Rheumatology International (2019) 39:947–955
https://doi.org/10.1007/s00296-019-04261-4

Rheumatology
INTERNATIONAL

REVIEW

The Greek (Hellenic) rheumatology over the years: from ancient to modern times

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Received: 07 January 2019 / Accepted: 20 February 2019 / Published online: 25 February 2019

Abstract
Rheumatology has its roots in ancient Greece. Hippocrates and other prominent Greek (Hellenes) physicians in ancient times, Hellenistic, Roman, and Byzantine period were acute observers of disease course and of patients and were able to define many disorders. They wrote books on various aspects of medicine and these writings were the basis of medical practice and education in Europe and the Arabic world well into the seventeenth century. In 1821, Greece emerged from a long occupation by the Turks. In 1930, Adamantiades, a Greek Ophthalmologist, before Behcet of Turkey, described what is known as (Adamantiades)–Behcet disease. The first scientific Hellenic Society for Rheumatology (ERE) was established in 1960 and today ERE having been merged with the Professional Union of Greek rheumatologists (EPERE) is known as ERE-EPERE. Rheumatology is a strong specialty with 348 rheumatologists for a population of around 11 million. Greek rheumatologists have contributed to rheumatology science and practice, and are active physicians participating in the American College of Rheumatology and the EULAR annual congresses and in many educational postgraduate courses. ERE-EPERE formed therapeutic protocols for inflammatory and autoimmune rheumatic diseases which were incorporated in the electronic National prescription system. Rheumatologists are authorized to use this platform to prescribe biologicals free of charge for patients. ERE-EPERE publishes a peer-reviewed English language journal, the Mediterranean Journal of Rheumatology (MJR), an open access journal with no publication fees. MJR is a quarterly journal with international Editorial Board.

Keywords Arthritis · Behcet's disease · Byzantine · Galen · Gout · Hippocrates · Hellenistic · Mediterranean

Introduction

Medicine as we know it today has its roots in ancient Greece (Hellas). At that time, prominent Greek physicians were acute observers of disease course and patients, and they were able to accurately define disorders and treat them. Greek physicians at that time had broad education and were also anatomists, philosophers, mathematicians, teachers and writers. What these Greek physicians left behind in writings were astonishing and formed the basis or even were the sole source of medical practice and teaching in Europe and the Arabic world for hundreds of years, and many are still valid today. Honoring these authors, many medical terms today have Greek names. Rheumatology itself comes from the Greek (Hellenic) word ρεύμα (rheuma) which means flowing current, because ancient Hellenes believed that diseases are caused by flowing fluid (humor). What we will describe in the next few pages about rheumatic diseases is the tip of the iceberg of what ancient Greek authors have written on various aspects of Medicine.

Ancient Greece (Hellas)

At first, physician-priests in Greece practiced mostly spiritual healing. Asklepios, the son of God Apollo and mortal Coronis from Thessaly in central area of Greece, was a demi-God hero and Asklepions, devoted to Asklepios, were sanctuary of healing based on dreams and appeared first in Thessaly and then throughout Greece [1, 2].

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Fig. 1 A statue of Hippocrates in Larissa, in central Greek area of Thessaly

Hippocrates (circa 460–370 BC) was born in the island of Kos and practiced medicine in Kos, Athens, and finally in the city of Larissa in Thessaly, where he died (Fig. 1). Hippocrates is widely considered as the father of Medicine, as he moved physicians away from spiritual healing and founded Medicine as a rational discipline (Figs. 2, 3). His total works, known as "Corpus Hippocraticum" were taken by the king of Egypt Ptolemy I, one of Alexander the Great successors, to Alexandria. Alexandria became the cultural and scientific center of the ancient world. The Corpus Hippocraticum was widely used by eminent physicians during the Hellenistic and Roman periods, was translated into Arabic and later into Latin and was the main book of medicine through the seventeenth century. Hippocrates systemically studied diseases and patients to make a diagnosis "learning from the common features of the diseases and the specific features of each one, learning from the patient, from the diet, from the profession, from the age of each one" (Hippocrates work: Epidimion A, Sect. 23) [3]. Hippocrates's work "On Joints" advised physicians to avoid nerve damage when reducing joint dislocations. Hippocrates describes gout as an affection of the rich and he says in his aphorisms:

