

SPECIAL ARTICLE ΕΙΔΙΚΟ ΑΡΘΡΟ

From Hippocrates to George N. Papanicolaou A medical journey in time

It is a truism that Ancient Greece has influenced the Western World, indeed the whole world, in more ways than one. The contributions of the ancient Greeks across the entire spectrum of human activity, be it science, technology, art or literature, cannot be overestimated. This essay focuses on the *métier* that the medical doctor of today serves daily through teaching, laboratory and clinical research or practice; namely, medicine and the related sciences. This, inevitably, will bring to mind the Hippocratic Oath, our constitutional Charter of Ethics, attributed to Hippocrates, the most outstanding figure in the history of Western medicine. It will also remind us of the *Corpus Hippocraticum*, a collection of more than sixty medical treatises carried down to us from antiquity under the name of Hippocrates, but most probably produced largely by his disciples and followers between the 5th and 4th centuries B.C. This *Corpus* laid the foundations for the scientific analysis, development and growth of medicine as it is known today. Modern Greece, however, may also in her own right lay claim to being a true heir to the legacy left by Hippocrates, a claim most admirably exemplified in the person of Dr George Papanicolaou, the renowned 19th century Greek pioneer in cytology and early cancer detection, and inventor of the “Pap smear”. This essay is itself a short journey into the past, drawing special attention to certain important features of the lasting achievements of both Hippocrates and Papanicolaou and the impact they have had on the history of medicine, and identifying a number of questions concerning the ethics of modern medical research.

1. THE ERA OF HIPPOCRATES AND THE HIPPOCRATIC TRADITION

Hippocrates was born on the island of Cos, off the southeast coast of Asia Minor, present-day Turkey, around the year 460 B.C. He is said to have died some 90 years later, around 370 B.C., in Larissa, the capital city of Thessaly. He belonged to the Asclepiadae, a school of physicians boasting to be descendants of Asclepius, the mythical god of healing whose temples, the Asclepieia, scattered all over Greece, fulfilled various of the requirements of institutions created for healing and provided medical training. According to an ancient biographical tradition, Hippocrates, who traced his descent from the god Asclepius, but also from the mythical hero Heracles, was taught medicine by his father Heracleides and the Thracian gymnastics trainer Herodicus. His other teachers included the sophists Gorgias and Prodicus, and Democritus, the famous Thracian philosopher who, as we all know, is credited with putting

forward the atomic theory of the universe. Around 430 B.C., Hippocrates founded a medical school, in effect a healing center, on his native island of Cos; its ruins can still be seen standing there, one of the main attractions of the island today. Hippocrates had many pupils, including his son-in-law Polybus, all of whom, although themselves maintaining a lower profile, were instrumental in passing on ably the Hippocratic tradition to their successors.

The name of Hippocrates has always been connected with the *Corpus Hippocraticum*, the surviving body of treatises expounding his doctrines on various medical issues. It must be admitted, however, that even in antiquity the authorship of these works and the nature of his own contributions to medicine were the subject of speculation. Is it possible to ascribe with certainty any individual treatise to Hippocrates himself? The answer is, no. The consensus of opinion among scholars is that while the *Corpus Hippocraticum* is traditionally attributed

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Από τον Ιπποκράτη
στο Γεώργιο Ν. Παπανικολάου:
Ένα «ιατρικό ταξίδι» στο χρόνο

Περίληψη στο τέλος του άρθρου

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BASIC GLOSSARY

ASCLEPIADAE: *A school of physicians boasting to be descendants of Asclepius*

ASCLEPIUS: *The mythical God of healing*

ASCLEPIEIA: *Temples devoted to Asclepius*

CORPUS HIPPOCRATICUM: *A collection of more than sixty medical treatises*

DEMOCRITUS: *A famous Greek philosopher credited with inventing the atomic theory*

EMPEDOCLES: *A 5th century B.C. Greek philosopher from Sicily*

GALEN: *A Greek physician*

GORGAS: *A Greek sophist*

HIPPOCRATES: *An ancient Greek physician of the age of Pericles, considered one of the outstanding figures in the history of medicine*

