The timeless influence of Hippocratic ideas on diet, salicylates and personalized medicine

Tom C Karagiannis[1],[2] MD, PhD

1. Epigenomic Medicine, BakerIDI Heart and Diabetes Institute, Melbourne, 3004, Vic, Australia
75 Commercial Road, Melbourne, VIC, Australia
2. Department of Pathology, The University of Melbourne, Parkville, 3052, Vic, Australia
Email: tom.karagiannis@bakeridi.edu.au, Phone: +613 8532 1309, Fax: +613 8532 1100

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Abstract

At a time when superstition and deities were thought to be responsible for health and disease, Hippocrates of Kos emerged as a rational thinker assigning disease to natural causes. His insights, which principally arose from what may be considered almost compulsive examination and comparison, formed the basis of Hippocratic Medicine. There are still unresolved questions regarding the authenticity of the approximately 70 works shaping the Hippocratic Corpus. Assigning authorship precisely presents difficulties and given that the various treatises in the collection appear to span a period of between 100 and 300 years, it is clear that they may not be ascribed to a single author. Ancient commentaries, including translation and annotation by the Hellenic physician Galen and more recently by Émile Littré have helped preserve and structure our knowledge of Hippocratic ideals. Further, a large school of contemporary scholars are constantly refining our understanding. Despite the controversies and uncertainties, the underlying themes of Hippocrates' influence on medicine which involve meticulous observation, comparison, prognosis and prediction are evident. Importantly, the Hippocratic Oath remains a masterpiece of medical morals and ethics, analogous forms of which are still used today. Indeed, the Hippocratic Corpus teaches timeless concepts which do not only relate to medical thought and methodology but also to the more gentle aspects of the art. In this essay Hippocratic observations are considered in relation to three important matters preoccupying modern medicine: a) nutrition, b) drug development and c) personalized medicine.

Introduction

That Hippocrates of Kos, the Asclepiad, is known as the Father of Medicine is a trite statement but one that is true nevertheless. Given his importance during the Classical and Hellenistic periods, Hippocrates (circa 460 BC-370 BC), was mentioned by Socrates and appears in the writings of Plato and Aristotle. It is important to note that there are controversies surrounding Hippocratic Medicine, details of which are still being resolved by Historians. For example, the question remains as to whether Hippocratic Medicine truly represents a quantum leap in medical thinking. It is evident that there was influence from Egyptian and Assyrian physicians. There is also evidence for a move away from deities as being the forces accounting for health and disease in Ancient Hellenic Medicine preceding Hippocrates [1, 2]. Nevertheless, that Hippocrates: a) recognized natural causes for disease and eliminated superstition and deities as potential origins, b) was a master of careful observation, comparison, prognosis and prediction and c) was very cautious and prudent with therapeutic intervention, is widely agreed upon. These gentle ideals form the basis of the Hippocratic Oath which is undoubtedly the most famous masterpiece of moral and ethical beauty in medicine. Although we must point out the irony in that the Oath was taken in the name of mythological deities (Apollo and Asclepius, Hygieia and Panacea). Further, to avoid over-romanticizing, in my opinion and if I were to give a frank assessment, the Hippocratic collection as a whole is convoluted, in places self-contradictory and on occasion inaccurate. Nevertheless, as is explored in this essay, apart from the Hippocratic Oath, there are medical gems that can be distilled from the Hippocratic works that remain relevant.

The Hippocratic Corpus (*Corpus Hippocraticum*) consists of approximately 70 treatises and given the time span of the collection (between 100 and 300 are thought to separate the early treatises from the later works) we may be certain that more than one author is responsible [3]. For this reason the Corpus has been viewed as a Hippocratic collection rather than works produced exclusively by Hippocrates. The treatises have been the subject of extensive analyses, translation and annotation most notably by Galen. A more recent and quite well known translation is that of Émile Littré in the 19th century and here we rely predominantly on the translation and thoughts of William Henry Samuel Jones who produced a series of Volumes for the Loeb Classical Library in the 1920s and 30s [3-5]. To align with the 2nd Medical Olympiad held in 2013 in Thessaloniki, Greece, this work was inspired by a lecture and accompanying limited edition manuscript distributed by Prof. Ph. Grammaticos entitled *"Neohippocratic Medicine"*, who has also co-authored a related review recently [6].

