Nephrology between Reductionism and Complex Systems: the Role of Philosophy – Review of Evidence and Opinion

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History

- Received: May 26, 2020
- Accepted: June 09, 2020
- Published: June 20, 2020

DOI : http://doi.org/10.5334/ejmcm.280

ABSTRACT

Nephrology emerged as autonomous discipline in the 1950s, after the publication of the landmark treatise of Homer Smith entitled The Kidney Structure and Function in Health and Disease (1951). The official foundation took place in 1961. For decades, during the collection of the critical mass of data that granted its autonomy, Nephrology investigated acid–base and electrolyte disorders. However, driven by biopsy, dialysis machines and transplantation its growth has been unstoppable in terms of journals, articles, books, meetings, number of specialists, clinical divisions, university chairs, and specialty schools. The most propulsive force has been, however, the switching of the focus from the care of dialysis patients to the >10% of the population who, in a country, suffer from silent or overt disease leading to chronic kidney disease, requiring a demanding and costly therapy consuming 2–3 % of the total health budget.

Historical analysis disclosed that Nephrology as a specialty was born and nurtured in contact zones with other disciplines. These include chemistry, physics, pathology, immunology, pharmacology, genetics, engineering, pediatrics, geriatrics, oncology and cardiology and many more. However research focused on kidney disease, although still lush and appealing, is felt to be stagnant. Another approach based on complexity and holism rather than on strict reductionism – indispensable to provide successful care – may better serve future needs. The potential of complexity is explored along with new techniques, Big Data, and a wider use of artificial intelligence, as well as the links with philosophy, and Systems Biology, Systems Medicine, Systems Pharmacology.

Keywords: Nephrology, CKD, Toxins, Kidney Stone Disease, Philosophy, Reductionism Complex systems

I am attracted the most by the motion of stars. It can be described by mathematical formulas.

HANS–GEORGE GADAMER

WHAT IS NEPHROLOGY?

Disciplines play a great role in disseminating and furthering knowledge. They are born–without aiming to eternity–in order to warrant the originality of the scientists who existed, exist and will exist in the future. Investigators attempt to achieve original findings with the hidden desire to be indicated as originators of ideas. Theirs is a battle to find an own role in the scientific enterprise, to be recognised; thus they scrape smaller niche disciplines and topics. Disciplines however are like fractals; their boundary regions are zones where exchanges are wider than those occurring in the internal zones (Ziman 2000).

On Nephrology

Although it had existed long before, Nephrology as a discipline was born in the 1950s after the publication of the landmark treatise of Homer Smith *The Kidney Structure and Function in Health and Disease*. The discipline used to investigate, diagnose and take care of the so–called renal diseases and of nephritides well before Richard Bright (1827). However, the progress of kidney physiology, at least until 1930, had been very slow, that on the pathogenesis and therapy of uraemia had been insufficient, whereas growth in infectious disease studies was much quicker. From 1950 onward, the growth of nephrology has been progressive, relentless and spectacular, benefitting from new therapeutic means, including diuretics, antihypertensive drugs, dialysis, transplantation and erythropoietin.

For long, Nephrology investigated electrolyte and acid–base disorders; this was possible in boundary zones with chemistry, physics and pharmacology. However, recently Nephrology has moved towards other boundary zones of development and exchange and new achievements were generated in the intersection with cellular and molecular biology.

In the boundary with engineering and physical chemistry, dialysis machines were born. These were the product of technological research into developing artificial organs (liver, heart, pancreas, ear, etc.) where progress can be achieved by interaction with specialists on those organs and functions. By contrast–in the boundaries with immunology, pathological anatomy, microscopy and surgery–progress has been achieved on glomerulonephritis and renal transplants. In the boundaries with pharmacology and genetic engineering, erythropoietin was produced; this also anchored nephrology to pharmacoeconomics and bioethics. The kidney generates hypertension and it is its target. From this originated a vast theoretical and practical corpus. Much was also learned through statistics and evaluation of results in huge numbers of diseased and healthy persons.

EJMCM

Cite this article: De Santo NG. 2020. Nephrology between Reductionism and Complex Systems: the Role of Philosophy – Review of Evidence and Opinion. European Journal of Molecular & Clinical Medicine, 7(1), pp. 59–69, DOI: https://doi.org/10.5334/ejmcm.280

For Gabriel Richet–a giant in nephrology and great supporter of the importance of history in understanding and humanising medical treatment–"Nephrology is one of the flowers of medical biology and medical pharmacology, a flower permeated by genetic and molecular biology" (Richet 1993).

Paediatric Nephrology, which emerged as a subspecialty in 1965 and by 1970 was established in many countries, grew on the boundary with paediatrics (Chessney 2002). Paediatric kidney units had been however in function since 1953 in Glasgow, Helsinki and Paris (Arneil 2001). All started in 1920–1930 with the studies on diarrhoea by John L. Gamble (1883–1959)–a fellow of Lawrence J Henderson (1878–1959)–and Daniel C. Darrow (1885–1965). "The other disease of childhood that contributed to the emergence of nephrology is the nephrotic syndrome. The discovery of adrenal cortical tropic hormone (ACTH) and steroids after World War II led to their successful use in the nephrotic syndrome of children. The prohibitive cost of these therapies at the time led to the foundation in 1948 of the Nephrosis Foundation, which was to become the National Kidney Foundation (NKF) in 1950" (Eknoyan 2005).

Geriatric Nephrology, Onco–Nephrology and Cardio–Nephrology have developed on the boundaries with Geriatrics, Oncology and Cardiology. This naturally caused the birth of specific journals and associations. Nephrologists have even been associated with the conquest of space from the very beginning and have identified key roles of the kidneys in cardiovascular adaptation to weightlessness and in space–mediated bone loss (Drummer 2002).

