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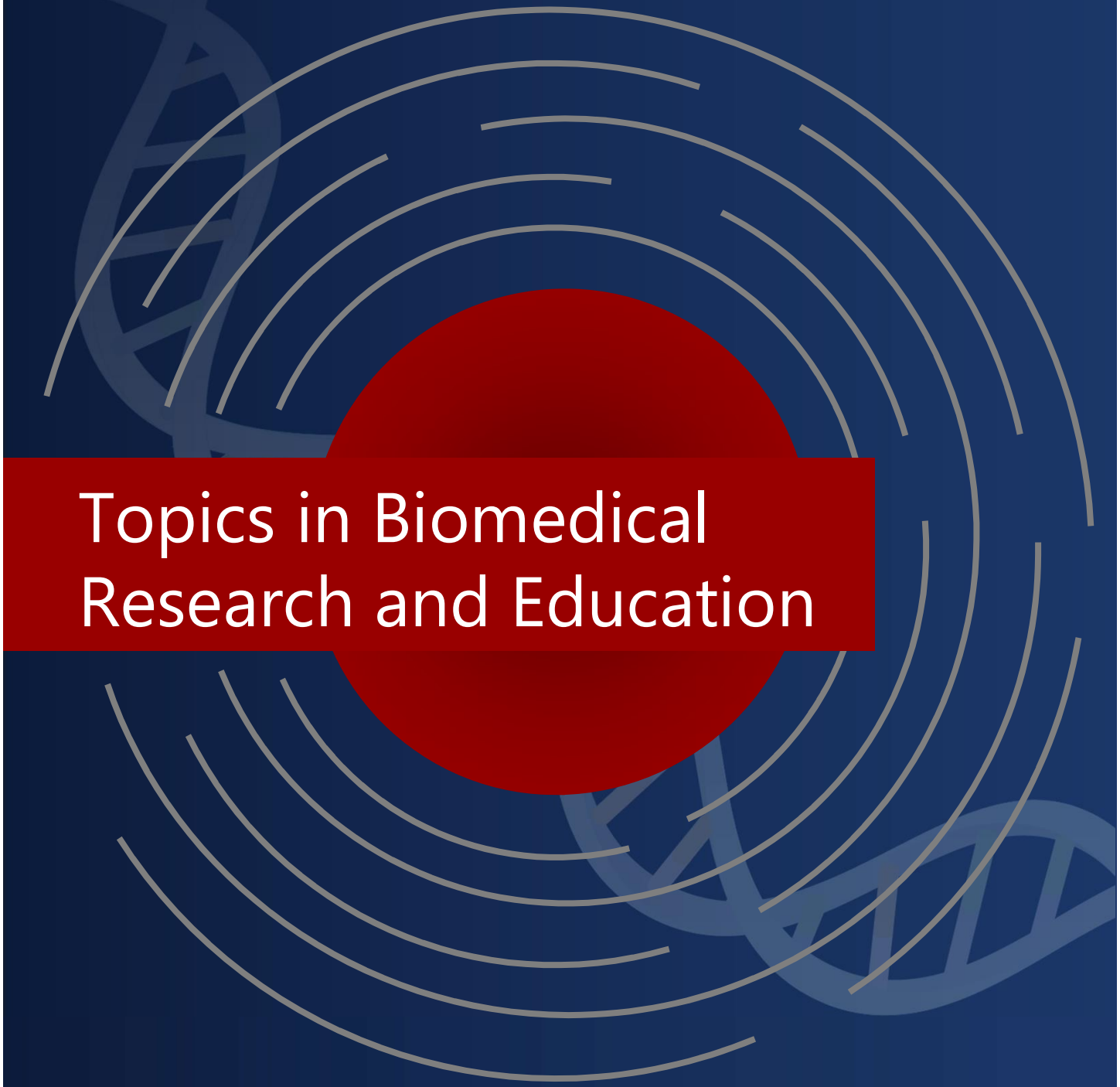

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Editorial

Revolutionizing Medical Writing with ChatGPT: A Game-Changer in Healthcare Communication

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In recent years, the field of medical writing has experienced a paradigm shift with the introduction of advanced language models like ChatGPT. This cutting-edge artificial intelligence (AI) technology has emerged as a game-changer in healthcare communication, offering unparalleled assistance to medical writers, researchers, and healthcare professionals alike. This article explores the pivotal role of ChatGPT in transforming medical writing, its applications, and the implications for the future of healthcare communication.

ChatGPT, developed by OpenAI, represents a breakthrough in natural language processing (NLP) technology. Trained on vast amounts of text data, ChatGPT is capable of generating human-like text responses based on input prompts. Its ability to understand and generate contextually relevant content has made it an invaluable tool in various domains, including healthcare. One of the key applications of ChatGPT in medical writing is assisting researchers and clinicians in drafting scientific manuscripts, grant proposals, and research reports. By generating concise and coherent text based on provided information, ChatGPT streamlines the writing process and helps researchers articulate their findings effectively. Furthermore, ChatGPT serves as a valuable resource for medical communication professionals tasked with creating educational materials, patient information leaflets, and healthcare content for the general public. Its ability to generate clear and accessible language ensures that complex medical information is conveyed accurately and comprehensibly to diverse audiences.

ChatGPT facilitates collaboration among healthcare professionals by providing real-time feedback and suggestions during writing tasks. Whether it's refining the language of a clinical study abstract or drafting a patient-friendly brochure, ChatGPT's interactive nature fosters collaboration and enhances the overall quality of written communication in healthcare. Moreover, ChatGPT significantly improves efficiency in medical writing by reducing the time and effort required for drafting and revising content. Its ability to generate text quickly and accurately allows writers to focus on higher-level tasks, such as data analysis and interpretation, thereby accelerating the pace of research and publication in the medical field.

While ChatGPT offers numerous benefits in medical writing, there are certain challenges and considerations to be addressed. One significant concern is ensuring the accuracy and reliability of generated content, particularly in the context of conveying medical information to patients or interpreting complex scientific concepts. Safeguards must be in place to verify the accuracy of information generated by ChatGPT and mitigate the risk of misinformation. Additionally, ethical considerations surrounding the use of AI in healthcare communication, such as data privacy, consent, and transparency, must be carefully navigated to maintain trust and accountability in medical writing practices.

Looking ahead, the integration of ChatGPT and other AI technologies into medical writing is poised to revolutionize healthcare communication further. Continued advancements in NLP and machine learning algorithms will enhance ChatGPT's capabilities, enabling it to provide personalized and contextually relevant writing assistance tailored to the needs of healthcare professionals and patients alike. Furthermore, the ongoing development of AI-powered virtual assistants and chatbots equipped with ChatGPT technology holds the potential to revolutionize patient education and engagement, providing on-demand access to

accurate and easily understandable medical information.

ChatGPT, a state-of-the-art language model developed by OpenAI, has garnered attention for its potential to revolutionize various fields, including medical writing. However, like any technology, ChatGPT comes with its own set of problems, limitations, and advantages, particularly when used by students and young scientists in the medical field.

The are various problems related to chatGPT and limitations to its applications for academic and scientific purposes.

One of the primary limitations of ChatGPT is its lack of specialized medical knowledge. While it excels at generating text based on general language patterns, it may struggle to accurately convey complex medical concepts or terminology without proper guidance. Due to its reliance on pre-existing text data, ChatGPT may generate responses that are contextually incorrect or misleading, especially when confronted with ambiguous or nuanced medical topics. This can pose a risk of misinterpretation, particularly for students and young scientists who may not have the expertise to discern inaccuracies.

The use of AI in medical writing raises ethical considerations, such as the potential for biased or inappropriate content generation. Students and young scientists must be mindful of these ethical implications and exercise caution when relying on ChatGPT for sensitive medical communication tasks. The use of artificial intelligence (AI), including language models like ChatGPT, in medical writing raises a myriad of ethical considerations that must be carefully examined and addressed. These considerations encompass various aspects, including accuracy, privacy, accountability, bias, and the potential impact on patient care and professional practice. Below is an analytical and detailed exploration of these ethical considerations:

AI-generated content, including medical writing, may not always be accurate or reliable. ChatGPT relies on pre-existing text data, which may contain errors or outdated information. As a result, there is a risk of misinformation or inaccuracies being propagated in medical literature and patient education materials. Inaccurate medical information can have serious consequences for patient care, leading to misdiagnosis, inappropriate treatment decisions, and potential harm to patients. Healthcare professionals have a moral obligation to ensure the accuracy and reliability of medical writing, whether generated by AI or authored by humans.

The use of AI in medical writing involves the processing of sensitive patient data and medical records. This raises concerns about data privacy and security, particularly regarding the protection of patient confidentiality and compliance with regulations such as the Health Insurance Portability and Accountability Act (HIPAA).

Ethical implications: Unauthorized access to patient data or breaches of confidentiality can compromise patient trust and confidentiality, undermining the ethical principles of beneficence and nonmaleficence. Healthcare organizations and AI developers must prioritize data security measures to safeguard patient privacy and uphold ethical standards.

The integration of artificial intelligence (AI) into medical writing has brought about significant advancements in efficiency and accessibility. However, there are several limitations in terms of accuracy and reliability that must be carefully considered. These limitations stem from the inherent characteristics of AI models, such as ChatGPT, as well as the complexities of medical language and knowledge. Below are detailed descriptions of the possible limitations in accuracy and reliability of AI in medical writing:

AI models like ChatGPT lack domain-specific knowledge, particularly in complex fields like medicine. While they excel at understanding and generating human-like text based on patterns in the data they were trained on, they may not possess the deep understanding of medical concepts and terminology necessary for accurate medical writing.

Medical writing often requires specialized knowledge of anatomy, physiology, pharmacology, and medical terminology, which may not be adequately captured by AI models. As a result, AI-

generated medical content may lack accuracy and relevance, particularly in contexts requiring precise medical terminology and scientific accuracy.

Inability to Interpret Context and Nuance:

AI models like ChatGPT may struggle to interpret context and nuance in medical writing, leading to inaccuracies or misinterpretations. Medical language is complex and context-dependent, with subtle nuances that can significantly impact the meaning of written content. For example, medical writing often involves interpreting patient symptoms, clinical findings, and treatment recommendations within the broader context of individual patient characteristics and medical history. AI models may not fully grasp these contextual nuances, leading to inaccuracies or misrepresentations in generated medical content.

AI models like ChatGPT are trained on vast amounts of text data, which may contain biases, errors, or outdated information. As a result, AI-generated medical content may inherit the limitations and biases present in the training data, leading to inaccuracies or misrepresentations in the generated text. For example, if the training data contains biased or outdated medical information, the AI model may inadvertently generate biased or inaccurate medical content. This can undermine the reliability and trustworthiness of AI-generated medical writing, particularly in critical healthcare contexts.