> A woman does not get gout unless her manses are stopped
> A young man does not take gout until he indulges in coition
> Eunuchs do not get gout nor become bald

Fig. 2 Amphiaraus treats a shoulder disorder in a Temple (400–350 BC). National Archaelogical Museum of Athens (with permission)

Fig. 3 Anathem of Lysimachides, son of Lysimachus of Athens to the Temple of hero-physician Amynos. The anathem shows a leg with varicose vein, indicating patient's affection (fourth century BC). National Archaeological Museum of Athens (with permission)

In gouty affections inflammation subsides within 40 days [4]

Others relevant to rheumatology aphorisms include

What remains in diseases after the crisis is apt to produce relapses
Swellings and pains in the joints of the gouty nature and sprains are generally improved by copious affusion of cold water which reduces the swelling and removes the pain.

"All disease begins in the gut". Today we know that the microbiota of the gastrointestinal tract plays a crucial role in shaping the immune response and this is convincingly shown to be involved in the pathogenesis of rheumatoid arthritis [5].

"When bubbles settle on the surface of the urine, they indicate disease of the kidneys and that the complaint will be protracted". Later Galen explained: "Bubbles are created when the liquid contains something sticky". We now know that protein increases surface tension and explains this phenomenon [6].

Hippocrates also described a condition that resembles was it is known as (Adamantiades)–Behcet's disease. In his 'Epidimion' Book 3, Case 3, he described an endemic disease: "There were other fevers which will be described. Many had oral ulcers and aphthae. Genitals with ulcers. Nodules external and internal in the groin. Watery inflammation of eyes painful, chronic, growths on the eyelids, external and internal, reducing the sight in many cases… Herpetic lesions many and large" "Ησαν δε και άλλοι πυρετοί περ ιών γεγράφεται. Στόματα πολλοίσιν αφθώδεα ελκώδεα, ρευματα περι αιδοία πολλά ελκώματα φύματα έξωθεν, έσωθεν τα περί βουβώνας. Οφθαλμίαι υγραί μακροχρόνιοι μετα πόνων, επιφύσιες βλεφάρων, έξωθεν, έσωθεν, πολλών φθείροντα τας οψίας. ..Εκθύματα μεγάλα, έρπητες πολλοίσι μεγάλα [3, 7, 8]. Many medical terms today are the same as used by Hippocrates [9]. Even more importantly, Hippocrates stressed the ethics of medical practice "do good not harm" and today graduates of medical Schools in Greece and other parts of the world still take the Hippocratic oath [10–12]:

I will give regimen for the benefits of the ill in accordance with my ability and my judgement
I will not give a lethal drug to anyone if asked (for it) nor will I give an advice for such a plan
I will not give a woman a destructive pessary' and whatever I see or hear in the lives of my patients, whether in connection with my professional practice or not, which ought not to be spoken of outside, I will keep silent, considering all such things private.

Aristoteles (Aristotle) (384–322 BC), born in Stageira, Chalkidiki in the northern Greek area of Macedonia, studied in Plato's Academy in Athens. He was the teacher of Alexander the Great in Macedonia and established his own School, the Lyceum, in Athens. Aristotle became a great scientist, teacher, and the greatest philosopher of all times. He laid the foundations of comparative anatomy, and he is regarded as the first biologist. Above all, he is the founder of formal logic which changed the way of human thinking [13].

Hellenistic/Roman period

During the Hellenistic period, Ptolemy I, one of Alexander the Great successors and king of Egypt, made Alexandria in Egypt the cultural and scientific centre of ancient world. Herophilos of Alexandria, a Greek physician born in Chalkedon and lived in Alexandria, taught in the famous Medical School of Alexandria, excelled in anatomy and is widely considered the father of anatomy [14]. Erasistratus (310–250 BC) was a collaborator of Herophilus in anatomical dissections [15].