Recently, the dream to slow–arrest the progression of renal disease was made possible through the analysis of data on the effects of glitazones on diabetic kidney disease. They emerge as important drugs beyond their antidiabetic effects (Prischi 2018). Finally, we now know that uraemia is a systemic disease (Zoccali et al. 2017) and that there is an ongoing conversation between the failing kidneys and the brain (Viggiano et al. 2019). Hopefully, this will be conducive to a new comprehensive rationale for treatment.

Nephrology, a prototype of a discipline generated by complexity

Nephrology is a young discipline that effectively "entered the parlance of medicine in 1961" the year of the birth of its International Society. However, it was the advent of maintenance dialysis that fuelled its growth after 1970 (Eknoyan 2011, Eknoyan 2017).

Many omics databases have been published which can be utilised for diagnostic purposes, to generate new hypotheses for clinical interventions as well as in research concerning IgA Nephropathy and diabetic nephropathy (Jang et al. 2013; Moon et al. 2011; Papadopoulos et al 2016).

However, the most successful steps in nephrology were driven by two main ideas: (i) the classification of Chronic Kidney Disease (CKD) based on the estimated glomerular filtration rate (eGFR) and (ii) the identification of CKD and uraemia as systemic diseases.

On eGFR

All originated from an NIH–sponsored study on the Modification of Diet in Renal Disease (MDRD), aiming to evaluate the effect of dietary protein restriction and strict blood pressure control on kidney disease progression. The study results were controversial and seen as negative for slow progression of kidney diseases by low protein alimentation (Klahr et al. 1994). However, "a major outcome of the study was the derivation of a formula to estimate the glomerular filtration rate (GFR) from serum creatinine level. Validated and improved, this new predictive formula proved to be a clinically reliable index of kidney function in health and disease that would significantly affect the course of things to come" (Levey et al. 1999).

As Nobel laureate Eugenio Montale says in *Before the trip* "the unforeseen is our hope". eGFR was the unforeseen, the outcome of those studies. "As a result of this paradigm shift, the opportunity to improve outcomes changed from that of the thousands on maintenance dialysis therapies to the estimated (>10% of population) millions of individuals with CKD. The favourable response and rapid adoption of the new definition and classification of CKD worldwide by the nephrology community, as well as by other medical disciplines and public health officials, was overwhelming. It was a transforming event that broadened the reach of nephrology well beyond its limited borders theretofore" (Eknoyan 2017).

CKD and uremic systemic diseases amenable to cures

The complex and systemic nature of CKD was demonstrated by Zoccali et al (Zoccali et al 2014; Zoccali et al 2017). Their studies revealed the limits of the reductionist approach. Thus, a systems biology approach was identified as potentially capable of exploring the pathophysiology of this systemic disease and unraveling critical pathways that can be targeted for CKD prevention and therapy. Those studies address the effects of CKD on (i) the energy–immunity link, (ii) metabolism, bone and heart, (iii) the gut–kidney link, (iv) the lung–kidney link and (v) the link of the kidney with the nervous system. This is in accordance with the systemic nature of the uremic syndrome (Vanholder et al. 2016) for which an algorithm was devised to tackle this condition and may be conducive to assessing death and dialysis (Vanholder et al. 2018a). A new tool should also take into consideration "An age–adapted definition" of CKD (Delanaye et al. 2019).

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

Revisiting uremic toxins using systems biology

Recently, the biological/biochemical impact (toxicity) of 71 uremic retention solutes assessed over the past 50 years was reviewed (Vanholder et al. 2018b) after grouping them according to the guidelines of the European Uremic Toxin Work Group: (1) small water–soluble compounds; (2) protein–bound compounds; (3) the so–called middle molecules, which are mostly small peptides. "All but one solute (glomerulopressin) affected at least one mechanism with the potential to contribute to uremic syndrome. In general, several mechanisms were influenced for each individual solute or group of solutes, with some impacting up to 7 different biological systems of the 11 considered. The inflammatory, cardio–vascular and fibrogenic systems were those most frequently affected and they are one by one major actors in the high morbidity and mortality of CKD. A scoring system was built with the intention to classify the reviewed compounds according to the experimental evidence of their toxicity (number of systems affected) and overall experimental and clinical evidence. They must be integrated into diagnosis, therapy and prognosis.

Perna and Ingrosso et al extensively studied the role of hyperhomocysteinaemia in uraemia (Perna et al. 2003, Ingrosso et al. 2003). They found that a moderate increase in plasma homocysteine is an independent risk factor for cardiovascular disease. Plasma homocysteine is frequently elevated in chronic renal failure and in uremic patients, and the major causes of death in these patients are cardiovascular accidents. Homocysteine elevation in blood leads to the intracellular increase of its precursor, adenosylhomocysteine, a powerful inhibitor of adenosylmethionine–dependent transmethylations. They also showed that (i) global DNA methylation was reduced in patients with uraemia and hyperhomocysteinaemia. (ii) this hypomethylation was linked to defects in the expression of genes regulated by methylation. (iii) hypomethylation can be reversed by administration of folate. Global results suggest that hyperhomocysteinaemia affects the epigenetic control of gene expression, which can be reverted by folate treatment (Ingrosso et al. 2003). Thus, the data support the hypothesis that the toxic action of homocysteine can be mediated by macromolecule hypomethylation. In particular, it was shown that DNA hypomethylation affected the expression of two genes, namely a pseudoautosomal gene (*SYBL1*) and an imprinted gene (*H19*), (Ingrosso et al. 2003). However, population studies have failed to show benefits of folate therapy, probably due to excessive use of folates before enrolment for the studies. Thus hyperhomocysteinaemia should be seen just as a marker and not as the cause of enhanced cardiovascular risk in uraemia (Mallamaci et al. 2002).

Reduced renal function, hypertension and myocardial infarction in renal stone a multi–systemic disorder

Kidney Stone Disease (KDS)—which spans the whole history of human medicine—is a worldwide common mineral metabolism disorder with a rising prevalence. In the USA, 1 in 11 persons has a history of kidney stones and the prevalence is similar in Europe, representing about 10% of patients in ESRD. Recurrence is 30–50% in five years. Calcium KSD is the second most prevalent kidney disease after arterial hypertension. Kidney stones are also associated with a higher prevalence of CKD and cardiovascular damage or events when compared with non–stone formers. It has been suggested that the link between kidney stones and cardiovascular disease may be insulin resistance. A new approach must be generated to understand the stone–forming process, since progress has been slow.