Medical writing often involves ambiguity and uncertainty, particularly in diagnostic and prognostic contexts where definitive answers may not exist. AI models like ChatGPT may struggle to handle ambiguity and uncertainty, leading to inaccuracies or misleading conclusions in generated medical content. For example, if a patient presents with vague symptoms that could indicate multiple possible diagnoses, AI-generated medical content may not accurately capture the uncertainty and complexity of the diagnostic process. This can lead to inaccuracies or over-simplifications in the generated text, potentially impacting clinical decision-making and patient care.

While AI models like ChatGPT excel at generating text based on patterns in the training data, they may have limited ability to generate original insights or creative solutions in medical writing. Medical writing often requires critical thinking, problem-solving, and synthesis of complex information, which may be challenging for AI models to replicate.

For example, if a medical writing task involves synthesizing disparate pieces of evidence to draw novel conclusions or recommendations, AI-generated content may lack the originality and depth of analysis necessary for reliable medical writing.

AI-generated content may lack transparency regarding its source and the criteria used for content generation. Users may not always be aware of the limitations or biases inherent in AI models like ChatGPT, leading to potential misunderstandings or misinterpretations of the generated content. Lack of transparency and accountability in AI-generated medical writing can erode trust in healthcare communication and undermine professional integrity. Healthcare professionals have a responsibility to critically evaluate AI-generated content and ensure transparency in its use, including disclosing any limitations or biases to patients and colleagues.

AI algorithms, including language models like ChatGPT, are susceptible to biases present in the data used for training. This can result in biased or discriminatory content generation, particularly in sensitive areas such as medical diagnosis and treatment recommendations.

Ethical implications: Bias in AI-generated medical writing can perpetuate disparities in healthcare access and quality, reinforcing existing social inequalities. Healthcare professionals must be vigilant in identifying and mitigating bias in AI-generated content to ensure fair and equitable healthcare communication.

The use of AI in medical writing may raise questions about professional autonomy and responsibility. Healthcare professionals must balance the benefits of AI assistance in medical writing with their ethical duty to exercise independent judgment and critical thinking in patient care and communication.

Ethical implications: Overreliance on AI-generated content without critical evaluation or independent verification can undermine professional autonomy and ethical decision-making in healthcare. Healthcare professionals have a responsibility to use AI as a tool rather than a substitute for their clinical judgment, maintaining ethical standards and patient-centered care. Ethical considerations surrounding the use of AI in medical writing are complex and multifaceted, encompassing issues of accuracy, privacy, accountability, bias, and professional responsibility. Healthcare professionals and AI developers must collaborate to address these ethical challenges, ensuring that AI technologies like ChatGPT are used responsibly and ethically to improve healthcare communication while upholding patient safety, privacy, and trust.

Despite its limitations, ChatGPT can serve as a valuable learning tool for students and young scientists by providing instant feedback and generating alternative perspectives on writing tasks. Its interactive nature fosters collaboration and encourages critical thinking skills in medical writing.

ChatGPT offers a time-saving advantage by expediting the writing process and reducing the need for extensive manual editing. This is particularly beneficial for students and young scientists who may be juggling multiple research projects or coursework assignments.

Compared to traditional writing resources or consultation services, ChatGPT is often more accessible and affordable for students and young scientists with limited budgets. Its user-friendly interface and availability on various platforms make it a convenient option for medical writing assistance.

Summarizing, while ChatGPT presents both challenges and opportunities for students and young scientists in medical writing, its potential to enhance learning, efficiency, and accessibility cannot be overlooked. However, it is essential for users to be aware of its limitations and exercise critical judgment when incorporating ChatGPT into their writing processes. By leveraging its advantages while navigating its pitfalls responsibly, students and young scientists can harness the power of ChatGPT to improve their skills and contribute to the advancement of medical research and communication.

Letter to the Editor

The mean value of god

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Abstract

Divine always exist inside communities since Prehistoric times and carves the evolution of health care. To discuss the value of god in relation to the history of medicine is a hard task and mathematics may provide a way to achieve it.

***Key words**: divine, health care, mathematics.*

Dear Editor,

For someone to discuss the value of god is a path between blasphemy and psychic anguish. It is an issue which should be approached with humility, seriousness but above all by holding a distance from realistic measurements. It is a value which can't and shouldn't be calculated. Modern mathematics sometimes however, enables us to speak by using a more secure language. Believers, church, atheists, pantheists, antitheists, agnostics, secular humanists and all, need medicine and desire the best health care possible. Religion through gods and priests has always been an instrument for coping and remediation, a way to reach the anticipated therapy, for some a panacea and foe some a tool for growth and self-cultivation. Priests understand the "attributes" of gods and religions serve the all-too-human needs of believing and belonging. Meanwhile health professionals also experience a closer relation to God who works with them for the benefit of the people, (1) while priests feel that patients always traverse disease with the presence of Holy Spirit and in cases of need God becomes Godly. (2) Is God though, a participant in the process of treatment, a key in the evolution of medicine?

In Prehistoric times, daemons possessed the brain to render the afflicted in an apoplectic state. Healer-priests tried hard through ecstasy, fumigation and trepanism to excommunicate the untouchable beings. Then, the first female gods, like Venus, primordial mother Gaia and Hera appeared and alongside theurgic medicine and pilgrimage were introduced in early societies. The philosophical thought tried to unveil the discovery of secrets for macrocosmos and of the construction of microcosmos, made effort to explain physiology and art and endeavored to set aside the gods and focus on nature and human. Soon, social needs and religion thirst gave birth to the Classical era gods and the creation of Panthea in the Italian and Hellenic peninsulas, promoting prayers, votive offerings and theurgic and priest medicine. Disease was defined as a punishment from the divine. Laypeople often believed that god punishes transgressions; however, their inferences about god's punishment motives remain unclear. (3) Spirituality enables the direct experience of connection between the individual and God, and can exist with or without an intermediary such as a religious institution. Via meditation or spiritual practice one may find god within oneself. (4) The Hippocratics had strived to sterilized medicine from the divine; the Alexandrian School through empiricism had de novo reduced the influence of gods. It was Christianity which

emerged soon after, to reconnect God with healing, until the fall of Rome from Odoacer's barbarians which limited the power of church. Soon though, during Medieval times in the west, church through Inquisition and pursuit of money succeeded to control science and subdue Kings of the Western World, while in the East, Christianity became the official religion of the Byzantine Empire (Eastern Roman Empire). Medicine and health care were closely guarded within clergy and monasteries. The church desired the power of knowledge to remain hidden within its walls and most scholars were somehow connected with priesthood or the church. (5) Participants strongly endorsed a loving, but not a punitive God. In addition, belief in a loving God corresponded with reports of less aggressive and more benevolent behavior. (6)

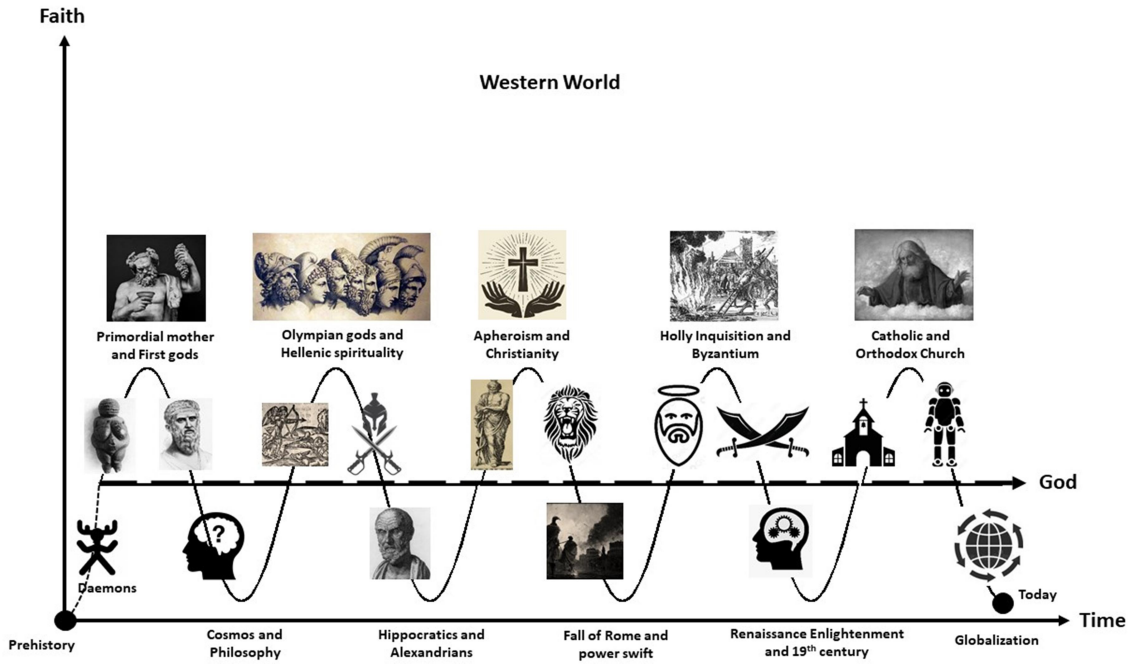

***Figure 1**. The wave patterns of influence of religious faith through time and its mean value depicting God among a series of peaks and dives. This pattern represents the known history of medicine of the Western World.*

Renaissance and Enlightenment restored art and science and medicine gradually returned to the commoners. Meanwhile numerous medics became saints. Two revolutions later, in the New World and in France, and two industrials, helped society to promote medicine and introduce a series of innovations. Modern medicine was born during 19th century. For the next two centuries, campaigns, patience, social work and philanthropy assisted both Catholic and Orthodox churches to co-exist with health care, while people still were praying to God even when visiting a health professional. Globalization transformed 21st century to an ever-changing world that led people towards changes, atheism or indifference for the divine. Although during late 19th and early 20th century social scientists predicted the demise of religion, religious traditions continue to play important roles in the lives of many individuals. (6-7)

An acute detachment from God had been many times attempted. This timeless wave pattern may be depicted in a diagram of two axes of faith and time [*Figure 1*]. And what emerges through faith during time? God is! Religious faith is founded on the principle that human life is sacred, a gift from the divine who generously offers great hopes of living, and bereavement support for grieving. (8) This mean value, being represented by a straight stable line, is the icon of the constant and continuous presence of god, portrayed with the help of mathematics. A close and strong interaction of health care and god is historically considered uninterrupted, even though peaks and dives do exist. Representations of God in art, literature and discourse, range from the highly anthropomorphic to anthropomorphized God, icons which concretely interpreted religious ideas from artists and philosophers importing their understanding of human affairs into their understanding of divine affairs. (9) As religious traditions worldwide differ in their cosmology, ontology, epistemology, aesthetic and ethics, and interact with specific cultures and various conceptual theories, they offer a diversity of health care concepts. (10)

This inseparable unbroken relationship is a result of this invisible but tangible mean value of the existence of god among our beliefs, even when this fact is not perceived by man or is isolated by the skeptics, or even suppressed by our way of life. This mean value can't be calculated in numbers, its significance should not be measured, we may even be lesser beings to discuss it, but as a continuum it affects us in such a many ways, one of them being the evolution of health care and our hopes for a swift remedy.