In the present essay *no* attempt is made to reanalyse the works of professional historical scholars, including those from the Loeb Classical Library in relation to, a) ac-

curacy of translations and b) the interpretation of texts. Further, *no* attempt is made to ascribe the authenticity of the various treatises to the Hippocratic Corpus. These issues remain topics of considerable debate. Instead, the translations are entrusted and the treatises discussed, are viewed as belonging to the collection influenced by Hippocrates and collectively referred to as Hippocratic Medicine. Despite the controversies and difficulties in precisely assigning the works, Hippocratic Medicine has had an important and lasting influence and in this essay we distil certain medical concepts which are very relevant today. Overall, the aim is to align Hippocratic concepts in the context of three major concerns of Modern Medicine: a) nutrition, b) drug development (using acetylsalicylic acid as an example) and c) personalized medicine.

Nutrition

It is difficult to understand why human nutrition is such a problem in modern society. Metabolic syndrome, obesity and type II diabetes are increasing at alarming rates and are projected to keep inclining in the coming decades [7, 8]. Obesity seems to be a central problem being correlated with both metabolic syndrome and type II diabetes, with a particularly strong correlation between decreased insulin sensitivity and body mass index [9, 10]. There are numerous professional journals dedicated to human nutrition, all sorts of diets are published in popular magazines and it is difficult to avoid some type of weight loss advertisement online. Unfortunately, the results from most popular diets and even from diets designed from professional dieticians remain disappointing. We can safely say that the majority of diet plans work long-term only on a tiny fraction of occasions. Many popular diets are reasonable and in particular those prepared by dieticians are nutritionally correct and appropriate for improving health. The question is, why then do diets not work most of the time? Firstly, diets are by definition restrictive requiring considerable prolonged will-power. Secondly, diets especially those originating from dieticians are very prescriptive. It is not uncommon, that these may specify amounts in grams of carbohydrate, protein, lipid and quantities of micronutrients that should be consumed each day. Therefore, long-term sustainability becomes a major problem. Thirdly, particularly when considering the health effects of micronutrients, there is considerable complexity and confusion, not only in the professional literature but also in popular media and online. Confusion is further amplified by aggressive marketing and advertising of the next super-food, super-nutrient or super-supplement. Despite these concerns, perhaps the biggest issue is that we are designed to crave calories, particularly from fatty foods and sugar. It is a possibility that evolution imparted these traits to ensure our ancestors were motivated our hunter-gatherer lifestyle; significant effort was required to hunt and sugar was particularly sparse, requiring seasonal foraging or going to great lengths and taking risks for example, invading a hive for honey in Archaic times. In this context, it is interesting to note that it is difficult to find images of fleshy Archaic hunters and gatherers prior to the Agricultural Revolution. The complex association between our ancient genome, modern dietary habits and diet-related diseases is now becoming apparent [11, 12].

If we agree to our genetic predisposition, it is not surprising to find that countries with a plentiful supply of easily affordable calories are also the ones with the highest rates of obesity; the USA leads the way with 69.2% of people over the age of 15 being classified as either overweight or obese and other anglophone countries including the UK, New Zealand, Australia and Canada are high up on the list [13]. Indeed, for 86% of the countries with published OECD Economic, Environmental and Social Statistics in 2013, greater than 40% of people over the age of 15 are either overweight or obese [13]. Given these statistics and the considerations mentioned above, using simple Aristotelian deduction we may conclude that a) people are have evolved to crave calories, b) in developed countries affordable calories are readily available and therefore, c) most people that can be overweight or obese are overweight or obese. In the final deduction (c), the qualification "most" allows for people with high will power who may exercise restraint or those who have habitual well-established dietary routines. The clarification "can" in (c) allows for the influence of genetics. The genetic component becomes more plausible with the very recent identification of the role of the kinase suppressor of Ras 2 (*KSR2*) in regulating hunger, metabolic rate and obesity [14]. It is anticipated that role of genetics will be elucidated with further research.

Despite the details, it is certainly true that nutrition is problematic and in many cases associated with poor health. When considering Hippocratic Medicine for guidance, it may appear prudent to consult the treatise entitled *"Nutriment"*. At best this treatise can be described as ambiguous and on a quick glance essentially unintelligible. For example, there is the suggestion that unlike the rest of the body the lungs are nourished only by air indicating either a lack of understanding or disrespect for pulmonary circulation. This is by no means the most obscure assertion in *"Nutriment"*. However, through this treatise Hippocratic Medicine does impart some lasting wisdom. Most notably, that nourishment is not proportional to amount - in other words, nutritional quality does not necessarily correspond with caloric intake. This is analogous to our current understanding of empty calories, where certain foods, particularly those high in simple carbohydrates (sugars) and processed fatty foods contribute energy with negligible nutritional value.