KSD has emerged as a multi–systemic disorder, a concept initially introduced by Baggio and Gambaro in 1996. Indeed, the association of KSD and hypertension, cardiovascular risk and in particular myocardial infarction goes in the direction of a systemic condition that manifests in the kidneys with a stone forming phenotype. So far, the approach to the study of KSD mainly through a reductionist approach, focused on single urinary parameters and missing the overall picture. This allowed the identification of several risk factors and has so far guided the therapy of this condition. The treatment of KSD besides a dietary approach, alkali supplements, probiotics and thiazide diuretics (Gambaro et al.2016a; Gambaro et al. 2016b; Gillen, Worcester & Coe 2005). There are great expectations for novel approaches in pathophysiology and therapy. An investigational approach able to integrate metabolic, proteomics and physiological aspects all together could address this point (Vinaiphat 2017). Kidney stone disease thus appears as a systemic disease amenable to treatment using the so called 4P Medicine. However new strategies have to be designed and put to work. The small–step theory is not applicable.

Systems biology and kidney disease: present state

A systems biology approach to CKD seems now feasible and potentially capable of easing the nephrologists' work in the near future (Hanna & Dalla Gassa 2017; He et al. 2012; Keller et al. 2011;Mariani et al. 2016). Data have been collected on Diabetic Nephropathy, IgA nephropathy, focal segmental glomerulosclerosis and steroid resistant nephrotic syndrome (Becherucci et al. 2016; Feehally et al. 2010; Genovese et al. 2010; Schelling et al. 2008). The hope is for a bright future, although the present findings may weaken enthusiasm (Groopman et al 2019).

Nephrology is a complex discipline in terms of the reasons it came to life, its goals, the high prevalence of patients it should care for, its costs, the models it pursues in clinical care(Bellasi et al. 2019; De Boer 2018; Piccoli et al. 2018) and cannot be taught as done to date (De Santo 2019 a,, De Santo 2019b; De Santo 2019c).

Embedding Nephrology– CKD into Complexity

Specialisation, which started with Galileo Galilei (1564–1642) and Renée Descartes (1596–1650) peaked with the discovery of DNA (1953) and the Higgs boson (2012). It has accompanied the advent of modernity and provided solutions that have been of benefit to humankind**.**

In *Les sept saviors necessaries, l'education du future* (1999), Edgar Morin , born in Paris in 1929, warned readers that "in the era of globalisation specialisation drives the progress of knowledge; however, it also drives to breaking down knowledge which should be kept as a whole. The disjunction between disciplines hides the connections and the complexity of the whole human being. We are in extreme need of transdisciplinarity, to extract, assimilate and integrate knowledge which is broken down, separated, compartimentalized and fragmented. We have to find a way to have full knowledge of the zeitgeist and to push specialisation to understand multidimensionality and much more to acquire a complex thought through an interdisciplinary route".

There is a need for complexity –a word derived from the Latin stem *complexus*, meaning woven together. Complex thought, says Morin, sheds light on "emergence", a strange word of our times. Emergence occurs when in a whole, in a system a new quality that was not present in the constituent parts, appears (Morin 2015).

Morin aims to generate a method embodying the irreducible link between things and refers to Fragment 72 of Pascal's *Penseés.* "Since everything then is cause and effect, dependent and supporting, mediate and immediate, and all is held together by a natural though imperceptible chain, which binds together things most distant and most different, I hold it equally impossible to know the parts without knowing the whole, and to know the whole without knowing the parts in detail" (Morin 2015).

Knowledge of fundative elements does not allow understanding the whole, since a whole is made of its constituent elements as well as of the actions and feedback between the parts and the whole. Morin departs from the open systems of Ludwig von Bertalanffy. "In a system made of various parts, the greater the unity arising from diversity, the greater the diversity arising from unity, the greater the complexity of the system". Indeed, complexity is given by "the degree of variety in the system. The unity in the diversity builds a unity of two contrasting terms (unity and diversity") (Morin 2015).

For Morin, we have to learn how to learn, that is learning by separation while linking at the same time, through a process of contemporary analysis and synthesis. We have to learn to overcome linear causality (cause–effect) by learning reciprocal, relational, circular causality–the latter encompassing feedback and recursion. Furthermore, we should be aware of the uncertainty of causality. Causes do not always lead to identical effects since the reaction of systems may be different. Last but not least, different causes may be conducive to identical effects. Thus, we have to rise to the challenge of complexity arising from all fields of knowledge and action. To meet the challenge we have to create a new thought" (Morin 2015 , 2017).

There has been a strong quest for holism. Nicholas A. Christakis, Professor of Social and Natural Sciences and of Medicine at Yale has explained his attraction to the towers made of minute silica crystals.

"Some people like to build sand castles, and some like to tear them apart. There can be much joy in the latter. But it is the former that interests me. You can take a bunch of minute silica crystals, pounded for thousands of years by the waves, use your hands, and make an ornate tower. Tiny physical forces govern how each particle interacts with its neighbours, keeping the castle together; at least until the force majeure of a foot appears. But, having built the castle, this is the part that I like the most: you step back and look at it. Across the expanse of beach, here is something new, something not present before among the endless sand grains, something raised from the ground, something that reflects the scientific principle of holism". He is aware that "The properties arise because of the connections between the parts. I think grasping this insight is crucial for a proper scientific perspective on the world. You could know everything about isolated neurons and not be able to say how memory works, or where desire originates. It is also the case that the whole has a complexity that rises faster than the number of its parts" (Christakis, www.edge.org.).