References

1. Simon EB, Hodges R, Schoonover-Shoffner K. Experiencing God in Nursing. J Christ Nurs 2020;37(2): 94-99.

2. Campbell RT. No One Is Alone: Remembering God Is Always With Us. J Pastoral Care Counsel 2021;75(1): 68-69.

3. Lee YE, Dunlea JP, Heiphetz L. Why Do God and Humans Punish? Perceived Retributivist Punishment Motives Hinge on Views of the True Self. Pers Soc Psychol Bull 2023: 1461672231160027.

4. Grossman T. The god within and the god without. Subst Use Misuse 2013;48(12): 1150-1156.

5. Jackson M. The Oxford Handbook of the History of Medicine. Oxford University Press, Oxford, 2011.

6. Shepperd JA, Pogge G, Lipsey NP, Miller WA, Webster GD. Belief in a Loving Versus Punitive God and Behavior. J Res Adolesc 2019;29(2): 390-401.

7. Turner L. Bioethics and religions: religious traditions and understandings of morality, health, and illness. Health Care Anal 2003;11(3): 181-197.

8. Irish TL. Christianity. Cancer Treat Res 2023;187: 181-202.

9. Shtulman A, Rattner M. Theories of God: Explanatory coherence in religious cognition. PLoS One 2018;13(12): e0209758.

10. Fowler MD. Religion, bioethics and nursing practice. Nurs Ethics 2009;16(4): 393-405.

Original Research Article (Brief Communication)

Resident doctors and medical specialty preferences in Greece: The example of Eastern Macedonia and Thrace

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Abstract

Aims: The present study is intended to describe the current status regarding the preferences of resident doctors evaluating real-world data from the Region of Eastern Macedonia - Thrace, and to evaluate the potential occupational and territorial discrepancies that may be observed.

Methods: The official website of the Region of Eastern Macedonia - Thrace was accessed on June 8, 2023, and December 28, 2023, for official data regarding the absolute numbers of occupied and vacant places per specialty and Regional Unit. Five medical specialties, namely Surgery, Orthopedics, Internal Medicine, Cardiology, and General Medicine, were explicitly assessed using paired data. Data regarding all other medical specialties had been additionally retrieved and used when appropriate. The Chi-square test was used to test goodness of fit.

Results: The distribution of occupied places by resident doctors per medical specialty (Surgery, Orthopedics, Internal Medicine, Cardiology, and General Medicine), and per Regional Unit is unequal at both June and December 2023 ($p < 0.001$). The ratio between occupied and offered places was comparable between June 2023 and December 2023 regarding all medical specialties and Regional Units. There are no vacant places for specialization in Pediatrics, Ophthalmology, Otolaryngology, and Psychiatry, Only scarce vacant places are offered for specialization in Obstetrics and Gynecology and Anesthesiology. On the contrary, there is no interest to specialize in Oncology, Pathology, and Occupational Medicine.

Conclusion: In conclusion, resident doctors are highly reluctant to specialize in General Medicine, while a heavy imbalance is observed between the Regional Units concerning the occupation of offered places for specialization. These observations indicate that incentives for specialization in General Medicine should be prioritized and imply the need for further investigation to evaluate the underlying causes and the potential focused solutions.

Introduction

The Region of Eastern Macedonia and Thrace is located in North-Eastern Greece [1], covers an area of 14,179 km2 [2], and is inhabited by 562,201 people [3]. Six civil hospitals are located within its district; two of them (University General Hospital of Alexandroupolis [4] and General Hospital of Didymoteicho [5]) are located in the Regional Unit of Evros, while the other four in the Regional Units of Rodopi (General Hospital of Komotini "Sismanogleio" [6]), Xanthi (General Hospital of Xanthi [7]), Kavala (General Hospital of Kavala [8]), and Drama (General Hospital of Drama [9]).

Greece is characterized by adequate, if not abundant, medical specialists. According to the latest available data for 2022, there are 6.4 physicians per 1,000 inhabitants [2]. Even though the whole medical population has increased from 2018 to 2022 by 0.3 per 1,000 inhabitants, the ratio of General Medicine specialists per total physicians has constantly waned during these years. In detail, General Medicine specialists represented 6.3% of the total physicians in 2022, while this percentage was 0.3% higher four years ago. These data imply that, while as much as one physician per 156 inhabitants exists, only 1 General Medicine specialist per 2,500 inhabitants is available. General Medicine specialists outnumber for short Obstetricians/Gynecologists and are comparable to Pediatricians. On the other

hand, specialists in medical and surgical group count about three- and eight-fold the number of General Medicine specialists [2].

General Medicine is under-resourced in all European countries, thus affecting recruitment [10]. Mariolis et al. explicitly stated that Greek medical students are highly reluctant to choose General Medicine as a career [11]. A recent Japanese study identified a large gap between the interest of medical students to specialize in General Medicine and motivation. In this study, the only two perceptions that had been positively associated with motivation to become a General Medicine specialist were the needs of society, and the lack of General Medicine educators. On the contrary, the fact that medical students experienced limited exposure to General Medicine during their curriculum discouraged them [12].

Interestingly, choosing General Medicine was positively correlated with "work-life balance" though negatively with "scientific orientation" [13]. However, General Medicine perceptions have substantially altered after the COVID-19 outbreak [14]. Lastly, artificial intelligence (AI) is expected to impact the role of General Medicine specialists significantly; the most favorable version of this revolutionary change focuses on the potential supporting role AI could contribute [15].

There are significant differences in the preferences of young doctors among medical specialties. Pehlivanidou et al. report that statistically significant correlations were verified between the field of specialization and scientific interest, waiting time for commencement of training, higher remuneration, and higher social status [16]. In addition to General Medicine, other specialties such as Anesthesiology are considered understaffed. To compensate for, the recent Law 4999 / 2022 introduced an additional allowance of 250 Euros per month to doctors who choose the specialty of Anesthesiology.

The present study is intended to describe the current status regarding the preferences of resident doctors evaluating real-world data from the Region of Eastern Macedonia - Thrace, Greece, and to evaluate the potential occupational and territorial discrepancies that may be observed.

Materials and Methods

The official website of the Region of Eastern Macedonia - Thrace was accessed on December 28, 2023, for official data regarding the absolute numbers of occupied and vacant places per specialty and Regional Unit [17]. These data were compared with those accessed on June 8, 2023, and used in a recent relevant publication in the local media [18]. Paired data (June 2023 vs. December 2023) were available for five medical specialties, namely Surgery, Orthopedics, Internal Medicine, Cardiology, and General Medicine.

Five medical specialties, namely Surgery, Orthopedics, Internal Medicine, Cardiology, and General Medicine, were explicitly assessed using paired data (June 2023 vs. December 2023). Moreover, data regarding all other medical specialties had been additionally retrieved and used when appropriate.

The Chi-square test was used to judge the goodness of fit between observed and expected results of categorical variables; if ≥ 25% of cells had expected values < 5, the Fisher's exact test was alternatively preferred. The online statistical tool available freely at https://www.quantitativeskills.com/sisa/statistics/fiveby2.htm was used for that purpose. Similarly, the online statistical tool available freely at https://home.ubalt.edu/ntsbarsh/Business-stat/ otherapplets/ PairedProp.htm was preferred for comparing between two dependent proportions. The level of statistical

significance was set to p = 0.05. All reported p-values are two-sided.

Results

The distribution of occupied places by resident doctors per medical specialty concerning Surgery, Orthopedics, Internal Medicine, Cardiology, and General Medicine is depicted in Table 1; this distribution is unequal at both time points, namely December 2023 ($\chi2 = 36.63$; df = 4; $p < 0.001$), and June 2023 ($\chi2 = 29.40$; df = 4; $p < 0.001$).

The ratio between occupied and offered places was comparable between June 2023 and December 2023 concerning Surgery (p = 0.328), Orthopedics (p = 1.000), Internal Medicine (p = 0.389), Cardiology (p = 0.338), and General Medicine (p = 0.258).

Specialty	*June 2023*	*December 2023*	*p-value*
Surgery	*38/64 (59%)*	*42/64 (66%)*	*0.328*
Orthopedics	*18/29 (62%)*	*18/29 (62%)*	*1.000*
Internal Medicine	*58/73 (79%)*	*55/73 (75%)*	*0.389*
Cardiology	*17/26 (65%)*	*21/28 (75%)*	*0.338*
General Medicine	*16/51 (31%)*	*12/49 (24%)*	*0.258*
Total	*147/243 (60%)*	*148/243 (61%)*	

Table 1. Occupancy of resident positions in the Regional Units of the Region of Eastern Macedonia and Thrace by specialty (comparison between June and December 2023)

The distribution of occupied places by resident doctors per Regional Unit concerning the medical specialties of Surgery, Orthopedics, Internal Medicine, Cardiology, and General Medicine is depicted in Table 2; this distribution is unequal at both time points, namely December 2023 ($\chi2 = 68.36$; df = 4; $p < 0.001$), and June 2023 ($\chi2 = 35.99$; df = 4; $p < 0.001$).

The ratio between occupied and offered places was comparable between June 2023 and December 2023 concerning the Regional Unit of Evros (p = 1.000), Rodopi (p = 0.248), Xanthi (p = 0.162), Kavala (p = 0.153), and Drama (p = 1.000).

There are currently no vacant places for specialization in several medical specialties, including Pediatrics (33 offered places in total), Opthalmology (17 offered places in total), Otolaryngology – ENT (12 offered places in total), and Psychiatry (8 offered places in total, all in the University General Hospital of Alexandroupolis). Moreover, there are only scarce vacant places for medical specialties such as Obstetrics and Gynecology (1 out of 18 offered places) and Anesthesiology (2 out of 22 offered places).