THE HIPPOCRATIC OATH: *One of the oldest binding documents, perhaps the most widely known of Greek medical texts*

PRODICUS: *A Greek sophist*

THE FOUR ELEMENTS THEORY: *Earth, water, fire, air*

THE HIPPOCRATIC THEORY OF FOUR HUMORS: *Blood, phlegm, yellow bile and black bile each of which correlates with one of the four primary elements of Empedocles*

PHYSIS: *A faculty innate to the body*

PNEUMA: *The breath or vital force*

to Hippocrates, it is doubtful whether any of its sections preserves Hippocrates' own original text. Differences in content and style among the individual treatises strongly suggest that the works included in the *Corpus* were written by as many as 20 different authors and were compiled largely in the 5th and 4th centuries B.C. Such problems of authorship notwithstanding, modern scholars of Hippocrates are unanimous in attributing to him what can be securely surmised from existing sources, the *Corpus* itself, that is, and the commentaries written on Hippocrates by later commentators, including, *par excellence*, Galen in the second century B.C. It is important to concentrate on some of the most significant features of Hippocrates' theories.

Firstly, the Hippocratic Oath, probably the most famous document of the *Corpus* and one of the oldest medical documents on the ethics of medical practice; it is a document still held in veneration by doctors today, whether in the form in which it came to us from antiquity, or in its

modern derivatives. In about 40 short lines the Oath encapsulates the ethos, that is to say the characteristic spirit of Greek classical medicine, indeed the ethos of ancient Greek thought as a whole. In the words of W.H.S. Jones, an expert on Hippocrates: "*The little document is [...] a priceless possession. Here we have committed to writing those noble rules, loyal obedience to which has raised the calling of a physician to be the highest of all the professions. [...] That medicine is an art, a difficult art, and one inseparable from the highest morality and the love of humanity, is the great lesson to us of the Hippocratic writings. The true physician is "vir bonus samandi peritus" ("a virtuous man skillful in healing").*"

Secondly, the Hippocratic theory of four humors: Throughout antiquity, there was a keen debate over what were the primary constituents, or elements, of the physical world, the elemental substances into which everything in the world could be resolved. In this connection, Empedocles, a 5th century B.C. Greek philosopher from Sicily, named four elements, earth, water, fire, and air, which were sometimes analyzed, respectively, in terms of dry, wet, hot, and cold. In turn, Hippocrates put forward the four-humor theory, according to which the human body is composed of four humors, or fluid substances, namely blood, phlegm, yellow bile and black bile, each of which correlates with one of the four primary elements of Empedocles. According to Hippocrates, the perfect balance of primary elements and fluids meant health, whereas their imbalance meant illness. He taught that the *physis*, or physical constitution, is a faculty innate in the body which can re-balance the humors if they are disturbed and thus restore the body to its prior state of health. The *physis* is propelled by the *pneuma*, the breath or vital force, which when combined with the innate heat is suffused from the lungs via the heart into the blood; and in this way life is sustained. Because for Hippocrates the human body functioned as a unified organism, and therefore needed to be treated in health or disease as one coherent, integrated whole, he must be considered the first advocate of the holistic understanding of the human organism.

Central to the teaching of Hippocrates was the notion of clinical diagnosis, one more word adopted in English from the Greek, meaning, literally, "perceiving through, discerning thoroughly". Diagnosis, in Hippocrates' teaching, was the careful, regular recording of various physical symptoms, such as complexion, pulse, fever, pains, sounds of breathing, body odor, movements, excretions, etc., so that the physician, by looking beneath surface appearances, could arrive at a sure and certain knowledge or conclusion as to their root causes. Such an inquiry called for the physician to disengage himself from all forms of

superstition, claiming that diseases were caused naturally and were not inflicted as punishment by the gods; medical treatment, therefore, should be applied by natural means and practical methods provided by reasonable and controlled experience only, without recourse to the divine. It was in this way that Hippocrates, followed by his disciples, transformed the art of medicine into a science, since, for the first time in human history, medicine was freed from the shackles of magic, superstition and the supernatural.