Indeed, in the history of humankind, foxes have lived along with hedgehogs; however sometimes the depth of specialists prevails along their capacity to analyse problems thoroughly. Sometimes generalists prevail. Being capable of getting through the frontiers of knowledge they can produce new ideas. […] In 14th century Florence, the initial group of humanists rejected scholasticism and looked for a culture bridging philosophy and poetry, science and arts. This generated the works of Filippo Brunelleschi, Leon Battista Alberti and Leonardo. Later, Wilhelm Von Humboldt founded the new university in Berlin based on a vast cultural program that went beyond just schooling and military service. The same happened in the USA after WWI, when contemporary civility was introduced at Columbia for all freshmen and after Worl War II, when a selected core group of general disciplines were offered to all students at Harvard" (da Empoli 2013).

"The real problem –Morin says– "is to substitute the method which drives to know by disjunction and reduction with a new method obliging us to know by distinction and conjunction" (Introduction to complex thinking). However, "we have to be aware that we are not yet landed in the society of knowledge, but rather in the society where knowledge is fragmented, and consists of various *tesserae*, each separated from the others. Such separation does not allow us to bind them in order to understand the fundamental and global problems related to our personal lives as well as to our collective destinies (Morin 2011).

On the other hand, for Edgar Morin "a discipline is a kind of organizing category which introduces in the field of knowledge division as well as specialisation and a certain degree of autonomy. Disciplines developed in the XIX and XX century along with scientific research and were fertile in the history of science. They in fact unveil, extract or build up a non–trivial object. However, they remain something which has been extracted from a context or made *de novo*. This should be changed to give the specialty a general view" (Morin 2000).

From 7 to 8,000 disciplines

At the beginning of the 13th century, universities in Europe were based on the *trivium* (literally the place where three roads meet), which included Grammar, Rethoric and Dialetic and on *quadrivium* (the place where four roads meet), which included Arithmetic, Geometry, Music and Astronomy), as described in the seventh book of Plato's Republic and represented the so–called liberal arts. These disciplines represented the basic curriculum for the study of Theology, Medicine and Philosophy (Martins 2018).

According to Nicholescu and Ertas (2011), there was a big bang and the number of disciplines skyrocketed to 8,000 in 2012. The decision for fragmentation is wrong, as the rapid advance of communications means that a connected world is driven by complexity. "The new education has to invent new methods of teaching, founded on new logics. The old classical binary logic, that of "yes" and "no", i.e. the logic of the excluded middle, is no more valid in the context of complexity.

Timeline of reductionism and holism

Reductionism is the philosophical tool that has allowed the progress of modern medicine– as reported in Table 1 and in Table 2– spanning from Archilochus of Paros (c.680–c.640 BC) to the Higgs boson.

In Fragment XXIV of Archilochus, we read "The fox knows many things, but the hedgehog one big thing", meaning that the fox uses many tricks to escape hunters and dogs, while the hedgehog only one, but at this it is the best of all. Archilochus had many followers, among them Erasmsus of Rotterdam (1470–1530) who translated the above passage in Latin "multa novit vulpes, verum echinus unum magnum (*Adagiorum collectanea*)", and Isaiah Berlin (1909–1997) who in the tale *The hedgehog and the fox* (1553) distinguished writers and thinkers either as hedgehogs (one principle to explain everything), or foxes (utilising many possibilities).

For Thales (born 636 BC) the universal principle was water, for Anaximander the *Aperion* (boundless, infinite, limitless, indefinite), for Anaximenes Air, for Parmenides the Being ("All things are one and this one is Being". "Being is the only and homogeneous substance permeating all things".

For Heraclitus of Ephesus the universal principle was Fire. Anaxagoras identified four elements (Earth, Water, Air, and Fire) governed by intelligence (*nous*). Empedocles of Akragas identified Air, Water, Earth and Fire as primary elements; however they were governed by Love and Hate. Love unified them, Hate separated them.

Xenophanes of Colophon identified Water, Earth and the Whole as primary elements, Ion of Chios Fire, Earth and Air. Air was the universal principle for Diogenes of Apollonia, atoms for Leucippus, atoms and the void for Democritus, the One and the undetermined Dyad for Spesusippus.

Hippocrates based his science on four humors (Blood, Yellow Bile, Black Bile and Earth), Plato on Fire, Earth, Air and Water (*Timeus*).

Epicurus of Samos and Lucretius identified Atoms and Emptiness as fundamental principles, Chrysippus of Soli Air and Fire as active roots, and Earth and Water as passive roots. "Any motion requires a cause. All effects are driven by prior causes. All things happen by fate. Whatever happens, happens by fate".

Galen was an Aristotelian, as evident in *The Construction of the Embryo*. He utilised four humors (blood, black bile, yellow bile and phlegm), four elements (Air, Fire, Earth and Water), four qualities (hot, cold, dry and moist), four temperaments (sanguine, choleric, melancholic and phlegmatic). However, for Galen (131–200 AD) recovering health requires the drug(s) correcting the humors and the willingness of the patient, his mind.

The frontispiece of *Il Saggiatore/The Assayer* by Galileo Galilei, a member of the Accademia dei Lincei/Linx Academy —published by Giacomo Mascaldi in October 1623 — has illustrations with the personification of Natural Philosophy on the left and Mathematics on the right. Therein, the polymath and great technician, in the sixth chapter wrote: "Philosophy [nature] is written in that great book whichever is before our eyes — I mean the universe — but we cannot understand it if we do not first learn the language and grasp the symbols in which it is written. The book is written in mathematical language, and the symbols are triangles, circles and other geometrical figures, without whose help it is impossible to comprehend a single word of it; without which one wanders in vain through a dark labyrinth".