Regional Unit	*June 2023*	*December 2023*	*p-value*
Evros†	*70/94 (74%)*	*70/94 (74%)*	*1.000*
Rodopi	*19/30 (63%)*	*15/30 (50%)*	*0.248*
Xanthi	*9/35 (26%)*	*5/35 (14%)*	*0.162*
Kavala	*34/46 (74%)*	*43/46 (93%)*	*0.153*
Drama	*15/38 (39%)*	*15/38 (39%)*	*1.000*
Total	*147/243 (60%)*	*148/243 (61%)*	

† Data from both hospitals of Evros Regional Unit are included (Alexandroupoli and Didymoteicho).

Table 2. Coverage of offered positions for the specialties of Surgery, Orthopedics, Internal Medicine, Cardiology, and General Medicine per Regional Unit (comparison between June and December 2023)

There are many medical specialties for which plenty of vacant places are offered, including Hematology, Nephrology, Urology, Biopathology (Microbiology), and Radiology. Unfortunately, no interest has been demonstrated in Oncology, Pathology, and Occupational Medicine, for which all offered places are currently vacant.

Discussion

The present study describes the current status regarding the preferences of resident doctors evaluating official data from the Region of Eastern Macedonia – Thrace, Greece. We have demonstrated that only a minority of resident doctors prefers key

medical specialties such as General Medicine and that the occupation of places offered for medical specialization is unequally distributed among the Regional Units, rendering the hospitals of Evros and Kavala overcrowded compared to the other Regional Units.

It is questionable why only 24% of the places offered for the General Medicine specialty are currently occupied. Interestingly, this negative trend intensified during the last six months, as the corresponding percentage of coverage of the General Medicine positions offered in June 2023 was 31%. This evidence is in keeping with previous relevant reports [11] and, in combination with the observed diminishing ratio of General Medicine specialists per total physicians [2]. Whether this discrepancy can be attributed to parameters such as the quality of the training curriculum, the adequacy of instructors, and the prospects for employment remains to be investigated.

Resident doctors prefer the hospitals of the Regional Units of Evros and Kavala. Interestingly, while in June 2023, the total coverage of the offered positions for the specialties of Surgery, Orthopedics, Internal Medicine, Cardiology, and General Medicine was similar in both Regional Units (74%), in December 2023, the Kavala Hospital prevails (93%). On the contrary, the corresponding percentage for the Xanthi Hospital is meager (14%), revealing that the Xanthi Hospital is the least attractive for newcomers; the reasons for this utter discrepancy must be sought and addressed.

A limitation of the present study is that the official sources' data does not include resident doctors who may still be in service by extension of their initial contract. Nevertheless, there is no indication that the nature of this missing data is "missing not at random" (MNAR); thus, these data are believed to be indicative of the choices of young doctors regarding obtaining a specialty in the Region of Eastern Macedonia and Thrace.

Conclusions

In conclusion, resident doctors are highly reluctant to specialize in General Medicine, while a heavy imbalance is observed between the Regional Units concerning the occupation of offered places for specialization. These observations indicate that incentives for specialization in General Medicine should be prioritized and imply the need for further investigation to evaluate the underlying causes and the potential focused solutions.

References

1. Region of Eastern Macedonia and Thrace. https://www.pamth.gov.gr/index.php/en. Accessed on Jan, 2024.

2. Hellenic Statistical Authority. Greece in Figures; October - December 2023. https://www.statistics.gr/documents/20181/18074233/GreeceinFigures_2023Q4_EN.pdf/1e72c05a-0802-1b9d-aca0-dbcb5be5d355.

3. Hellenic Statistical Authority. Results of the Greek 2021 Census. https://elstat-outsourcers.statistics.gr/Census2022_GR.pdf. Accessed on Jan 4, 2024.

4. University General Hospital of Alexandroupolis. https://pgna.gr/. Accessed on Jan 4, 2024.

5. General Hospital of Didymoteicho. https://did-hosp.gr/. Accessed on Jan 4, 2024.

6. General Hospital of Komotini "Sismanogleio". http://www.komotini-hospital.gr / Accessed on Jan 4, 2024.

7. General Hospital of Xanthi. https://hosp-xanthi.gr/. Accessed on Jan 4, 2024.

8. General Hospital of Kavala. https://kavalahospital.gr/. Avessed on Jan 4, 2024.

9. General Hospital of Drama. https://www.dramahospital.gr/. Avessed on Jan 4, 2024.

10. Harding A, Vallersnes OM, Carelli F, Kiknadze N, Karppinen H, Simmenroth A. European standards for undergraduate medical education in general practice; a blueprint - for action. Educ Prim Care. 2023 Jan;34(1):2-6. doi: 10.1080 / 14739879.2022.2155997. Epub 2023 Feb 2. PMID: 36730558.

11. Mariolis A, Mihas C, Alevizos A, Gizlis V, Mariolis T, Marayiannis K, Tountas Y, Stefanadis C, Philalithis A, Creatsas G. General Practice as a career choice among undergraduate medical students in Greece. BMC Med Educ. 2007 Jun 1;7:15. doi: 10.1186/1472-6920-7-15. PMID: 17543106; PMCID: PMC1899489.

12. Nishikawa K, Ohta R, Sano C. Factors Associated with Motivation for General Medicine among Rural Medical Students: A Cross-Sectional Study. Int J Environ Res Public Health. 2022 Apr 22;19(9):5102. doi: 10.3390/ijerph19095102. PMID: 35564495; PMCID: PMC9100026.

13. Windak A, Frese T, Hummers E, Klemenc Ketis Z, Tsukagoshi S, Vilaseca J, Vinker S, Ungan M. Academic general practice/family medicine in times of COVID-19 - Perspective of WONCA Europe. Eur J Gen Pract. 2020 Dec;26(1):182-188. doi: 10.1080/13814788.2020.1855136. PMID: 33337939; PMCID: PMC7751383.

14. Kawamoto R, Ninomiya D, Kasai Y, Kusunoki T, Ohtsuka N, Kumagi T, Abe M. Factors associated with the choice of general medicine as a career among Japanese medical students. Med Educ Online. 2016 May 11;21:29448. doi: 10.3402/meo.v21.29448. PMID: 27172894; PMCID: PMC4865794.

15. Summerton N, Cansdale M. Artificial intelligence and diagnosis in general practice. Br J Gen Pract. 2019 Jul;69(684):324-325. doi: 10.3399/bjgp19X704165. PMID: 31249070; PMCID: PMC6592326.

16. Pehlivanidou A, Souliotis K, Kalafati M, Belali T, Tsamadias J, Giannaka F, Tountas J. Criteria that affect the selection of the field of medical specialization in Greece. Archives of Hellenic Medicine 2008; 25(2): 167-176.

17. Region of Eastern Macedonia and Thrace, Medical Specialties. https://www.pamth.gov.gr /index.php/el/politis/iatrikes-eidikotites. Accessed on Dec 28, 2023.

18. Papadopoulos V. Resident doctors in the Region of Eastern Macedonia and Thrace – evidence and concerns (Greek). Agonas (Xanthi). 2023 June https://agonas.gr/2023 /06/09/%ce %b5% ce%b9%ce%b4%ce%b9%ce%ba%ce %b5% cf%85 %cf%8c%ce%bc%ce%b5%ce%bd%ce%bf %ce %b9- %ce%b9%ce%b1%cf%84%cf%81 %ce%bf%c e%af-%cf%83%cf%84%ce%b7%ce%bd-%ce%b1-%c e%bc-%ce%b8-%cf%83%cf%84%ce%bf%ce%b9/. Accessed on Jan 4, 2024.

Review Article

Diagnosis and treatment delays during the covid -19 pandemic

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Abstract

Aim: This review aims at investigating the diagnosis and treatment delays caused by the shift of health services towards corona virus pandemic management.

Methods: An extended literature search using reliable databases and the Terms: coronavirus disease, diagnostic delays, screenings, resulted in 48 relevant records. Out of them 9 were excluded and the remaining 39 were included in the study, 28 Pubmed, Websites10 and 1 Book.

Results: During pandemic, cancer screening programs, especially for the second deadliest colorectal cancer, have been decreased from 28 to 100% in different countries, endangering delayed diagnosis and poor treatment and survival outcomes. Delays were reported in care of patients with chronic limb-threatening ischemia and a higher major limb amputation rate (2.6% to 32.2%). Skin cancers biopsies decreased by 18% and 27% for non-melanoma and melanoma cases respectively. A substantial decrease in the number of cutaneous squamous cell carcinoma and basal cell carcinoma diagnoses (-29% and -50% respectively), when compared to those expected from March to May 2020, was documented in a study, where the skin lesions behind the masks, kept on faces, remaining unnoticed. In the COVID-19 era, the national TB control program received less attention, leading to a worsening of the global TB epidemic. Additionally a new challenge for cholera control efforts in 2020 emerged, disrupting the hard-won years of progress against cholera in Africa, the continent bearing 54% of the global cholera burden. Moreover due to changes in routine health services, leprosy patients under multi- drug- therapy experienced drug shortages and limited access to medical care.

Conclusions: It is not an easy task to combine both preventive and emergency medicine under pandemic situation, but it deserves to try, by all means, to alleviate the potentially devastating consequences.

Key words*: coronavirus disease, diagnostic delays, screenings*

Introduction

An increase in diagnostic and treatment delays for a range of medical conditions were observed during (COVID-19) pandemic. The Coronavirus disease 2019 (COVID-19), caused by an RNA virus SARS-COV2 (severe acute respiratory syndrome coronavirus), was declared a pandemic by the World Health Organization (WHO) on March 11, 2020. By May 22, 2021, 3,437,545 deaths had been registered by WHO, confirming the disease's severity. By the summer of 2022 official death toll from SARS-CoV-2 infection was approximately 6 million. [1]

Globally, the number of new cases decreases by 58% during the 28-day period of 8 January to 4 February 2024 as compared to the previous 28-day period, with over 503 000 new cases reported. The number of new deaths decreased by 31% as compared to the previous 28-day period, with over 10 000 new fatalities reported. As of 4 February 2024, over 774 million confirmed cases and more than seven million deaths have been reported globally. [2]

During COVID-19 lockdowns (first from March to May 2020), healthcare systems had been challenged as they had to be focused on the care of patients with COVID-19, postponing many scheduled, especially preventive and non-urgent medical activities, for non-COVID patients. High risk individuals (patients and those with chronic diseases, at greater risk for complications from COVID-19) avoided themselves to visit healthcare services in fear of contracting the virus.

However all the other diseases did not vanish due to the emergence of corona virus and were not

at all drawn away, instead they were neglected, endangering increased morbidity and mortality.

