦ ἀντιμωτάτου καὶ φιλελεήμονος.
ΚΥΡΙΟΥ ΙΩΑΝΝΟΥ ΠΡΟΣΚΥΝΗΤΟΥ
Ὅπως ἔχῃ ἡ Βίβλος αὕτη πρὸς ἰδίαν αὐτῦ τε
καὶ τῶν ἄλλων εὐσεβῶν ψυχικὴν ὠφέλειαν.
Ἐν τῷ εἰς τὸ Μαχμετπασάχαν Ἑλληνικῷ
Τυπογραφείῳ. Ἐν ἔτει 1812.

Figure 2. The title page of Nikiphoros Kallistos Xanthopoulos' book (1256–1335) on the miracles in the church of the Life-Giving Spring in Constantinople in compendium translation in vulgar Greek, published in 1812.

Renal ailments were present in 11 cases: bladder stones with dysuria, haematuria, pyuria or urine retention in 9 and hydrops in 2. Emperor Justinian (527–565) was healed from an obstructive bladder stone. In all cases, help was sought after doctors' treatments had failed or after a previous miraculous healing experience.

Interestingly, in two cases water drinking was applied despite medical advice for the opposite and, in two others, side effects of the doctor's drug-therapy were healed. Even if incorrect, the above statements reveal the limits and errors of the then traditional medicine.

3. DISCUSSION

The epithet Life -Giving Spring was given to Maria because she revealed the sacred spring in Constantinople, to a soldier who later became the Byzantine Emperor Leo I (457–474). Leo I built the historic Church of Maria of the

Life -Giving Spring over the sacred fond. Since then, the Spring has witnessed numerous reported miracles and miraculous healings.

In the compendium edition of Nikiphoros Kallistos Xanthopoulos' book on the miracles of the Life -Giving Spring in Constantinople, the healing of renal disorders was often reported (20%). The most frequent kidney ailments healed were lithiasis and urinary tract infections. This publication implies a close relationship of Greek scholars, during the Hellenic Enlightenment (1750–1821), with Palaeologian Byzantine Humanism.

4. CONCLUSION

Collections on miraculous healing are often found in Byzantine bibliography. They have an obvious resemblance to the collections of clinical cases in the medical works of antiquity, for example those of Hippocrates.[5] These collections of miracles may be seen as case studies and help to draw some conclusions about epidemiology[6] and therapeutic practices during the period they refer to.[6,7] The book presented here allows us to hypothesise that renal disorders were not rare in Byzantium and that their treatment, even for the rich and powerful, entailed considerable difficulties.

ΠΕΡΙΛΗΨΗ

Θαυματουργικές θεραπείες νεφρικών παθήσεων στην εκκλησία της Ζωοδόχου Πηγής στην Κωνσταντινούπολη. Εγκόλπιο (1812) από το πλήρες κείμενο του Νικηφόρου-Κάλλιστου Ξανθόπουλου (1256–1335)

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Ο Νικηφόρος Κάλλιστος Ξανθόπουλος (1256–1335) υπήρξε ιερέας στην Αγία Σοφία και μελετητής. Θεωρείται ο τελευταίος Έλληνας εκκλησιαστικός ιστορικός. Εκτός από το έργο του «*Ecclesiasticae Historiae* (Εκκλησιαστική Ιστορία)», το οποίο ήταν αφιερωμένο στον αυτοκράτορα Ανδρόνικο-ΙΙ Παλαιολόγο (1282–1328), έγραψε ποιήματα, λειτουργικούς ύμνους και «συναξάρια» της Ορθόδοξης Εκκλησίας. Το βιβλίο του για τα θαύματα στην εκκλησία της Ζωοδόχου Πηγής στην Κωνσταντινούπολη δημοσιεύθηκε σε μία συνοπτική μετάφραση στην απλή ελληνική γλώσσα (1812). Η μετάφραση αυτή, που ξεκίνησε ο πρώην Επίσκοπος Σταγών (Μετέωρα) Παΐσιος (1784–1808), είχε στόχο να προσφέρει στους σύγχρονους Έλληνες ένα βιβλίο πιο κατανοητό και επομένως πιο χρήσιμο από το πρωτότυπο. Στόχος μας ήταν να αναλύσουμε τις μορφές θαυματουργής θεραπείας που εφαρμόστηκαν και τις νεφρικές παθήσεις που θεραπεύτηκαν, όπως καταγράφονται σε αυτή τη σύνοψη. Οι θαυματουργές θεραπείες (54 μεταξύ 63 θαυμάτων) περιελάμβαναν προσευχές, οράματα και το νερό της πηγής. Πόση του νερού εφαρμόστηκε σε 43 περιπτώσεις, πλύσεις σε 11 και επιθέματα λάσπης σε 8 περιπτώσεις. Νεφρικές παθήσεις παρουσιάζονταν σε 11 περιπτώσεις: Λίθοι της ουροδόχου κύστης με δυσουρία, αιματουρία, πυουρία ή κατακράτηση ούρων σε 9 και εξίδρωμα σε 2. Ο αυτοκράτορας Ιουστινιανός (527–565) θεραπεύτηκε εκεί από λιθιασική απόφραξη της ουροδόχου κύστης. Ζητήθηκε βοήθεια αφού οι θεραπείες των ιατρών απέτυχαν. Σε δύο περιπτώσεις, η πόση νερού εφαρμόστηκε παρά τις ιατρικές συμβουλές και οι παρενέργειες της φαρμακευτικής αγωγής θεραπεύτηκαν σε δύο άλλες. Στη συνοπτική έκδοση του συγγράμματος του Νικηφόρου Καλλίστου Ξανθόπουλου σχετικά με τα θαύματα της Ζωοδόχου Πηγής στην Κωνσταντινούπολη, η θεραπεία των νεφρικών παθήσεων ήταν ένα συχνό φαινόμενο (20%). Η παρούσα έκδοση υποδηλώνει τη στενή σχέση Ελλήνων μελετητών, κατά τη διάρκεια του Ελληνικού Διαφωτισμού (1750–1821), με τον Βυζαντινό Ανθρωπισμό της εποχής των Παλαιολόγων.

Λέξεις ευρετηρίου: Ζωοδόχος Πηγή, Θαυματουργικές νεφρικές θεραπείες, Νικηφόρος Κάλλιστος Ξανθόπουλος

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