Descartes disagreed with the Aristotelian unity of spiritual and physical. He aimed to replace Scholasticism with a philosophy based on natural principles. A separation between *res extensa* (body) and

Table 1. Timeline of reductionism from Thales to the discovery of the Higgs Boson (636 BC to 2013)

Scientists/Philosophers	Lifespan	Principle(s)
Thales	born 636 BC	Water
Anaximander	610-546 BC	Aperion: boundless, infinite, limitless, indefinite
Anaximenes	586-526 BC	Air
Parmenides of Elea	born c515 BC	The One, the Being"all things are one and this one is Being"."Being is the only and homogeneous substance permeating all things".
Anaxagoras of Clazomene	500-428 BC	Earth, Water, Air, and Fire governed by the intelligence (*nous*)
Empedocles of Akragas	492-423 BC	Air, Water, Earth and Fire governed by Love and Hate
Xenophanes of Colophon	died 475 BC	Water and Earth, the Whole
Ion of Chios	490-421 BC	Fire, Earth an Air
Diogenes of Apollonia	born 450 BC	Air
Leucippus of Miletus	460-370 BC	Atoms
Democritus of Abdera	460-360 BC	Atoms and Void
Hippocrates	450-377 BC	Blood, Yellow Bile, Black Bile and Earth
Plato	429?-347 BC	Fire, Earth, Air and Water (*Timeus*) Universe based on Eternal *Forms*. Knowledge innated. Order imposed by an outside mind. Both concepts accepted by Newton.
Speusippus	died c.339 BC	The One and the undetermined Dyad
Epicurus of Samos	341-279 BC	Atoms and Emptiness
Chrysisppus of Soli	331-232 BC	Air and Fire active roots, Earth and Water passive roots. There is a cause for everything
Lucretius	98-55 BC	Atoms and Empiteness
Avicenna	980-1037	Hot, Cold, Moist, Dry
Hugue de Saint Victorie	1096-1141	Fire, Air, Water Earth (*Didascalion*)
Nicholas Copernicus	1473-1543	*De revolutionibus orbium coelestium* (1543)
Paracelsus	1493-1591	3 elements (Sulphur, Mercury, Salt) governed by a Vital spirit(Archeus)."Water the matrix of the world and of all creatures"
Giulio Cardano	1501-1576	Air Water and Earth governed by the celestial Heat
BernardinusTelesius	1508-1588	2 opposites (Warm, Cold) eternal and guided by Heaven and Earth
Giordano Bruno	1548-1600	Water principle of all things (*De la causa, principio et Uno*, London 1545)
Francis Bacon	1561-1625	*Novum Organum Scientiarum* (1620). Empirical method
Tommaso Campanella	1568-1639	Living organisms characterized by Cold, Heat and Body Mass
Johannes Kepler	*1571-1630*	*Astronomia Nova ΑΙΤΙΟΛΟΓΗΤΟΣ seu physica coelestis, tradita commentariis de motibus stellae Martis ex observationibus G.V. Tychonis Brahe*(1609)
Galileo Galilei	1569-1642	*Discourses and Mathematical Demonstrations Relating to Two New Sciences* (1638), *Il Saggiatore*/The assayer (1623):"The book is written in mathematical language"
William Harvey	1578-1657	Aristotelian in physiology discussed the relation between whole and the parts. *De motu cordis* (1628)
René Descartes	1596-1650	*Le Discours de la méthode* (1637) Bodies of humans and animals complex machines
Isaac Newton	1643-1717	*Philosophia Naturalis Principia Mathematica* (1687) Laws of motion and universal gravitation
Julien Offray de La Mettrie	1709-1751	*L'Homme machine* (1747)
Immanuel Kant	1724-1804	4 temperaments. *Kritik der reinenVernunft* (1781) Against Aristotle
Pierre Simon Laplace	1749-1827	Identified the universe as a great machine that could be described by rational mechanics
Claude Bernard	1813-1879	Claude Bernard, *Leçons de physiologie expérimentale appliquée à la médecine*, París, Baillière, 1855-1856.
Louis Pasteur	1822-1895	Microbes responsible for souring alcohol. Germ theory of disease. Vaccines. The misteries ofAnthrax and Rabies
Robert Koch	1843-1910	Discoverer of the causative agents of tuberculosis, Anthrax, Cholera, Tuberculosis and identified Koch's Postulates. *Investigations into bacteria: V. The etiology of anthrax, based on the ontogenesis of Bacillus anthracis*. Cohns Beitrage zur Biologie der Pflanzen (1876). *Die Aetiologie der Tuberkulose* Mitt Kaiser Gesundh 1888.
Albert Einstein	1879-1955	*Theory of Special Relativity* (1905) *Theory of General Relativity* (1916).
Watson JD & Crick FHC	1953	*A structure for deoxyribose nucleic acid*
Peter Higgs	1964	*Spontaneous Symmetry Breakdown without Massless Bosons* (God particle)
Jacques Monod	1910-1976	*The chance and the necessity* (1971). Life originated by chance: "Pure chance, absolutely free but blind, at the very root of the stupendous edifice of evolution".
CERN	3/2/1912-6/2013 10/8/2013	Demonstration of the boson Nobel Prize to F.Englert and P. Higgs

res cogitans (mind) was created; thus the tenet "*Cogito ergo sum* / I think therefore I am". Therefore, nature followed its own path based on mechanics without the need for a soul. Animals were compared to watches". "The Cartesian Philosophy and paradigm (Dualism and Mechanicism) appeared as a need to change the old paradigm of the Middle Ages (cure the body without knowing exactly the causes of the disease) to a scientific paradigm based on mechanics and natural causes (cure the body after knowing the causes of the disease), as pointed pout by Montomoli (2011).