Materials and Methods

An extended literature search in English was conducted, using the MESH terms: coronavirus disease, diagnostic delays, and screenings. The chosen data bases were PubMed, Google Scholar and the websites of valid organizations such as the World Health Organization. A total of 48 relevant records were studied. After processing the literature, 39 publications were considered as pertinent to our key words search criteria, and finally included in the article. *(Figure 1)*

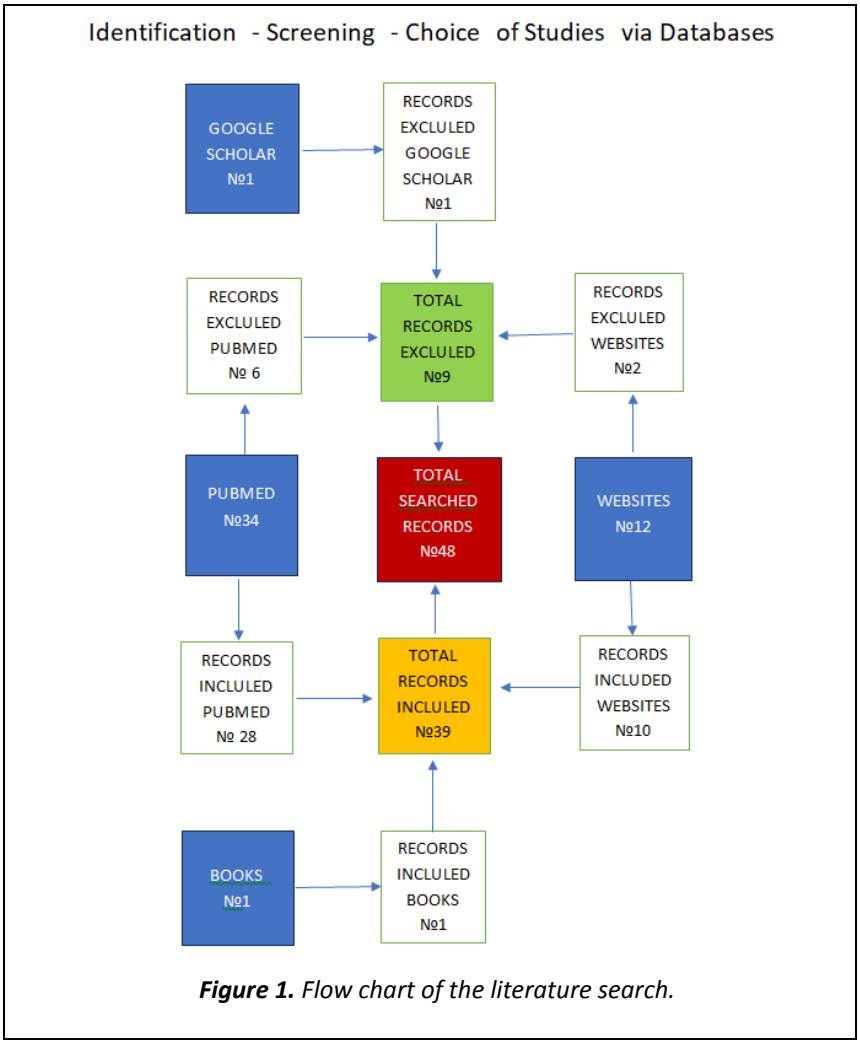

Figure 1. *Flow chart of the literature search.*

Results and Discussion

Cancer screening programs have been suspended in many countries, after the onset of the COVID-19 pandemic. Delays in diagnosis result in a more advanced stage of disease at presentation, requiring more complex care, higher costs and poorer response to both therapy and survival outcomes. [3, 4] Delays in any step may alter the outcome of the next step in the chain of cancer management. Interruptions in cancer screening led to reductions in the numbers of diagnosed cancer cases or their recurrence, ranging from 6% in Denmark to 52% in the United States. [5] Colorectal cancer is the third prevalent and second deadliest cancer in the world. So, early detection through screening is essential to reduce the mortality associated with this cancer. [6]

The decreased number of cancer screening programs has led to increased risk of a late diagnosis of colorectal cancer. [7, 8] In Italy, a decrease of more than 30% in colorectal cancer screening was observed between March 2020 and May 2021. [9] In the USA, a decrease in colonoscopies during 2020 was observed, especially among the population with a lower socioeconomic status. [10]

In general, colorectal cancer screening has decreased, from 28 to 100%, in different countries during pandemic period. Surveillance colonoscopy showed a decrease of 44.6 to 79%, prescription colonoscopy decreased 60 to 81%, and referrals to colonoscopy showed a 43% decline. However, emergency colonoscopy showed a 2 to 9% increase. The use of the fecal immunochemical test also declined although in specific areas used as a colonoscopy alternative. [11]

Treatment of colorectal cancer (surgery, chemotherapy, and long-term radiation therapy) has also decreased significantly or has been delayed, interrupted, or stopped. Only cases of emergency surgery and short-term radiotherapy increased. The waiting time for hospitalization and the length of hospital stay after surgery has been reported to be higher. Changes in patients' treatment plans and complete to partial cessation of hospitals activities-that provided treatment services-were reported. [12]

In a study reviewing strategies employed, and limb salvage outcomes, during the COVID-19 pandemic, delays were reported in care, affecting major limb amputations in patients with chronic limb-threatening ischemia. A higher major limb amputation rate (2.6% to 32.2%) during the pandemic surge was reported in 5 of 6 publications. Four of 6 studies also reported minor amputations; 3 of these demonstrated an increase in minor amputations (7% to 17.7%). Further data are required to improve strategies for treating this population to minimize negative outcomes. [13]

The problem of diagnostic delay of skin cancers during the COVID-19 pandemic has been recognized by several studies. Canadian authors compared the number of biopsies for skin cancers during the first 15 weeks in 2020 and during the same period in 2019. They found a decrease in the number of biopsies for non-melanoma skin cancer and melanoma of 18% and 27%, respectively. A multicenter study, performed in northern-central Italy, showed that the number of skin cancer diagnoses fell by 56.7% in weeks 11 to 20 of 2020, compared with the average number noted in the same periods of 2018 and 2019 . Furthermore, a single-center retrospective study in Italy demonstrated that the number of advanced skin cancers, surgically treated between May 18 and November 18, 2020, was significantly higher than in the same period in 2019. [14- 16]

Slotman E et al 2022 investigated the impact of the COVID-19 pandemic on trends in diagnoses of keratinocyte carcinoma (cutaneous squamous cell carcinoma (cSCC) and basal cell carcinoma (BCC) in renal transplant recipients and the magnitude of diagnostic delays in The Netherlands. During the COVID-19 pandemic, due to diagnostic delays, the number of cSCC and BCC diagnoses substantially decreased when compared to the number of diagnoses expected from March to May 2020 (cSCC -29%, BCC -50%), across all age groups, both sexes, and all regions in The Netherlands. An additional reason for the diagnostic delay was the fact that, the skin lesions behind the mask remained unnoticed, since masks were kept on faces during most examinations. [17] Two renal transplant recipients developed skin cancers during the COVID-19 pandemic, and the tumors were diagnosed with a significant delay, after having postponed their medical visits and examinations for skin cancer screenings. Moreover, during clinical visits the patients were commonly asked to keep their protective masks on, increasing the risk of overlooking their facial skin changes

These were two women 66 and 67-year-old, having received renal allografts from deceased donors in 2010 and 2014 respectively and under tacrolimus, mycophenolate mofetil, and steroid maintenance. In June 2020 and January 2020 both noticed erosion at her left infraocular area the first and a reddish squamous lesion on her right cheek the second. Both patients did not inform their family physicians about their skin changes, because they avoided all non-nephrological medical visits during the pandemic and postponed the dermatologic examination, to avoid social contact

as much as possible. Some months later they were both diagnosed with basal cell carcinoma the first and cutaneous squamous cell carcinoma the second. The additional reason for the diagnostic delay was the fact that they kept the masks on their faces during most examinations, with the skin lesions behind the mask consequently remaining unnoticed. [18]

During the pandemic, deaths attributed to cardiac events or strokes have increased more than deaths for any other non-COVID-19 diagnosis. [19, 20] Finlay et al 2023 examined the pandemic effects on health care systems and particularly the care deficits caused (or exacerbated) by health care delayed or foregone during the COVID-19 pandemic. These were deferred/delayed acute care for urgent conditions; the shift to virtual provision of outpatient care; shortages of drugs and devices and reduced access to diagnostic testing, cardiac rehabilitation, and homecare services. [21]

The same negative impact, of relocation of health services, was documented regarding the established and re- emerging infectious de diseases, potentially becoming more transmissible or more pathogenic. All-cause lower respiratory tract infection (LRTI) death in 2022 (57 per 100 000 children younger than 5 years) was 28% higher than in the pre-pandemic period. The higher incidence of all-cause LRTI admissions to hospital in 2022, compared with the pre-pandemic period, is partly due to ongoing COVID-19 admission to hospital and could worsen if other endemic respiratory pathogens revert to pre-pandemic incidence. [22]

In the COVID-19 era, the national TB control program received less attention, leading to a worsening of the global TB epidemic, though TB remains a major public health priority and is the second leading cause of mortality from infectious disease worldwide. TB, an ancient disease, remains one of the top 10 causes of human death. It is estimated that, approximately one quarter of the world's population is infected with latent Mycobacterium tuberculosis. [23, 24]

The lower incidence of admission to hospital for pediatric tuberculosis is consistent with the lower rates of tuberculosis notification in South Africa during the COVID-19 pandemic. [25]

Maryam Koupaei et al 2021, in their systematic search included 20 case reports and 11case series on TB/COVID-19 co-infection published from January 1, 2019 to February 24, 2021, from 18 countries, the majority being from India (N = 6) and China (N = 4). A total of 146 patients (114 men and 32 women), co-infected with TB and COVID-19, were enrolled. The mortality rate was increased to 13.0% and the rate of discharged patients was 87.0%.Since TB, due to prolonged disease incubation time, is usually diagnosed later than COVID-19, the severity of the co-infection worsens. [26]

Finn McQuaid et al 2022, investigated if disruptions in TB services due to the COVID-19 pandemic, may have exacerbated inequalities in detection rates by age or sex. They compared trends in age- and sex- disaggregated case notifications for all forms of new and relapse TB, reported to the World Health Organization for 45 high TB burden countries from 2013 to 2019, to trend predicted notifications to observed notifications in 2020 to estimate the number of people with TB likely to have missed or delayed diagnosis. Some setting-specific inequalities had been observed, indicating that TB notification rates amidst COVID-19 pandemic were lower than expected for adults (with a similar rate for both men and women), whilst for children and the elderly notification rates were also lower than expected, that‘s to say, a large number of individuals are likely suffering from untreated TB disease directly as a result of the pandemic. [27]

The COVID-19 pandemic posed a new challenge for cholera control efforts in 2020, having disrupted the hard-won years of progress against cholera in Africa, bearing 54% of the global cholera burden. [28] It also led to a decrease in health workforce and control efforts to reform the healthcare system and promote universal access to safe drinking water, sanitation, and hygiene infrastructure. [29] It is worth remembering, that cholera was never fully eradicated and since 1817, seven cholera pandemics have spread from Asia to much of the world, the seventh still present, having begun in Yemen in October 2016 and still

continuing to being currently the largest outbreak in the world, with 5000 new infections a day. [30, 31, 32]

Between 2015 and 2019, ten cholera outbreaks affected Sub-Saharan African countries: [33] The WHO and the Lebanese Ministry of Health announced on the 10 October 2022 the re-emergence of Cholera in Lebanon [34] As of December 19, 2021 and sudden increase in the number of cholera cases in April 2021 amidst COVID-19 pandemic, children aged 5 -14 appear to be hardest hit , the case fatality ratio reaching 3.3%, twice that associated with COVID-19.[35.]