During the Roman empire, it was the Greek physicians who established the medical practice in Rome. In Rome, there were no native physicians and Archagathos of Sparta was the first Greek physician to introduce Greek medicine to Romans around 218 before current era (BCE). Many Greek medical Schools flourished in Rome, including the Methodiki school (founded by Asclepiades of Bithynia and his student Themison of Laodicea), the Pneumatiki School (founded by Athenaeus), the Empiriki school (founded by Serapion of Alexandria and Philinus of Kos), and Eklektik school (founded by Agathinus of Sparta).

Asclepiades of Bithynia (130–40 BCE) established Greek medicine in Rome. Asclepiades studied in Athens and Alexandria before moving to Rome. Based on Democritus and Epicurus theories, he proposed that the human body composed of atoms and pores whereas the disease is associated with interruption of the free flow of atoms. He also distinguished acute from chronic diseases [16].

Claudius Galenus, better known as Galen of Pergamus (129–216 AD) was the most famous Greek physician in the Hellenistic/Roman period. He was born in the Greek city of Pergamus (Asia Minor), studied in Athens and Alexandria, and practiced medicine in Rome where he achieved a great authority, becoming physician to a number of Roman Emperors. Galen is considered as a father of experimental physiology. He dissected animal bodies (not human cadavers) to understand how the body functions and his experiments span every specialty of medicine. For a patient with numbness and paralysis of fingers, he writes "leaving the affected parts alone you will reach the spine from which you

will treat the disease". Galen described tophi as a manifestation of long-standing podagra. He was a prolific writer, writing over 600 treatises. His complete treatise on anatomy was translated into Latin in fifteenth century and had a dominant impact on the practice and teaching of medicine in Byzantium, the muslim world, and Europe during middle Ages well into the seventeenth century [17, 18].

Aretaeus the Cappadocian (second century AD), a Greek physician born in Cappadocia, studied in Alexandria and practiced Medicine in Rome. Aretaeus excelled in the art of observation of disease course. In his books "On the causes and manifestations of acute diseases", "On the causes and manifestations of chronic diseases, "Treatment of acute diseases" and "Treatment of chronic diseases", he described many diseases with accuracy, including pneumonia, pleurisy, spinal paralysis, peripheral paralysis and diabetes. In fact, he gave diabetes its name. He also described arthritis and sciatica. He named podagra the arthritis of foot (ποδός[podos]), and cheiragra the arthritis of hand (χειρός [cheiros], hand). He mentioned that podagra may be constant or absent for long. "Women suffer less often than men but suffer more". "άνδρες μέν παθών ρηίτεροι γυναικών δε ελαφρότερον. Γυναίκες δέ αραιότερον μέν ανδρών, χαλεπώτερον δέ». Aretaeus recognized that gout could be inherited and described it as a gouty "diathesis". The treatment of exacerbation of arthritis included botanical dressings ('επίπλασμα'), botanical infusions ('αφέψημα') and cold. The remedies were beneficial in some cases. His work was first translated into Latin in Venice in 1552 and the first Greek edition was printed in Paris in 1554 and had an immense influence on the sixteenth century and onwards Medical Schools and medical practice [4, 19].

Soranus of Ephesus (90–138 AD), born in Ephesus on the coast of Asia Minor, studied in Alexandria and practiced medicine in Rome. His most important work "Gynaecology" has been considered for more than 1500 years a reference book for gynaecology. Soranus was the first to describe rickets: "if the infant is eager to sit up too early and for too long a period it usually becomes hunchbacked and if the infant is prone to stand up and desirous of walking the legs may become distorted in the region of the thighs. This is observed to happen particularly in Rome" [20].

Rufus of Ephesus (80–150 AD), a famous physician, wrote a guide for medical practitioners "On questioning the patient" in which he explains what a physician should ask the patient (order of symptoms, medications used, etc.) to correctly diagnose the disease stressing that each patient is unique [21]. Rufus also stressed the importance of anatomy to diagnose and treat diseases and wrote "On the names of the parts of the human body" [22].

Apollonius of Citium (first century BC) in his work "Treatise on joints", based on Hippocratic work "On joints", simplified methods and techniques of reductions of joint dislocations so that non-physician can use them [23].