In 1682, Isaac Newton celebrated reductionism in *Philosophia Naturalis Principia Mathematica.*

Table 2. Timeline of holism from Archilocus (c.680-c.640 BC) to Erwin Chargrafff (1905-2002)

Scientists/Philosophers	Lifespan	Principle(s)
Archilocus	c.680-c.640 BC	The fox knows many things, the hedgehog one big thing
Aristotle	384-322 BC	Fire, Air, water and Earth Mobile, can be transformed each one into another Soul is the principle of life The unity of spiritual and physical phenomena The whole is more than the sum of parts
Galen	129-216 AD	Blood, Black Bile, Yellow Bile, Phlegm Air, Fire, Earth, Water Hot, Cold, Dry, Moist Temperaments: sanguine, choleric, melancholic, phlegmatic Aristotelian. The Construction of the Embryo
Thomas Aquinas	1225/6-1274	4 sublunary elements Air, Fire, Water, Earth) directed by heavenly bodies
Leonardo Da Vinci	1452-1519	The Universal Man of Renaissance, embodied the spirit of transdisciplinarity and explored the boundaries between art and science: anatomist, architect, botanist engineer, mathematician, musician, painter, scientist sculptor and writer but not a philosopher (according to Benedetto Croce and Giovanni Gentile). Many contributions remained unknown so the effects of his genius were minimal. (F. Capra, The Science of Leonardo: Inside the man of the genius of Renaissance, 2007).
Giambattista Vico	1668-1774	Against Descartes. Knowledge possible through history, however art is central to knowledge. For Edgar Morin Vico has authored the first complete philosophy of complexity
Jean Baptiste Joseph Fourier	1766-1830	The discovery that apart from effects of gravity bodies exchange heat (not explained by mechanics). Mathematics no longer synonymous of Newtonian science
George Wilhelm Friedrich Hegel	1770-1831	Although the whole is equal to the parts it is not equal to them as parts; the whole is reflected by unity (Science of Logic)
Friedrich Hölderlin	1770-1843	The earth should be lived poetically
Charles Darwin	1809-1882	*On the origin of species* (1859) was a holist: for him the object, or target, of selection was primarily the individual as a whole
Anton Dohrn		Founder of the Zoological Station in Naples (1872) Supported the theory of evolution by natural selection The present mission of the Zoological Station is to conduct basic research in biology with a focus on marine organisms and their biodiversity, tightly linked with studies on biological evolution and marine ecosystem dynamics, using an integrated and interdisciplinary approach
Ernst Mach	1838-1916	Anticipated Einstein's theory of relativity and criticized Newton
Carl Gustav Jung	1875-1961	Mental images exits in the unconscious are actualized in the conscious state
Niels Bohr	1885-1962	The father of quantum mechanics *On the Notion of Causality and Complementarity*.
Erwin Schrödinger	1887-1961	*What is life?* (1947) "[living matter, while not eluding the 'laws of physics' is likely to involve 'other laws,' [which] will form just as integral a part of [its] science".
Martin Heidegger	1889-1976	Take care of "things" around us, let things to present themselves to us. In The origin of art work (1960) art is seen as the origin of community shared understanding.
Werner Karl Heisemberg	1901-1976	Pioneer in quantum physics. Heisemberg Uncertainty Principle (1937)
Max Delbrück	1906-1981	Attracted to biology by Bohr in order to search on complementarity out quantum physics
Merleau-Ponty	1908-1961	The body is not a machine, primacy of perception
Philip Anderson	1923	*More is different* (Science 1972)
Murray Gell-Mann	1921-2019	Discoverer of the quarks, Nobel Prize 1969 Co-founder Santa Fe Institute (1984) to study complex systems and complexity *The Quarks and the Jaguar. Adventures in the Simplex and the Complex* (1994)
Benoit B. Mandelbroth	1924-2010	*The fractal geometry of nature* (1982)
Arthur Eddington	1929	The arrow of time (asymmetry of time)
Benedetto Croce	1855-1952	"Reality is history, nothing but history not written by us" projected into physical reality Life originated by chance: "Pure chance, absolutely free but blind, at the very root of the stupendous edifice of evolution".
Ludwig Bertanlaffy	1901-1971	*General Theory of Systems* (1968) Systems are made by elements open to the environment and capable of self-regulation and acquiring new qualities. They cannot be explained on the basis of their constitutive elements
Niels Kai Jerne	1911-1994	Network theory of the immune system (1974):antibodies not only attach themselves to an antigen, but also can become attached to other antibodies.
Ilya Prigogine	1917-2003	The link between medicine and philosophy. Irreversible processes create complex structures (Dissipative Structures). La nouvelle Alliance (1980)
Edgar Morin	born 1921	*La Méthode* (1977), *Introduction à la pensée complexe* (1990).The birth of complex thought, complexity
Zygmunt Bauman	1925-2017	*Liquid modernity* (2000) Uncertainty for ever

E.O. Wilson	born 1929	Consilience: The Unity of Knowledge (1999) Consilience is jumping together Finding the rule governing the unity of disciplines *Biodiversity* (NAS, Washington, 1988)
B. Nicholescu, E.Morin, L. de Freitas	1994	*The Charter of Transdisciplinarity* (Monastery of Arrabida in Portugal)
B. Nicholescu	1996	*The Manifesto of Transdisciplinarity*
Giacomo Rizzolatti	1996	Mirror neurons
Erwin Chargraff	1905-2002	*In dispraise of reductionism* (1997)
TrygveTollefsbol	2017	*Handbook of epigenetics*

"Newton developed a complete mathematical formulation of the mechanistic view of nature accomplishing a synthesis of the works of Copernicus, Kepler, Francis Bacon, Galileo and Descartes. Newtonian physics provided a coherent mathematical theory of the world which was the fundament of the scientific thought until the 20th century. The Newtonian Universe is an immense mechanistic system operating under exact mathematical laws" (Gembillo & Anselmo 2019).

Pierre Simon Laplace (1749–1827) identified the universe as a great machine "which could be described by rational mechanics, a tool to understand the universal determinism, as natural extension of the relation between cause and effect". He was preceded by "the invention of infinitesimal calculus and by the formalisation of mathematical physics introduced by Joseph–Louis Lagrange (1736–1813)"(Abbot 2009).

Claude Bernard (1813–1879) is identified as the first system biologist for his studies of the *Milieu Intérieur* that was governed by mathematical laws. "This application of mathematics to natural phenomena is the aim of all science, because the expression of the laws of phenomena should always be mathematical" (Abbot 2009). Although he rejected the idea that physiology was not a science described by physics or chemistry, he was a determinist; he rejected Darwin's theory of evolution, negated the value of experiments in humans and even rejected epidemiology" (Abbot 2009).