In African countries with health care systems being overwhelmed by COVID-19, not only the fight against cholera was neglected, but moreover the pandemic negatively affected humanitarian programs to reduce cholera morbidity and mortality by 67% by the year 2023, targeting to eliminate cholera by 2030. [36]

Coronavirus disease 2019 has also limited the access of patients with Hansen's disease to care, due to changes in routine health services. [37] Along with COVID-19 spread, there was a reduction in leprosy diagnosis in the general population and children under 15 years-old, and also an increase in multi bacillary cases diagnosed, signaling a serious impact of the pandemic on leprosy control strategies in Brazil. [38] The pandemic has therefore created a backlog of undiagnosed Hansen's disease cases and a wave of delayed treatment initiation in Espírito Santo and across Brazil, equivalent to an entire years' worth of cases (approximately 400 in the state and 28 000 nationally). [39]

In a study by Barbara de Barros et al 2021, it was documented that, the measures implemented to control transmission of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2, in some areas led to medications shortages for leprosy, affecting individuals who need multidrug therapy (MDT) and long-term follow-up. Many patients were not able to travel to alternative referral centers, developed to counteract the negative impacts of the COVID-19 pandemic on leprosy diagnostic services, 80% percent reduced in endemic countries. [40]

The fight against COVID-19 pandemic became the center of the health systems worldwide, resulting in diagnostic delays and increased incidence of morbidity, according to the relevant literature from previous studies. Since large numbers of people are at particular risk of severe consequences from diagnosis and treatment delays, it is of great importance to implement policy options towards mitigating this risk. Clinicians, policymakers, and public health practitioners should be alert to the variety of presenting morbidity, from various agents during a pandemic, and not only from the pandemic itself.

Conclusions

When healthcare sources are turned away to cope with a devastating pandemic, challenges are raised by both old diseases re-emergence and neglected screening's negative impact. The findings reveal that the Covid-19 has marked serious diagnosis and treatment delays in a wide range of health issues. Of course it is not an easy task to combine both preventive and emergency medicine. The critical point is to maintain such an attitude, as to be able to do one thing without neglecting the other.

The author declares that there is no conflict of interest

References

1. World Health Organization WHO coronavirus (COVID-19) dashboard. Published June 13, 2022, Accessed June 14, 2022. https://covid19.who.int/

2. COVID-19 epidemiological update – 16 February 2024 (who.int)

3. Alkatout I, Biebl M, Momenimovahed Z, et al.. Has COVID-19 affected cancer screening programs? A systematic review. Front Oncol 2021; 11:675038 DOI: 10.3389/fonc.2021.675038

4. Patt D, Gordan L, Diaz M, et al.. Impact of COVID-19 on cancer care: how the pandemic is delaying cancer diagnosis and treatment for American seniors. JCO Clin Cancer Inform 2020; 4:1059–1071. DOI: 10.1200/CCI.20.00134

5. Hamilton AC, Donnelly DW, Loughrey MB, et al.. Inequalities in the decline and recovery of pathological cancer diagnoses during the first six months of the COVID-19 pandemic: a population-based study. Br J Cancer 2021; 125:798–805. PMCID: PMC8245662 DOI: 10.1038/s41416-021-01472-0

6. Lotfollahzadeh S, Recio-Boiles A, Cagir B. Colon Cancer.BookIn: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2023 Jan.2023 Jun 3.PMID: 29262132Bookshelf ID: NBK470380

7. Holland J, Cwintal M, Rigas G, et al. The impact of delaying colonoscopies during the COVID-19 pandemic on colorectal cancer detection and prevention. Surg Endosc. 2022; 15:1-10, DOI: 10.1007/s00464-022-09211-z

8. Boyle JM, Kuryba A, Blake HA, et al.. The impact of the first peak of the COVID-19 pandemic on colorectal cancer services in England and Wales: a national survey. Colorectal Dis. 2021; 23(7):1733-1744. DOI: 10.1111/codi.15622

9. Mantellini P, Falini P, Gorini G, et al. Rapporto sui ritardi accumulati dai programmi di screening Italiana in seguito alla pandemia da COVID 19: quarto rapporto al 31 Maggio 2021 [Report on the backlogged delays due to the COVID 19 pandemic. Fourth report at 31 May 2021], Published May 2021, Accessed June 14, 2022, https://www.osservatorionazionalescreening.it/sites/default/files/allegati/Report%20ripartenza%20IV.pdf

10. Fedewa SA, Star J, Bandi P, et al. Changes in cancer screening in the US during the COVID-19 pandemic. JAMA Netw Open, 2022;5(6):e2215490. doi: 10.1001/jamanetworkopen.2022.15490

11. Mazidimoradi A, Tiznobaik A, Salehiniya H, Impact of the COVID-19 Pandemic on Colorectal Cancer Screening: a Systematic Review J Gastrointest Cancer. 2022 Sep;53(3):730-744. doi: 10.1007/s12029-021-00679-x. Epub 2021 Aug 18.

12. Mazidimoradi A, Hadavandsiri F, Zohre Momenimovahed Z, Salehiniya H. Impact of the COVID-19 Pandemic on Colorectal Cancer Diagnosis and Treatment: a Systematic Review J Gastrointest Cancer. 2023 Mar; 54(1):171-187. DOI: 10.1007/s12029-021-00752-5

13. Miranda J, Chung J, Mills J. Influence of the COVID-19 pandemic on the management of chronic limb-threatening ischemia. Semin Vasc Surg. 2021 Sep; 34(3):89-95. doi: 10.1053/j.semvascsurg.2021.05.006. Epub 2021 Jul 16. DOI: 10.1053/j.semvascsurg.2021.05.006

14. Šitum M, Filipović N, Buljan M. A reminder of skin cancer during the covid-19 pandemic, Acta Dermatovenerol Croat. 2021 Apr; 291(1):58 PMID: 34477068

15. Gomolin T, Cline A, Handler MZ. The danger of neglecting melanoma during the COVID-19 pandemic, J Dermatolog Treat, 2020; 31(5): 444-445. DOI: 10.1080/09546634.2020.1762844

16. Villani A, Fabbrocini G, Scalvenzi M.The reduction in the detection of melanoma during the coronavirus disease 2019 (COVID-19) pandemic in a melanoma center of South Italy. J. Dermatol Treat. 2022 May; 33(3):1778. DOI: 10.1080/09546634.2020.1818674

17. Slotman E, Schreuder K, Nijsten TEC et al. The impact of the COVID-19 pandemic on keratinocyte carcinoma in The Netherlands: trends in diagnoses and magnitude of diagnostic delays. J Eur Acad Dermatol Venereol 2022; 36 (5): 680–687. PMID: 35092107 DOI: 10.1111/jdv.17976

18. Mokos M, Bašić-Jukić N, Diagnostic Delays for Non-melanoma Skin Cancers in Renal Transplant Recipients during the COVID-19 Pandemic: What is Hiding Behind the Mask? Acta Dermatovenerol Croat, 2021 Jul; 29(2):111-113.

19. Statistics Canada. Leading Causes of Death, Total Population (Age Standardization Using 2011 Population), Available at: 10.25318/1310080101-eng Accessed July 18, 2022.

20. Sidney S., Lee C., Liu J., Khan S.S., Lloyd-Jones D.M., Rana J.S. Age-adjusted mortality rates and age and risk-associated contributions to change in heart disease and stroke mortality, 2011-2019 and 2019-2020. JAMA Netw Open 2022;5 DOI: 10.1001/jamanetworkopen.2022.3872

21. McAlister FA, Parikh H, Lee DS, Wijeysundera H, Health Care Implications of the COVID-19 Pandemic for the Cardiovascular Practitioner. Can J Cardiol . 2023 Jun; 39(6):716-725. DOI: 10.1016/j.cjca.2022.11.014

22. Izu A, Nunes M, Solomon F, Baillie V, Erafin N, Verwey Cet al. All-cause and pathogen-

specific lower respiratory tract infection hospital admissions in children younger than 5 years during the COVID-19 pandemic (2020-22) compared with the pre-pandemic period (2015-19) in South Africa: an observational study Lancet Infect Dis. 2023 May 1;S1473-3099(23)00200-1. doi: 10.1016/S1473-3099(23)00200-1.

23. WHO. Global Tuberculosis Report (2021) (Accessed November 01, 2021).

24. Oga-Omenka C, Tseja-Akinrin A, Boffa J, Heitkamp P, Pai M, Zarowsky C. Commentary: Lessons from the COVID-19 global health response to inform TB case finding Healthc (Amst). 2021 Jun; 9(2):100487. doi: 10.1016/j.hjdsi.2020.100487. Epub 2020 Oct 22.

25. Lebina L, Dube M, Hlongwane K, et al. Trends in paediatric tuberculosis diagnoses in two South African hospitals early in the COVID-19 pandemic. S. Afr. Med. J. 2020; 110:1149–1150, DOI: 10.7196/SAMJ.2020.v110i12.15386

26. Koupaei M, Naimi A, Moafi N, et al, Clinical Characteristics, Diagnosis, Treatment, and Mortality Rate of TB/COVID-19 Coinfectetd Patients: A Systematic Review Front Med (Lausanne). 2021 Dec 1; 8:740593. doi: 10.3389/fmed.2021.740593. eCollection 2021

27. McQuaid CF, Henrion M, Burke R, MacPherson P, Nzawa-SokoR , Horton K, Inequalities in the impact of COVID-19-associated disruptions on tuberculosis diagnosis by age and sex in 45 high TB burden countries BMC Med. 2022 Nov 14;20(1):432. doi: 10.1186/s12916-022-02624-6.