The treatises under the "Regimen" umbrella in Hippocratic Medicine provide insight into the importance placed on nutrition. Hippocratic Medicine imparts very detailed accounts of what was considered proper nutrition both in health *("Regimen in Health")* and disease (there are numerous treatises entitled *"Regimen"* including *"Regimen in Acute Diseases"*). Overall, from the hundreds of pages of text, we learn from Hippocratic Medicine that humankind wrestled with the topic of nutrition even in Ancient times. One would expect that proper nutrition would have been intuitive particularly with the relatively

limited selection of natural and seasonal foods and without the influence of artificial processing and storage. This is not the case and Hippocratic Medicine describes in almost excruciating detail the: a) composition of diet according to ones physiological and health status, b) systems for preparation of foods and c) qualities of different foods mainly with respect to their balancing effects on the body (for example, warming and cooling) - in line with the underlying ideal of the Hippocratic thesis which involves balancing the humours. The detailed descriptions are not simple and perhaps the *Regimens* are on the whole more convoluted than even the more elaborate modern diet plans. Nevertheless, after close reading we may distil the lessons from Hippocratic Medicine with respect to nutrition into three recurring themes: a) timing and number of meals (one or at most two meals per day with numerous references made to dinner) as attributed to Hippocrates and stated in *"Neohippocratic Medicine"*, by Ph. Grammaticos: "Diet is the number one nosogenic factor in men… Greeks eat once a day. Some also have dinner. In Homer's Iliad this is reaffirmed: After a very hard battle of the Greek army against the Trojans, in the army generals' meeting that followed, Ulysses suggested: "to give breakfast next morning to the soldiers because they were exhausted fighting till late that day and next day they were also going to fight hard." b) Carefully regulating amount of food (caloric intake) and c) consuming fresh seasonal food (avoiding rancid food). Perhaps these three principles alone are adequate and may suffice in improving compliance and population health. Given our practises and the types of foods available to us, a major proportion of which are heavily processed or contaminated with various chemicals and antibiotics, we require some adaptations to the basic principles. Therefore, a modern translation of the underlying Hippocratic lessons may be to: a) limit caloric intake, b) avoid empty calories, (particularly, *trans* fatty acids and high corn fructose syrup) and c) eat fresh seasonal food avoiding processed foods.

Indeed, nutrition formed the basis of Hippocratic Medicine, particularly in acute diseases. It is interesting to note that very complex accounts were given for methods of administration of essentially three fundamental ingredients a) mixtures barley with water or milk (which have been translated to "barley-gruel" or "slops"), b) concoctions of honey and water (hydromel) or vinegar (oxymel), and c) wine (white, red or sweet either neat or blended with water). Further, Hippocratic Medicine indicated the cautious use of basic herbals most typically as purgatives (e.g. mercury and cabbage leaves) and emetics (e.g. hyssop).

The use of salicylates

When considering regimens noted in Hippocratic Medicine that translate to Modern Medicine, the recommendation of massage, exercise and in particular walking, which was highly valued and discussed in numerous Hippocratic treatises, are pertinent. Further, when considering traditional medications, the use of salicylates is also comparable. Most likely due to the influence of Ancient Egyptian and Assyrian physicians who prescribed willow bark tea, Hippocratic Medicine also made use of willow bark for relief from fevers and pain. Willow bark remained as an important source of medicine in folklore in numerous cultures until progress was made in the 18th century, firstly by Rev. Edward Stone who created a powder from willow bark which distributed to about fifty people and demonstrating its effectiveness as an astringent and for fevers – he published his findings in the *Royal Proceedings* in 1763 [15]. Following further developments which involved isolations and attempts at purification, relatively pure forms salicin and salicylic acid were produced [16]. In 1853, the French chemist Charles Frédérich Gerhardt combined sodium salicylate and acetyl chloride producing acetylsalicylic acid, the well known form of Bayer's aspirin which was registered in 1899 and has been widely used anti-inflammatory, antipyretic and analgesic [17, 18]. Interestingly, the patent for acetyl-salicylic acid was granted to Felix Hoffman, a Bayer chemist, who was inspired by the use of willow described in Hippocratic Medicine and Gerhardt's experiments. With the development and marketing of paracetamol and ibuprofen in 1956 and 1969, respectively, aspirin was relegated as the top analgesic. However, it has been revived in recent decades due its usefulness (in a specific dosology, not more than 100mg) as an antithrombotic in the prevention of heart attacks and stroke [16, 19]. Further, there is accumulating evidence that aspirin may prevent from colorectal cancer [20, 21].