Albert Einstein [*Theory of Special Relativity* (1907) and *Theory of General Relativity* (1915)] was a reductionist. For him, "The supreme test of the physicist is to arrive at those universal laws of nature from which the cosmos can be built up by pure deduction" (Gembillo & Anselmo2019).

Darwin "introduced historicity into science… He was a holist: for him the object, or target, of selection was primarily the individual as a whole. The geneticists, almost from 1900 onwards, in a rather reductionist spirit, preferred to consider the gene as the target of evolution. In the past 25 years, however, they have largely returned to the Darwinian view that the individual is the principal target"(Mayr 2009).

Watson and Crick celebrated reductionism in biology in 1953 by defining the structure of the DNA (Watson & Crick 1953). The peak of reductionism was however achieved with the demonstration of the Higgs mechanism and Higgs boson —hypothesised in 1964 (Higgs 1964)—, when the "God particle "was detected at CERN in 2012–2013. The discovery of Higgs Boson, announced at CERN in Geneve on 4 July 2012" is the most fitting tribute to the limitation of what has been the most potently philosophical of scientific discoveries –reductionism. Reductionism is what told us that molecules are made of atoms that the universe is expanding, that DNA is a double helix and that you can build lasers and computers (Jogaletr 2012).

Prigogine and Stengers proposed a link between biology–medicine and humanities and pointed out that irreversible processes could create complex structures, which they named Dissipative Structures (Prigogine & Stenger, 1980).

Ludwig von Bertanlaffy says the expression the whole is more than the sum of parts "is simply that constitutive characteristics are not explainable from the characteristics of the isolated parts. The characteristics of the complex therefore appear as new or emergent"… "Modern science is characterized by its ever–increasing specialisation, necessitated by the enormous amount of data, the complexity of techniques and of theoretical structures within every field. Thus, science is split into innumerable disciplines continually generating new subdisciplines. In consequence, the physicist, the biologist, the psychologist and the social scientist are, so to speak, encapsulated in their private universes, and it is difficult to get word from one cocoon to the other. In contrast to this mechanistic view, however, problems of wholeness, dynamic interaction and organisation have appeared in the various branches of modern physics. In the Heisenberg relation and quantum physics, it became impossible to resolve phenomena into local events; problems of order and organisation appear whether the question is the structure of atoms, the architecture of proteins, or interaction phenomena in thermodynamics. Similarly, biology, in the mechanistic conception, saw its goal in the resolution of life phenomena into atomic entities and partial processes. The living organism was resolved into cells, its activities into physiological and ultimately physicochemical processes, behavior into unconditioned and conditioned reflexes, the substratum of heredity into particulate genes, and so forth. In contradistinction, the organismic conception is basic for modern biology. It is necessary to study not only parts and processes in isolation, but also to solve the decisive problems found in the organisation and order, unifying them, resulting from dynamic interaction of parts, and making the behaviour of parts different when studied in isolation or within the whole"(von Bertanlaffy 1968).

American theoretical physicist Philip Warren Anderson (1923–2020), Nobel laureate (1972) supported the idea that *More is different* (1972). For him "it is not true…that we should cultivate our own valley and not attempt to build roads over the mountain ranges…between the sciences. Rather we should recognise that such roads while often the quickest shortcut to another part of our own science, are not visible from the viewpoint of science alone". Thus Anderson made clear his opposition to molecular biologists who seem determined to try to reduce everything about the human organism "to only" chemistry, from the common cold and mental disease to religious instinct".

Edwin Chargraff (1905–2002) was against reductionism (Heraclitean Fire 1978). In his last days he wrote his best known opposition, in the leaflet *In dispraise of reductionism* (Chargraff 1997).

"In my long career have often met other scientists–chemists, physicists, biologists–who declared themselves steadfast reductionists. When I asked, naively, what this meant, I usually got the answer that a reductionist holds the strong belief that all phenomena of life are governed by nothing but the laws of physics and chemistry. Later, becoming aware that reductionism was a much broader term, employed in philosophy, sociology, politics and other disciplines, I came upon a shrewd remark by the philosopher Roger Scruton, pointing out that the idiom of reductionism included, as a favourite expression, this very "nothing but". Life is never a "nothing but". "Excessive reductionism is, I believe, doing much harm in biology. It has become a subterfuge, an expedient through which researchers can increase their importance by claiming to be studying the problem of life. In reality, they are only scraping around the outworks" (Chargraff 1997).

Reductionism Big Datasets and omic platforms

The approach has obvious limits and Systems Biology seems to hold the holistic potential to "explain the forest without studying the trees individually" (Ahn et al. 2006a, Ahn et al. 2006b). This is indispensable when going from larger to smaller but does not disclose the interactions between the components (Lee & Yoon, 2017).

Big data are data whose scale, diversity, and complexity require new architecture, techniques, algorithms, and analytics to manage it and extract value and hidden knowledge from it. As the size of data increases above a critical point, quantitative issues of data are transformed into qualitative issues in the capture, processing, storage, analysis, and visualization of data (Rodriguez et al. 2019).

In Nephrology, if well collected, Big Data may provide outstanding results (Hood & Flores 2012).

We are far from the possibility of using them to turn medicine from reactive into a proactive and achieve 4P Medicine (predictive, preventive, personalised, and participatory) driven by a systems approach. However it is not without reason that the initiative "Big data to knowledge" was started at NIH (Margolis et al. 1914).

Omic platforms now provide a broad understanding of the genome, transcriptome, proteome and metabolome utilising information obtained through various techniques and much more is expected through the creation of models that are predictive and adaptive and of institutes established and equipped specifically for systems biology" (Mcilvain 2011). Recent examples are provided by the study of coordinate behaviour of coordinated protein response by means of the new algorithm known as the Systems Biology Triangle (Garcia–Marqués et al. 2016).