28. Uwishema O, Okereke M, Onyeaka H, Mehediasan M, Donatus D et al, Threats and outbreaks of cholera in Africa amidst COVID-19 pandemic: a double burden on Africa's health systems.Trop Med Health. 2021 Nov 24; 49(1):93. doi: 10.1186/s41182-021-00376-2.

29. The World Bank. Physicians (Per 1000 People)-Nigeria (2021): https://www.data.worldbank.org/indicator/SH.MED.PHYS.ZS?locations=NG

30. Kuna A, Gajewsk M. Cholera - the new strike of an old foe. Int Marit Health 2017; 68(3):163-167. doi: 10.5603/IMH.2017.0029.

31. Kaper C, Morris J, Levine M, Clin Microbiol Rev 1995 Jan; 8(1):48-86. doi: 10.1128/CMR.8.1.48

32. World Health Organization (19 October 2022), Disease Outbreak News; Cholera - Lebanon. Available at: https://www.who.int/emergencies/disease-outbreak-news/item/2022-DON416

33. Centers for Disease Control and Prevention (CDC). Cholera - vibrio cholerae infection, Africa by Country, Atlanta (GA): CDC; 2021 [cited 2021 Apr 28]. Available from: https://www.cdc.gov/cholera/africa/locations.html Centers for Disease Control and Prevention (CDC) Cholera - vibrio cholerae infection. Africa by Country, Atlanta (GA): CDC; 2021

34. World Health Organization (19 October 2022), Disease Outbreak News; Cholera - Lebanon. Available at: https://www.who.int/emergencies/disease-outbreak-news/item/2022-DON416

35. NCDCb. COVID-19 Nigeria (2021). Available from: Accessed https://www.covid19.ncdc.gov.ng January 10, 2022)

36. James O. Global Task Force on Cholera Control: Use of Cholera Vaccine, Nigeria (2019). Available from: https://www.gtfcc.org/wp-content/uploads/2020/08/6th-gtfcc-working-group-on-ocv-meeting-2019-james-onah.pdf

37. Marques NP, Teixeira Marques NC, Medeiros Cardozo I, Martelli D, et al . Impact of the coronavirus disease 2019 on the diagnoses of Hansen's disease in Brazil, Rev Soc Bras Med Trop. 2021 Jul 23; 54: e02512021. doi: 10.1590/0037-8682-0251-2021. eCollection 2021.

38. Silva da Paz W, Souza M, Dos Santos Tavares D, Ribeiro de Jesus A, et al . Impact of the COVID-19 pandemic on the diagnosis of leprosy in Brazil: An ecological and population-based study Lancet Reg Health Am. 2022 May; 9:100181. doi: 10.1016/j.lana.2021.100181. Epub 2022 Jan 15.

39. Deps P, Collin SM, de Andrade V, Hansen's disease case detection in Brazil: a backlog of undiagnosed cases due to COVID-19 pandemic. J Eur Acad Dermatol Venereol 2022 Oct; 36(10):e754-e755 doi: 10.1111/jdv.18307 Epub 2022 Jun 14.

40. de Barros B, Lambert SM, Negera E, et al . An assessment of the reported impact of the COVID-19 pandemic on leprosy services using an online survey of practitioners in leprosy referral centres. Trans R Soc Trop Med Hyg 2021 Dec 2; 115(12):1456-1461, doi: 10.1093/trstmh/trab084

Short Review – Historical Article

Unveiling Ancient Wisdom: Understanding Cancer through the Eyes of Greek Physicians

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Introduction. Cancer is a disease known since ancient times. Notable figures such as *Hippocrates, Galen, Archigenes, Leonides, Polydeuces*, and the later *Aetius Amidinos* and *Paul of Aegina* recognized its existence and studied its nature, causes, and properties. They applied various methods for its treatment, ranging from simple dietary interventions to surgical operations to resect tumors. This article aims to explore the historical insights and knowledge of ancient Greek physicians regarding cancer, along with their early attempts to comprehend and treat it, which often intersected with philosophy, mysticism, and rudimentary medical practices

Etymology and name origin. The origin of the word "cancer" is credited to Hippocratic doctors, who used the term "*καρκίνος*" (Greek word for crab) in an attempt to better describe tumors, as they were thought to grip healthy organs just as a crab does with its claws *"επί των τιτθών είδομεν πολλάκις ακριβώς όγκον όμοιον καρκίνω ζώω. Καθάπερ γάρ επ' τούδε του πάθους αι φλέβες αποτεταμέναι του παρά φύσιν όγκου το σχήμα καρκίνω παραπλήσιον εργάζονται"*. (1)

In the writings of many ancient Greek physicians, this disease is called by a variety of names. It is known as cancer (ulcerated and nonhealing), carcinoma (nonulcerated), carcinoid ulcer, carcinomatous tumor, carcinosis, and carcinomatous disposition. Some of the first names used to describe cancer in ancient Greek medical literature are "*σκίρρος*" (scirrhus), "*έλκος*", and "*θήριον έλκος*". The term used by Hippocrates to describe the mass was ***onkos*** (*όγκος*) a name that today is given to the entire specialty dealing with cancer i.e. oncology. Galen states: *''Καρκίνωμά εστιν όγκος κακοήθης και περίσκληρος, ανέλκωτος ή ηλκωμένος. Είρηται δε από του ζώου καρκίνου"* meaning that carcinoma is a malignant and persistent tumor, with or without ulcer, which comes from the animal crab. (2, 3)

Humoral theory. The theory of the four humours was formulated in 400 BC in the philosophical treatise "*On the Nature of Man"* of the Hippocratic School. It was based on the theory of the four elements of Empedocles. Galen used it to formulate his theory of disease and influenced physicians and scientists until the Middle Ages. The 4 humors of the human body are blood, black bile, yellow bile, and phlegm.

The four humors are also linked to four organs of the body, each responsible for producing one specific humor. When these four humors are in equilibrium within the body, the state is termed *'eucrasia'* (*ευκρασία*), indicating a condition of health or homeostasis. Conversely, *'dyscrasia'* (*δυσκρασία*) characterizes a state in which the balance of humors is disrupted, leading to a disturbance in homeostasis. Dyscrasia can manifest in various diseases, including cancer. (4)

Etiology. In ancient Greek medicine, cancer was believed to arise from an

imbalance of bodily humors, specifically an excess of black bile and melancholic juice. According to this theory, melancholic juice, derived from black bile and produced in the liver, was normally eliminated by the spleen. When either the liver overproduced or the spleen malfunctioned, the melancholic juice accumulated in the veins, circulating throughout the bloodstream. (5) This accumulation could result in the development of cancer locally in a specific part of the body or, if the melancholic juice spread diffusely, lead to conditions such as elephantiasis. The theory of humors posited that an excess of black bile disrupted homeostasis, contributing to the onset of various diseases, including cancer

However, certain dietary habits were also thought to be responsible for the development of cancer. Foods such as lentils, snails, donkey meat, and salted fish were considered to be carcinogenic whereas foods such as spelt porridge, milk, pumpkin, cabbage, vetches, and poultry were thought to not only have protective properties but also prevent the disease recurrence or progression. Therefore, specific dietary suggestions were made by physicians at the time to achieve the prevention of cancer. (6)

Types of tumors. In general, many types of cancer were known to the ancient Greek physicians. Among these are skin, oropharynx, larynx, breast, and cervical cancer. According to texts by *Hippocrates, Galen, Aetius, Polydeuces, Archigenes*, and other physicians, cancers can be classified into certain categories. In particular, they can be divided into "*ακρόπαθους*", i.e. superficial, and "*κρυπτούς*", i.e. deep, "*ανέλκωτους*" and "*ελκωμένους*" depending on the absence or presence of an ulcer, and "*προ της ήβης*", i.e. hereditary, and "*μετά της ήβης*", i.e. acquired. (7, 8)

Characteristics of the tumor. Despite the lack of modern technological means, the acumen of the ancient Greek physicians allowed them to identify some of the most important properties of cancer. Among these, they recognized that cancer cells can infiltrate neighboring healthy tissues, leading to the spread of the disease. They called this property "*νομή*" or "*επινέμησις*" as it is presented in the following two extracts from texts by *Aetius*: *"διαβιβρώσκων αεί και διά βάθους υποκάμπτων, στήναι αμηχανεί",* and *Orivasios: "όσα δε καρκινώδη τρόπον συνίστανται, χαλεπώτερα και τα εκφυόμενα της βαλάνου χαλεπώτερα των της πόσθης, και τα εν τη έδρα τα βαθύτερα των προχειρότερων. Ώφθη δε πότε επινεμόμενα εκ της έδρας προς το αιδοίον της γυναικός".*

It is noteworthy that ancient Greek physicians recognized cancer's ability to metastasize either via lymphatics or via blood vessels, which they referred to as *'sympathy*.' They observed that, apart from the primary tumor focus, secondary foci (metastases) could develop in distant organs, often resembling the organ of origin (distant metastases). Additionally, they noted that lymph nodes, referred to as *'bullae*', surrounding cancer-affected organs, would frequently become hardened and malignant (lymphogenic metastases). One of the most commonly identified relationships was between breast cancer and axillary lymph nodes. These observations find confirmation in passages from *Soranos: "'πάσχουσα μέντοι η μήτρα προς συμπάθειαν στόμαχον άγειν και μήνιγγας έστι δε τις αυτή και προς τους μαστούς φυσική συμπάθεια", Leonides: "ώστε κατά συμπάθειαν εν ταις μασχάλαις βουβώνας επανίστασθαι κακοήθεις"* and *Hippocrates: "Γυναικί όταν υστέραι σκληραί γίνωνται και εις τα αιδοία εξίσχωσι και οι βουβώνες σκληροί γίνονται και κάδμα εν*

τοισοιν αιδοίοισιν ενή, καρκινούσθαι άρχεται".

The recurrence ("*ανάμνησις*") of cancer was also well-known to ancient Greek physicians. It was particularly common for cancer to recur after surgery. This is the reason why doctors of the time sought surgical resections with healthy margins (Ro), taking care not to leave the slightest bit of cancerous tissue behind. *Leonides: "παραιτούμενα επί τούτων τα δριμύτερα των φαράκων και τα λυπαίνοντα, εις ανάμνησιν γαρ ταύτα άγει το πάθος" and Paul of Aegina:"χειρουργούμενος χείρων διατίθεται"* spoke of the risk of cancer recurrence in their writings.