Other prominent physicians/authors of the first century AD include Asklepiades Pharmakion, Servilius Democrates, and Xenocrates of Aphrodisias.

Byzantine period

During the Byzantine empire (fifth—fifteenth century AD), physician-scholars distilled the works of their Greek predecessors into manageable textbooks [24].

Alexander Trallianus (or Alexander of Tralles) (525–605 AD) is the brother of Asthenius of Tralles, a famous mathematician who, along with Isidore of Miletus, constructed Aghia Sophia, the famous Christian Temple in Constantinople (now Istanbul). Alexander Trallianus's most famous work is "The twelve Books of Medicine". In Book 1, Chap. 1, he states "Alopecia a disease of hair falling, is due to various causes". Book XII is devoted to podagra (gout) and considered it to be caused by a toxic substance in the blood. "podagra is generated from blood... and blood arises from every meat…and sweet wine. Much drinking of wine is harmful. Therefore, it is good for them to be prohibited from a drink of wine". Although many prominent physicians have written about gout since Hippocrates, Alexander was the first to use Hermodactylus (*Colchicum autumnale*) from crocus, a powerful purgative widely used in ancient Greece, as a specific treatment for podagra and describes recipes "to break-up tophi so that they never seen again" [25–27]. Today colchicine, the active ingredient of colchicum, is used as the first-line treatment for gout attack.

Paul of Aegina, born in the island of Aegina, near Athens, in 625 AD was an eminent Greek physician. He studied medicine in Alexandria and is the last great physician of the Greek-Alexandrian School of Medicine. He excelled in surgery, particularly neurosurgery performing laminectomies. He wrote seven books, Epitome of Medicine, which was translated into Latin in 1551 and 1567, in English in 1843, in French in 1855 and in Arabic in the ninth century. In Book 1, he writes on exercises and various types of exercises and also on the powers of food. In the relevant chapter on pain, he describes "A throbbing pain is characteristic of a strong inflammation" [28].

Other prominent Greek physicians of that era include Stefanus of Athens (550–630 AD), Aetius of Amida (500–550 AD), Oribasius of Pergamon, and Theophilus Protospatharius.

Apart from podagra [29], descriptions of apparent rheumatoid arthritis is found in many Greek physicians/authors

writings, including those of Hippocrates, Soranus of Ephesus, Aretaeus the Cappadocian, Michael Psellus and others [30]. Aretaeus describes polyarthritis "a general pain of all the joints..it is incredible how far the mischief spreads" [31]. Michael Psellus, a Christian Greek Scholar and physician in his Chronographia (1063 AD) gave a detailed account of polyarthritis of the Byzantine Emperor Constantine IX Monomachos: "Later on, the intervals between these attacks diminished and his relief became short-lived. As this condition developed, the flux gradually approached his hands, then, with a kind of upward flow, the humours attacked his shoulders, and finally occupied the whole of his body…His fingers, once so beautifully formed, completely altered from their natural shape…so that they were incapable of grasping anything at all. His feet were bent and his knees, crooked like the point of a man's elbow, were swollen, making it impossible for him to walk steadily" [32, 33].

Modern times

In 1453, Constantinople fell to the Turks who occupied Greece for 400 years, and the continuation of Hellenic rheumatology has been disrupted.

In 1930, in the annual Congress of the Medical Society of Athens, Adamantiades, a Greek ophthalmologist from Prussia, Asia Minor, described a 20-year-old patient with thrombophlebitis of left leg who subsequently developed in the next 2 years recurrent iritis with hypopyon, oral aphthous ulcers, scrotal ulcers and arthritis of both knees. Bacterial cultures from the anterior eye chamber and knees were negative and inoculation experiments into animals were negative. This case was published in the Proceedings of the Medical Society of Athens in 1930 [34] and in the next year Adamantiades, considering these constellations of manifestations as a single disease, published a paper in the French journal Annales d'Oculistique [35]. In 1937, Hulusi Behcet, a Turkish physician, described the triad of symptoms/signs of the disease in the German journal Dermatologische Wochenschrift [34].