2. THE ODYSSEY OF GEORGE PAPANICOLAOU

Moving from the 5th and 4th centuries B.C., Hippocrates' era, to the 19th and 20th centuries of the contemporary era, Papanicolaou's age, Dr George Nicholas Papanicolaou was born on the island of Euboia, the second largest Greek island, in 1883, and died 79 years later, in 1962, in Miami, Florida. He received his medical degree from Athens University in 1904, and was called into Greek military service for two years, after which, in early 1907, he left for Jena, Germany, to begin his postgraduate studies under the tutelage of an eminent Darwinian, Professor Ernst Haeckel. After a short stay in Jena and Freiburg, he moved to Munich where he received his PhD in Zoology in 1910. It should not pass unnoticed that Papanicolaou, when young, fell under the spell of the philosophy of Kant and Nietzsche, and wrote papers on matters philosophical for an Athenian literary quarterly. In October 1913 Dr Papanicolaou and his wife Andromachi (Mary) arrived in New York where he joined the Cornell Medical School in September 1914 and began his research on sex determination and sex control in guinea pigs. The results were first published in *Science*, in 1915 and in the *American Journal of Anatomy*, in 1917. Three years later, in 1920, he began studying human vaginal cytology, using a "special case", that of his own wife Mary, which he continued to study for the next 21 years. In 1928, Papanicolaou first reported that uterine cancer could be diagnosed by means of a vaginal smear, but the importance of his work was not recognized until the publication, in 1941 and 1943, of two papers co-authored with his colleague Professor Herbal Traut and entitled, respectively, "The diagnostic value of vaginal smears in carcinoma of the uterus", and "Diagnosis of uterine cancer by the vaginal smear". In 1954, the publication of his Atlas of exfoliative cytology created the foundation of the modern medical specialty of cytopathology.

Dr Papanicolaou's outstanding contributions to cancer research won him the distinction of the prestigious Albert Lasker Clinical Medical Research Award for 1950, the American equivalent to the Nobel Prize in Physiology or

Medicine. His achievements are best summed up in the Award's wording which is quoted in full:

"George Papanicolaou is presented a Lasker Award for 1950 for his outstanding contributions to research related to cancer, a prominent cause of death and disability. His discovery is of a method of defining, among the cells exfoliated from tissue surfaces, those which reveal the changes characteristic of specific biological processes. Among these is the one we know as neoplastic disease. The importance of exfoliative cytology has been amply established as providing a relatively quick, easy and accurate test of at least partial diagnostic value for cancer of some types. Less obvious, but equally meaningful, are certain research suggestions capable of being drawn from these data. It seems not impossible that repeated observations using this cytological method will reveal the earliest changes of cancer. These changes, when regularly demonstrable, may provide an index of the effectiveness of procedures designed to restore neoplastic cells to normal. This makes feasible for the first time a study of cancer prevention in human beings. The examination of desquamated cells provides a method for measuring precisely a variety of biological phenomena, particularly those resulting from hormone activity. By the application of the measure, new information unavailable by any other means has come to hand. From the evidence, more may be expected in the future. The work recognized by this Award provides once more evidence that knowledge tends to increase almost linearly with the availability of quantitative techniques. They are the extension of the perceptive mechanism of the investigator. Without perception, concept is difficult, if not impossible".

Dr Papanicolaou, also known as Dr Pap, was a born researcher who devoted his entire life to honoring the Hippocratic Oath which he had pledged as a young doctor receiving his medical degree in Athens University, swearing that he would practice his profession with conscience and dignity, and maintain the utmost respect for human life. His case can well serve as a paradigm of how clinical research can relate to one of the most fundamental concerns in moral theory; namely, when and to what extent is it ethically acceptable for investigators to expose a group of individuals, however small, sometimes very sick, to the risk of harm for the benefit of others? Perhaps the most prominent ethical documents for clinical research, the Nuremberg Code, delivered on August 19, 1947, resulting from the court's judgment on atrocities committed by Nazi doctors during World War II, and its sequels and after-products, the Declaration of Geneva in 1948, and the Declaration of Helsinki in 1964, were all conceived as a

modernized version of the ancient Hippocratic Oath and, more important, as a Charter of Medicine to govern the state of medical ethics in general and throughout the world.