Systems biology, Systems Medicine, Systems pharmacology for biomedical research and health care

Complex systems operate towards synthesis, towards the whole and oppose reductionism and dissection. They analyse parts aiming to understand the whole. They have the potential to predict by catching hidden regulatory mechanisms that cannot be revealed by concentrating on the single tesserae (Kroc, Balihar & Matejovic 2019).

Schleidgen et al (2017) identified not less than five descriptions of Systems Medicine:" (i) Systems Medicine is the successor of Personalised Medicine; (ii) Systems Medicine is a precursor of Personalised Medicine or P4–Medicine; (ii) Systems Medicine is an equivalent for Precision Medicine; (iv) Systems Medicine means the translation of Systems Biology into medical practice; and (v) Systems Medicine is an "assemblage of scientific strategies and practices that include bioinformatics approaches to human biology […]; 'big data' statistical analysis; and medical informatics tools". Thus ""Systems Medicine is an approach seeking to improve medical research (i.e. the understanding of complex processes occurring in diseases, pathologies and health states as well as innovative approaches to drug discovery) and health care (i.e. prevention, prediction, diagnosis and treatment) through stratification by means of Systems Biology (i.e. data integration, modelling, experimentation and bioinformatics). This also revealed the visionary character of Systems Medicine".

Longo and Montévil explain that there is no "current theory of biological organisation. It lies in the multi–level nature of biological interactions, with lower level molecular processes just as dependent on higher–level organisation and processes, as they in their turn are dependent on the molecular processes. The error of twentieth century biology was to assume far too readily that causation is one–way. As the authors say, "the molecular level does not accommodate phenomena that occur typically at other levels of organisation" (Longo & Montevil 2014).

Noble (2004) also explained how he learned this fact. "I encountered this insight in 1960 when I was interpreting experimental data on cardiac potassium channels using mathematical modelling to reconstruct heart rhythm. The rhythm simply does not exist at the molecular level. The process occurs only when the molecules are constrained by the whole cardiac cell to be controlled by causation running in the opposite direction: from the cell to the molecular components".

However, parts, as Thomas Dean Pollard says, are preliminary and important at the same time. We cannot progress without them (Pollard 2003). However "understanding dynamical processes is impossible from a list of their parts and their connections. Thus, many deep questions remain about" […] "The strategy is reductionism with an emphasis on understanding how systems of molecules interact and respond to changes of conditions in the short term, and how organisms adapt on evolutionary time scales using similar molecules to come to diverse solutions"[…] "Independently, none of the elements of this strategy can explain how a system works at the cellular or organismic levels. Rather, each approach contributes to reach a synthetic understanding" (Pollard 2004).

Science needs philosophy

Recently, Lucie Laplane and a group of outstanding humanists and scientists outlined why and how philosophy "can have an important and productive impact on science" (Laplane et al. 2019). They outlined four possibilities: "(i). the clarification of scientific concepts, (ii) the critical assessment of scientific assumption or methods, (iii). The formulation of new concepts and theories, (iv) the fostering of dialogue between different sciences, as well between science and society". They developed their reasoning departing from the analysis of studies on stems cells, immunogenicity and the microbiome, and the study of cognition and cognitive neurosciences. Their conclusion was that "We need a reinvigoration of science at all levels, one that returns to us the benefits of close ties with philosophy". They have illustrious predecessors. Don Howard (2005) reported on Robert A. Thornton, a young physicist who was just starting a course in physics at Puerto Rico University. Thornton faced many difficulties in persuading his colleagues to let him incorporate the philosophy of science in his lectures. Thornton wrote to Albert Einstein for support and received the following answer:

"I fully agree with you about the significance and educational value of methodology as well as history and philosophy of science. So many people today—and even professional scientists—seem to me like someone who has seen thousands of trees but has never seen a forest. Knowledge of the historic and philosophical background gives that kind of independence from prejudices of his generation from which most scientists are suffering. This independence created by philosophical insight is—in my opinion—the mark of distinction between a mere artisan or specialist and a real seeker after truth".

Nowadays, there is a renewed interest in bone changes in experimental and clinical nephrology. However, the need to understand the peculiarity of bones can be traced back to the 5th century BC, when Empedocles of Acragas put forward a theory of a world made of air, water, fire, and earth, governed by love and hate. By observing the various body tissues, he strove to demonstrate that they consisted of four elements assembled at different mathematical ratios (*logos*). Blood was considered the most perfect tissue, because the ratio between elements is one. Bone is a very unusual tissue because it is made of two parts of earth, two parts of water and four parts of fire (De Santo, De

Santo and Perna 2011). This kind of reasoning could be considered the first cry in the birth of quantitative chemistry.

CONCLUSION

Science progresses through the work of specialists; they are at the same time the most indispensable and also the most despised being charged of incapacity to catch the unity of knowledge. They were insulted by Umberto Eco in the 12th chapter of *The Pendulum of Foucault*.

Nephrology progresses now in small steps. This is at variance with a glorious past. The number of patients and the cost of their therapy is a burden for health budgets everywhere. The approach through reductionism introduced in 1637 by René Descartes, and working well for nearly four centuries, is less appealing than in the past. It is suggested that Nephrology (i).should shall adopt the method of complexity and (ii) and explore the zone of contact with philosophy. The latter link might represent a strategic tool in educating a cadre of Renaissance Scholars, like those who made the fortune of Florence at the time of Medici, in the XIV Century [47].

The adoption of a Nephrology based on Systems biology, Systems, Medicine, Systems pharmacology, transdisciplinary, integrative assessment, and complexity warrants an epochal change in teaching.

Ethics and consent: not applicable

Funding: none needed

Conflicting interests: the author reports no conflict of interest

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Cite this article: Gaspare De Santo N. 2020. Nephrology between Reductionism and Complex Systems: the Role of Philosophy – Review of Evidence and Opinion. European Journal of Molecular & Clinical Medicine, 7(1), pp. 59–69, DOI: https://doi.org/10.5334/ejmcm.280