In 1956, the first rheumatology clinic was founded in Greece. Rheumatology was recognized as an independent specialty in 1986 with 6 years of training. This training includes 2 years in internal medicine, followed by 4 years in rheumatology. The latter part contains training in immunology laboratory, physical therapy, and orthopedics. Today, rheumatology clinics and/or divisions are in all nine University Hospitals, nine General Hospitals of the National Health System and five Military Hospitals.

The first scientific society of rheumatology was founded in 1960 as the "Hellenic Society of Rheumatology and Hydropathy". It was renamed as "Hellenic Society for Rheumatology" in 1970. In 2012, the Hellenic Society of Rheumatology and the Professional Union of Rheumatologists merged into "Hellenic Society of Rheumatology-Professional Union of Rheumatologists (ERE-EPERE)", a scientific and professional non-profit society. The society is governed by a 6-member board elected every 2 years and has 348 regular members (specialized rheumatologists) and 65 associated members (residents in rheumatology). ERE-EPERE organizes a Panhellenic Congress of Rheumatology every 2 years, postgraduate courses in Rheumatology every 2 years, and "Spring Rheumatology Days" every year. ERE-EPERE also hosts study groups for autoimmune/inflammatory disorders with an intent to establish collaboration among rheumatology centers. Since Greece is a small country, the inclusion of patients with various autoimmune and inflammatory rheumatic diseases from all Rheumatology centers of Greece under common clinical practice increases the statistical power of studies. This collaboration is beginning to bear fruits, bringing clinicians close to each other and resulting in scientific publications [36–38].

Many Greek rheumatologists improved their knowledge and skills at European and American centers. Greek rheumatologists in and outside Greece significantly contributed to rheumatology science and practice, not only with their research papers but also with their participation in the shaping of rheumatology practice in Europe and beyond. Important contributions were made in Sjogren's syndrome [39–42], cardiovascular disease in rheumatoid arthritis (RA) [43, 44], treatment of systemic lupus erythematosus(SLE) [45–48], T cells in the pathogenesis of SLE [49, 50], treatment of (Adamantiades)–Behcet's disease [51–53], osteoarthritis [54, 55], T cells and B cells in the pathogenesis of systemic sclerosis (SSc) [56, 57], anti-B cell treatment in SSc [58, 59], rheumatoid arthritis [60], spondyloarthropathies [61, 62], Hepatitis B virus in immunosuppression [63, 64], infections as triggers of autoimmunity [65] and anti-phospholipid syndrome [66, 67], to name some contributions (Table 1). A new generation of rheumatologists brings new hope to academic Greek rheumatology [68–71]. Greek rheumatologists are active physicians participating in many post-graduate courses, and the American College of Rheumatology and EULAR annual congresses. For instance, 157 Greek rheumatologists participated in the EULAR 2018 annual congress with abstracts (each with a mean number of 1.4 abstracts).

The ERE-EPERE publishes a rheumatology journal. The first Greek Rheumatology Journal named "Chronicle of Rheumatology" has been published from 1971 to 1974. ERE published a new Greek journal "Hellenic Rheumatology" in 1989. The Journal was renamed to "Mediterranean Journal of Rheumatology (Mediterr J Rheumatol)" in 2015. Mediterr J Rheumatol is an English language, peer-reviewed

Table 1 Contribution of Greek rheumatologists to rheumatology science and practice