Symptoms. Ancient Greek doctors accurately described the main symptoms of cancer. They identified bitterness of the mouth, anorexia, indigestion, ulcers, lymphadenopathy (metastases), pain (local or reflective), and bleeding (especially in cases of uterine and bowel cancer). Often a hard visible and/or palpable mass was observed rapidly coalescing with the surrounding tissues (infiltration). Furthermore, it was perceived that the symptomatology was specific for every organ affected by cancer. Cachexia was considered a sign of advanced or even incurable disease as revealed by passages of Hippocrates, Galen, and other doctors. (8)

Diagnosis. Diagnosing cancer posed significant challenges and was a task reserved for seasoned physicians. The accuracy of the diagnosis held utmost importance, as it dictated the choice between pharmaceutical and surgical treatments. The differential diagnosis encompassed various conditions, including benign tumors, persistent and untreatable ulcers, gangrene, herpes, edema, and inflammatory foci.

To be classified as cancer, a mass had to exhibit specific characteristics—it needed to be firm and painless. Additionally, it should maintain a normal body temperature and not display heat, which could indicate inflammation. The final consideration leading to an unfavorable cancer diagnosis arose when conventional treatments proved ineffective in addressing the mass. (8)

Therapy. According to *Galen*, the treatment of cancer has two parts: *"αλλά και το θεραπεύειν διττον εστίν. Εν μεν το πάντα πράττειν ως υγιές αποφήναι το πεπονθός μέρος, έτερον δε το προνοείσθαι την αρμόττουσαν τω πάθει πρόνοιαν, όπερ έστι παρηγορείν τε και πραυνειν αυτό και μαλισθ' όταν η μεθ' ελκώσεως"*. In other words, the ancients sought either to treat the tumor completely by curing the patient or to soothe/relieve the patient's symptoms in the case of an incurable disease. In the first case, they used medicinal preparations of plants, herbs, and minerals in combination with a proper diet and nutrition. If these did not achieve their therapeutic goal and the cancer was considered operable, then surgery was performed to remove it. However, the sheer number of herbs and medicines used suggests that ancient physicians already knew how small the chances were for a cancer patient to survive the disease. (9)

According to Ancient Greek Medicine, the human body typically endeavors to expel excess melancholic humor that has gathered in the veins by directing blood flow towards the stomach, intestines, and skin surface. Ancient Greek physicians viewed processes such as menstrual bleeding and hemorrhoids as mechanisms for eliminating this excess melancholic humor, which they believed played a role in preventing the onset of cancer. Consequently, in addition to administering pharmaceutical preparations, doctors sought to facilitate the removal of excess melancholic humor from the patient's body to restore good health. (10)

They primarily pursued this goal through dietary interventions, advocating for the

consumption of foods such as milk, honey, and amaranth greens. Simultaneously, they employed a technique known as 'phlebotomy,' which involved bloodletting operations aimed at purging the body of melancholic humor by imitating the processes of menstruation and hemorrhoidal bleeding. Additionally, they employed purging methods, such as inducing vomiting and diarrhea, to cleanse the stomach and intestines of accumulated excess melancholic humor. (11)

Indicatively, some of the substances used by physicians in ancient Greece to treat cancer are the following: *Asclipias* (ivy) for cancer of the uterus and breast, *Acalypha, Aristolochia, Draconia, Elatirion (fig), Epithymium, Helleborus, Erica* fruit for oral carcinomas, *Cadmium, Lithargy* for breast and uterine carcinomas, Lead, *Strychnous* porridge, and *Chalcitis*. Particular mention needs to be made of *draconia "ταύτης ο καρπός ισχυρότερος ου φύλλων μόνον αλλά και της ρίζης εστί ώστε και καρκίνους και πολύποδας εκτήκειν πεπίστευται",* the "*καρκίνιους ποταμούς*", which was used by the majority of ancient Greek physicians, and "χαλκίτις" which was considered a very powerful medicine that burned cancer like fire. Of the above, others were derived from plants such as *draconia* and *erica* fruit, and others were derived from metals such as lead and litharge. These medicines were usually used together with other preparations such as honey and milk which had recognized nutritional and medicinal value. (8)

Surgery. When the various therapeutic methods failed, physicians resorted to surgical methods. The surgical treatment used was the so-called 'cut and burn' operation ("*δια τομής και καύσεως*"). However, this operation was not considered to be indicated and permissible in every case. On the contrary, it was reserved exclusively for so-called "*ακρόπαθους*" (or superficial) cancers and was prohibited for "*κρυπτούς*" (or deep) cancers. The experience of doctors at the time had shown that patients who underwent surgery for deep cancers died faster than those who did not have surgery. In fact, Galen reports that surgery for deep cancers led to their exacerbation, ultimately resulting in the patient dying unable to cope with post-operative stress. However, even for superficial cancers, surgical treatment was not universally accepted. Galen mentions that many notable doctors of the time would only proceed with surgery if the cancer was advanced. Paul of Aegina, one of the greatest physicians of the time, performed multiple surgeries on terminal tumors, both evolved and inoperable because he believed that this would be optimal for the patient. It is also noteworthy that doctors of the time recognized the importance of complete and radical resection of the neoplasm for the effectiveness of treatment. This can be seen from the following passages from *Galenos'* writings: "*Περικόψας δε πάντα ακριβώς το πεπονθός, ως μηδεμίαν απολείπεσθαι ρίζαν",*"and "*άμα δ' εν τοις τοιούτοις συστώσι μορίοις α μετά των ριζών εκτεμείν και καύσαι δυνατόν εστίν".* (12, 13, 14)

Regarding the methods used for cancer surgery in ancient Greece, Leo*nides' technique of mastectomy* has survived. According to this technique, the surgeon would divide the healthy part of the breast from the affected part and then use fire to cauterize the wound until the bleeding stopped. He would then repeat the same tactic of cutting and burning in order to effectively remove the lesion, achieving the 'perfect cut' where the remaining part of the breast would be free of any cancerous focus. (15, 16)

Immediately after the operation, the primary concern of the physician is the care of the wound and the recovery of the patient from the stressful stimulus of surgery. The wound was covered/tied with

dressings/patches which were moistened with water. Milk and honey were used to soothe and heal the burn wounds. The sick person was placed in a warm room as it was thought that cold weather could lead to a relapse of the disease. On the 2nd or 3rd postoperative day, the doctor would wash the wound with plenty of water, and cover it with a small amount of honey, vine leaves, or other plants before re-bandaging it. This is repeated until the scabs fall off. No drugs were used as it was thought that they would lead to the recurrence of the cancer. Instead, the only drugs the patient received were human or donkey milk. After the surgery, the patient had to follow a specific diet and exercise program to feel better. This included rehydration, abstaining from alcohol and cold drinks, and avoiding foods that cause indigestion. (7, 17)

Conclusion. It is surprising that in those ancient times, physicians had identified the role of stressful stimuli in the development of cancer. It is also noteworthy that, as can be deduced from Galen's writings, this brilliant physician believed that cancer does not appear overnight but is the result of the long-term effect of melancholic juice. He therefore recommended avoiding all habits that increase the body's bad juices.

It was also believed that diet also plays a decisive role in the onset of cancer, something that modern science only began to accept in the mid-20th century AD. 18 centuries ago, however, Galen prevented people from eating foods that caused an increase in melancholic juice and suggested people suffering from cancer were also cautious with their diet.

Hippocrates knew that cancer is a disease that progresses in stages (hence the current staging). They bequeathed to modern physicians a rich terminology about cancer. They made suggestions on the prognosis of the disease by observing the course of their patients and carried out the first clinical trials. At the same time, the Ancient Greek physicians pioneered in proposing surgical treatment of cancer by radical and complete resection of the tumor.

References

1. GALEN, A Method of Medicine to Glaucon, Book B, ch. iv, G.C.Kuehn, vol. XI, p. 140-141.
2. Hajdu, Steven I. “Pathfinders in oncology from ancient times to the end of the Middle Ages.” Cancer vol. 122,11 (2016): 1638-46. doi:10.1002/cncr.29955
3. Salaverry, Oswaldo. “La etimología del cáncer y su curioso curso histórico” [Cancer etymology and its historical curious course]. Revista peruana de medicina experimental y salud publica vol. 30,1 (2013): 137-41. doi:10.1590/s1726-46342013000100026
4. Hippocrates. The Genuine Works of Hippocrates: Translated From the Greek With a Preliminary Discourse and Annotations by Francis Adams. 2 vols. London, United Kingdom: Sydenham Society; 1849.
5. Wolff J. Die Lehre von der Krebskrankheit von den ältesten Zeiten bis zur Gegenwart. Jena: Gustav Fischer, 1907.
6. Karpozilos A, Pavlidis N. The treatment of cancer in Greek antiquity. Eur J Cancer 2004;40:2033–40.
7. Moulin D. A short history of breast cancer. Boston: Martinus Nijhoff Publ; 1983
8. Kouzis A. Cancer among ancient Greek physicians. Athens, Konstantinidis 1902 [in Greek].
9. Retsas, Spyros. "On the antiquity of cancer; from Hippocrates to Galen." Palaeo-oncology: the antiquity of cancer. Farrand Press, London, 1986. 41-53.

10. Park R. An epitome of the history of carcinoma. Bull Johns Hopkins Hosp. 1903: 14: 288–294.
11. Hajdu SI. A note from history: landmarks in history of cancer, part 1. Cancer. 2011; 117: 1097-1102.
12. Adams F. The seven books of Paulus Aegineta. Vol. 2. London: Sydenham Society; 1844. p. 332.
13. Graney, M.J., Graney, C.M. Colorectal surgery from antiquity to the modern era. Dis Colon Rectum 23, 432–441 (1980). https://doi.org/10.1007/BF02586797
14. Karamanou M, Diamantis A, Androutsos G. The first cases of cancer in antiquity. J BUON 2008;13:601-608.
15. Ekmektzoglou, Konstantinos A et al. "Breast cancer: from the earliest times through to the end of the 20th century." European journal of obstetrics, gynecology, and reproductive biology vol. 145,1 (2009): 3-8. doi:10.1016/j.ejogrb.2009.03.017
16. Papavramidou, Niki et al. "Ancient Greek and Greco-Roman methods in modern surgical treatment of cancer." Annals of surgical oncology vol. 17,3 (2010): 665-7. doi:10.1245/s10434-009-0886-6
17. Weiss L. Early concepts of cancer. Cancer Metastasis Rev 2000;19:205-217.