3. EPILOGUE

All of these documents were designed to forestall any possible activity, overtly or covertly involving clinical research, without securing the informed consent of the subject or his or her representative. Beyond and above all this, what stands out as the paramount duty of the

physician is, in the words of the Geneva Declaration, the health and life of the patient, the physician's utmost respect for human life and civil liberties. Albert Einstein once said, "Most people said that it is the intellect which makes a great scientist. They are wrong: It is character". Indeed, it is the physician's character that secures human existence, taking precedence over scientific research, however great a medical breakthrough might be in prospect. In this connection, Hippocrates, an almost legendary figure from the distant past, and George Nicholas Papanicolaou, a man of our time, command consent.

ΠΕΡΙΛΗΨΗ

Από τον Ιπποκράτη στο Γεώργιο Ν. Παπανικολάου: Ένα «ιατρικό ταξίδι» στο χρόνο

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Όντας αδιαφιλονίκητο γεγονός ότι η Αρχαία Ελλάδα έχει επηρεάσει αλλά και αποτελέσει πηγή έμπνευσης όχι μόνο για το δυτικό αλλά και για το σύνολο του σύγχρονου κόσμου με πολλούς τρόπους, η συνεισφορά της στο φάσμα της σύγχρονης ανθρώπινης παρουσίας και δραστηριότητας, από την επιστήμη και την τεχνολογία έως την τέχνη και τη λογοτεχνία, παραμένει ανεκτίμητη. Η προσέγγιση του τρόπου με τον οποίο ο σύγχρονος ιατρός καλείται να ασκήσει το λειτούργημά του, είτε πρόκειται για ιατρική πρακτική ή κλινική και εργαστηριακή έρευνα είτε για ακαδημαϊκή διδασκαλία, φέρει αναπόφευκτα στο νου τον Ιπποκράτη Όρκο αλλά και τον ίδιο τον εμβληματικό Ιπποκράτη στον οποίον αποδίδεται. Στον Ιπποκράτη και σε μια σειρά μαθητές του που διέδωσαν την κληρονομιά του ανάμεσα στον 5ο και στον 4ο π.Χ. αιώνα αποδίδεται και το επονομαζόμενο *Corpus Hippocraticum*, μια συλλογή που απαρτίζεται από >60 πραγματείες. Η εν λόγω συλλογή πρόσφερε τη βάση για την επιστημονική καθιέρωση και την εξέλιξη της Ιατρικής, όπως είναι γνωστή σήμερα. Η σύγχρονη Ελλάδα ευτύχησε όμως να προσφέρει στην παγκόσμια επιστημονική κοινότητα και έναν άξιο απόγονο του Ιπποκράτη, το Δρ Γεώργιο Ν. Παπανικολάου, πρωτοπόρο ερευνητή της Κυτταρολογίας, της πρώιμης ανίχνευσης του καρκίνου και δημιουργό του "Pap smear". Το όλο συγγραφικό εγχείρημα προσδοκά να προσφέρει ένα σύντομο ταξίδι στο παρελθόν, ιχνογραφώντας εξαιρετικά στοιχεία και συνεισφορές του Ιπποκράτη και του Παπανικολάου, την επήρειά τους στην ιστορική πορεία της Ιατρικής, αλλά και να αναδείξει μια σειρά ερωτημάτων που πηγάζουν από τη δική τους δράση και σχετίζονται με την ηθική της σύγχρονης ιατρικής έρευνας.

Λέξεις ευρητήριο: Δοκιμασία κατά Παπανικολάου, Δρ Γεώργιος Ν. Παπανικολάου, Ηθική, Ιπποκράτειος Όρκος, Ιπποκράτης, Κλινική έρευνα

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