Academic	Field of contribution	References
Andrew Andonopoulos	Anti-B cell treatment in SSc	[58, 59]
George Bertsias	EULAR guidelines for SLE treatment	[46–48]
Alexandros A. Drosos	Manifestations and treatment of RA	[60]
Dimitrios P. Bogdanos	B cells and infectious triggers of autoimmunity	[57, 65]
Xenofon Baraliakos (Germany)	Imaging and treatment of SpA	[61, 62]
Dimitrios Boumpas	Treatment of lupus nephritis EULAR guidelines for SLE treatment	[45–48]
Dimitrios Daoussis	Anti-B cell treatment in SSc	[58, 59]
Phaedon Kaklamanis	Treatment of BD Hand osteoarthritis	[51, 53–55]
George Kitas (United Kingdom)	Cardiovascular disease in RA	[43, 44]
Stamatis-Nick Liossis	Anti-B cell treatment in SSc	[58, 59]
Haralampos Moutsopoulos	Pathogenesis and manifestations of SjS	[39, 40]
Lazaros I. Sakkas	T and B cells in the pathogenesis of RA and SSc Infectious triggers in autoimmunity	[56, 57, 65]
Petros P. Sfikakis	Anti-TNF MoAb treatment in neuro-BD EULAR guidelines for BD treatment	[51, 52]
Maria Tektonidou	EULAR treatment guideline for SLE/APS	[46–48, 66, 67]
Athanasios Tzioufas	Pathogenesis and manifestations of SjS	[41, 42]
George Tsokos (USA)	T cells in the pathogenesis of SLE	[49, 50]
Dimitrios Vassilopoulos	HBV infection in immunosuppression	[63, 64]

APS antiphospholipid syndrome, *BD* Behcet's disease, *MoAb* monoclonal antibody, *RA* rheumatoid arthritis, *SpA* spondyloarthritis, *SLE* systemic lupus erythematosus, *SSc* systemic sclerosis, *SjS* Sjogren's syndrome

open access journal, with no publication fees. It has an international Editorial Board and publishes four issues per year. People in countries around Mediterranean basin have been communicated with each other since ancient times and have a lot in common, including diet. The Journal aspires to bring rheumatologists of the Mediterranean basin closer, sharing their experience of rheumatic disorders with others. Brucella spondylitis and (Adamantiades)–Behcet's disease are two examples of rheumatic disorders that are of particular interest for Mediterranean countries [72].

ERE-EPERE cooperates closely with the patient association groups, such as the Hellenic League Against Rheumatism, and the Hellenic Federation of patient groups with rheumatic diseases, aiming at the constitution and implementation of a National action plan for rheumatic diseases and patients with rheumatic diseases. In Greece, the prevalence of rheumatic diseases in adults is 26.9% [73]. Rheumatoid arthritis (RA) has a prevalence of 0.3–0,67% [74, 75], ankylosing spondylitis 0.27–0.29% [75, 76] and symptomatic osteoarthritis 8.9% [75, 77]. Rheumatic diseases represent a major public health problem in Greece since they are the most common cause of chronic health condition (38.7%), long-term disability (47.2%), short-term disability (26.2%) and physician office visits (20.5%), while they rank second for the use of prescription (24.0%) or non-prescription drugs (17.7%) [78].

Since 2010, the period of financial crisis in Greece, many issues have arisen regarding the provision of services to patients with rheumatic diseases. Nevertheless, the Public Health Care System still fully covers the cost of biological disease-modifying antirheumatic drugs (bDMARDs). In Greece, an obligatory electronic prescription platform is operated by the National Organization for provision of Health Care Services (EDIKA). The EDIKA electronic prescription system has therapeutic protocols for inflammatory and autoimmune rheumatic diseases composed by ERE-EPERE according to EULAR recommendations. Only rheumatologists are authorized to use these protocols and prescribe biologicals. The electronic prescription system allows the prescription of bDMAD in a patient with spondyloarthropathy (SpA), only if two different non-steroidal antirheumatic drugs (NSAID) have been ineffective. Similarly, the system allows the prescription of bDMARD to a patient with RA or psoriatic arthritis (PsA) only if conventional synthetic DMARDs have been ineffective. For off-label use of a drug, a rheumatologist applies to the National Drug Organization of Greece to get permission. Based on the data originated from this system, biological DMARDs are used in 27% of RA and 36% of SpA [79], a frequency similar to or lower than those reported in other European countries.

Compliance with ethical standards

Conflict of interest Author LIS has received speaker honoraria from Actelion, Janssen, Novartis, Abbvie, Roche Sanofi- Aventis, Pfizer. Author Panagiotis Trontzas has received speaker honoraria from Menarini, UCB, Pfizer, Roche, Bristol-Meyers Squibb, Novartis, Pfizer, MSD.

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