Do no harm

Apart from the interesting historical and modern medical perspectives, using salicylates as an example, we can also consider one of the most important and lasting principles of Hippocratic Medicine - the doctrine of *"do no harm"*. Salicylates, including aspirin, do have side effects ranging from minor gastrointestinal irritations to more serious gastrointestinal ulcers and bleeding and in certain case intolerance and allergy, some of which were noted in Hippocratic times. Today, a proportion of patients, particularly those on long-term, low-dose aspirin as an antiplatelet therapy are also prescribed a proton pump inhibitor to alleviate from gastrointestinal side effects [22]. This represents two difficulties. Firstly, in this specific case, there is evidence that proton pump inhibitors may reduce the efficacy of aspirin by inhibiting absorption, providing an example of the common problem of drug-drug interactions [23]. More generally, this highlights a major dilemma with modern therapeutics where side effects dictate that people are not only prescribed medications for their disease but also medications to alleviate from the side effects of those medications which in turn, may have other side effects of their own. This is most striking in oncology where the mainstays of therapy are typically non-specific chemotherapeutics which are cytotoxic to dividing cells, both malignant and normal, and radiation therapy which inevitably causes damage to normal adjacent tissues. Of course, in oncology, side effects even though in most cases serious, are tolerable given the alternative. Nevertheless, given these considerations we can conclude that there is a definite relativity and rather than

the Hippocratic ideal of *"do no harm"* in reality, in most cases, the dogma can be considered as *"on the balance, do more good than harm"*.

Personalized Medicine

To increase the efficacy of therapeutics and to perhaps decrease side effects, the concept of Personalized Medicine has become an increasingly important ideal of Modern Medicine [24, 25]. The concept relating to the importance of treating the individual is evident throughout the Hippocratic corpus. The classification between different compositions of *"men"* is clear and distinction between treating male and female and young and old is well-established. Even earlier when we were discussing the obscurity of the *"Nutriment"* treatise, there is in that section an understanding of individual differences which also incorporates habits and environmental conditions. Indeed, there are designated gynecological treatises (*"On the Nature of the Woman"*, *"On the Diseases of Women"*, *"Generation"*, *"On Sterile Women"*) and specific views on regimens for children (*"On the Nature of the Child"*). Of course, the classifications in Hippocratic Medicine can be considered as being crude, given the luxury of the modern tools and knowledge available to Modern Medicine. There has been great deal of effort in stratifying diseases and in identifying risk and therapeutic responses of individuals through-out medical history. With the advent of high-throughput and affordable genotyping, our current ability to consider personalized medicine is unprecedented. There are now enormous databases cataloguing the genetic basis of disease, even at level of the contribution of single nucleotide polymorphisms to various conditions. Further, on the basis of single nucleotide polyphormisms and given the affordability, individuals can now have not only insights into their ancestry (specific haplogroup) but also an analysis of relative risk for over 200 diseases as well as response to conventional therapeutics. For example, although controversial for both medical and ethical reasons, *23 and me*, now provides an analogous genotyping service for under $100 USD; providing scope for an enormous database.

Personalized medicine is largely touted as the new ideal for oncology and in the case of Gleevec (imatinib mesylate) we can see an almost optimal example [26, 27]. However, to date, Gleevec which targets a well-characterized fusion protein (Bcr-Abl) resulting from the Philadelphia chromosome in chronic myelogenous leukemia, represents the exception rather than the rule [28]. Targeting specific growth receptors on malignant is another direction in the context of personalized treatment in oncology. However, this approach has also seen its high and lows in the past few decades, with variability in both inter- and intra-tumoral receptor expression and absolute specificity being difficult to achieve. It is well known that cancer represents a heterogeneous group of diseases and intra-tumour heterogeneity is evident [29, 30]. Further, when we consider redundancy in molecular pathways, pleiotropic therapies such as the ones employed today may not be easily discounted. With the increasing affordability of high-throughput sequencing technologies, particularly next generation sequencing the premise is of greater stratification of cancers and identification of improved targets for personalized therapy.

In summation, the ideal of personalized medicine is one Hippocratic Medicine was well aware. Our unprecedented ability for large-scale population-based genotyping which, is already well and truly underway, provides the basis for optimism in the potential health impacts of this direction. Of course, environmental influences are also very important and in this context the intense research effort in the field of epigenetics will expand our knowledge [31]. Epigenetics adds enormous complexity to individual variance however, whereas the genetic code is essentially fixed, the dynamic nature of the epigenome may allow greater flexibility for intervention.

Overall, Hippocrates' professionalism and inclination to educate enabled, at least in part, the widespread adoption of Hippocratic Medicine. It is clear that the principals and methodologies of Hippocratic Medicine had a lasting influence not only during the Classical and Hellenistic periods but through to Medieval times, transcending different cultures and parts of the World. When we compare Hippocratic Medicine with other traditional systems of Medicine, it is not difficult to draw certain analogies. For example, the art of detailed observation and examination of all aspects of the individual are concepts seen in both Traditional Chinese Medicine and Ayurvedic Medicine. Further, like Hippocrates' cautious therapeutic regimens, both advocate gentle aspects of healing, with physical manipulation, nutrition and the use of herbals and dietary supplements forming the basis for prevention and treatment. Further, when we compare the differences in the nature of men detailed in Hippocratic Medicine we can imagine the likeliness to the classification of people into the different Doshas (Vata, Pitta and Kapha) considered in Ayurvedic Medicine. Hippocratic Medicine ascribes disease to a disturbed balance of the four humours that could be affected by external factors and this is not very dissimilar to the concepts of Yin and Yang and the external six pathogenic factors (excesses of natural forces) described in Traditional Chinese Medicine. Despite the wisdom of Hippocratic Medicine and other Traditional Medical Systems, it would be unreasonable to overlook the advances of Modern Western Medicine, particularly in the remarkable abilities to treat diseases and to improve quality of life. However, when we consider that the incidence of heart disease is 1:2 and of cancer 1:3 and the rising incidences of metabolic syndrome, diabetes and neurodegenerative conditions, perhaps we can conclude that the major shortcomings of Western Medicine, with the exception of vaccination, are related to prevention. Integrating concepts of Hippocratic Medicine and of other Traditional Medical systems, particularly the art of exhaustive observation, careful examination and consideration of all the aspects of the individual, including dietary and other lifestyle factors, may prove to be beneficial. Essentially, this would represent an extension of systems - which would perhaps need to be more proactive to achieve preventative outcomes - already in place in many Chinese hospitals, where Traditional and Western Medical practises coexist.

Conclusions

Finally, in thinking about the relationships of Ancient and Modern medicine an important paradox must be considered. On the one hand, there is as uneasiness with the perception that the ultimate direction of modern scientific and medical endeavours is to perhaps aim to create super humans of some sort or to attempt immortality. Genetic engineering, the use of stem cells and in certain circumstances nanotechnology have their share of critics; it has been voiced, strongly at times, that scientists are playing God. Of course, immortality is not a new ideal, but a difficulty in the consciousness of humankind probably from time immemorial. Indeed, the search for immortality is the topic tackled in the one of the oldest surviving works of literature - the Sumerian epic poem of Gilgamesh. Naturally, immortality defies the fact that humans are built not to last and increasing the proportion of humans reaching the Leonard Hayflick suggested limit of approximately 120 years (which, interestingly also corresponds with Genesis 6:3) may be a more realistic long-term achievement. Simultaneously, a common complaint of modern medicine is the inadequacy in dealing with chronic conditions - neurodegenerative diseases, representing an important example - and it is most likely, that the abovementioned technologies will in the future play a role in managing chronic ailments (unless preventative measures ultimately prevail). These considerations represent a very simplified account of only a fraction of the moral and ethical issues associated with modern medical and scientific activities. In this context, it is very difficult to argue against the enormous contribution of Hippocratic Medicine to medical ethics, with the Hippocratic Oath or analogous commitments having lasted through the ages. If we measure our medical and scientific activities against the ideals within the Hippocratic Oath there is a high likelihood that we will be heading in the correct direction. The ideals remain relevant and this is in itself is a splendid achievement. It follows then, that given the evolution of Medicine in our age, which involves multi-disciplinary teams, commitment to the Great Oath or appropriate variations should now be extended to the different sorts of Healthcare providers.

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