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Clinical research and prevention: fundamental elements of sustainable health care systems based on patients' needs

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Abstract

Problems in health care systems are present on a planetary scale due to a discrepancy between scarce resources and vast needs. These are mainly generated by the aging of the population. Everywhere in the world, state health care agencies simply reduce the quantity and eventually the quality of available services. This approach is unacceptable, at least in Europe, where health care is a legal right, granted from birth to death. This paper departs from the poor support available nowadays for clinical research and the trivial investments on prevention, and hypothesizes a new approach based on clinical research and prevention which, in the long term, would generate a just, efficient, sustainable health care system stemming from patients' needs. This is discussed from various viewpoints. It emerges that there is a need to switch the focus of health systems away from cures towards prevention and as well as a need for better translational research. It is of note that in France such a program based on clinical research and prevention was launched in 2008.

Key words: prevention, clinical research, sustainable health care, economists, philosophers, physicians

Introduction

Health systems worldwide tend to collapse because of their increasing costs. Thus, during the last two decades, success has been achieved by the so called *homo oeconomicus* (economical man) and health systems have been in the hands of managers who have levelled resources and expenditures by reducing the quantity and the quality of services granted. This was the end effect of the advent of managed care, a by-product of the up-rush of economy in all aspects of human life. In those two decades, even hospitals were turned into business enterprises which began to negate patients' rights. This has given rise to health care systems which are unjust, allowing rich people to live longer than poor people. For example the mean life span at the extremes of the Washington metro is 20 years shorter in the poor quarters; the mean life span in Turin of those who live in the suburbs is 5 year shorter than those who live on the mythical hill where rich people live, and in United Kingdom, based on the postal code number, one can trace the people who will live eleven year less than the mean life expectancy for the country. Managed health care, however, achieves some success only when minimum care is provided to the patient, otherwise expenditures never reach equilibrium with resources.

Nonetheless, the fact that in some countries (France, Germany and USA) health care systems utilize nearly 15% of the gross domestic product and in other countries (including Italy) 8.4% is certainly interesting. However, generally speaking, even with such differences within Europe there are no problems of accessibility to health care. In our Continent, health care is granted from birth to death. In the United States, even after the recent reform comes into action, there will still be 15 million people having no support. The problem of accessibility in the underdeveloped countries cannot be discussed here. In such areas, the main problem is having enough food, safe water and vaccination.

This paper is therefore devised in order to discuss the theoretical feasibility of health care systems based on prevention and clinical research. Reasons will be provided to discuss such a possibility.

The physician's peculiar job

Although clinical research was turned into a science in the 18th century, the history of medicine shows that it accompanied humans from the very beginning of history, as demonstrated by examples written in *Genesis* and in the *Book of Daniel*. Of course, prevention at the offset is expensive, but in the long run it promises to reduce the impact of chronic disease on health expenditure.

For Hans-George Gadamer, the philosopher of hermeneutic, even in the collective, imaginary, medicine is something that lies between science and art. In fact, medical art is devoted to re-establishing a natural condition or well-being. However, this art is centred on the physicians' judgement, and though any diagnosis represents "a new case in the generality of a disease, ... the true art consists in the capability to recognize the difference". Different from the artisan, the physician does not produce anything, not even the patients' health "although it is the scope of his activity. Health is not only a social fact, but also represents a moral-psychological finding". However, despite the progress of knowledge about health and disease, and the advent of a rational technique devoted to the conquest of new knowledge and practical applications, "there is still a large gap to be covered by rationalism. Even the concept of good/genial physician has affinity with an artists' characteristics and not with that appropriate for a man of science" [1].

Physicians have now lost their autonomy, and it is now the manager who decides who must be cured, how and for how long. At the end of the 1950s in the United States, the excessive power of physicians' guilds was thoroughly discussed. The question was: how could a democratic society tolerate such dominance. Now, state officials start worrying about the physicians' complete loss of power [2].

Just one example of the power of physicians taken from history highlights this point. The guild of physicians, apothecaries and grocers started in 1451 in Florence. To be admitted, physicians, after their university training, had to pass a local examination and discuss a thesis. Usually, the contest took place in the main square of the city. Anyone present could pose questions. There was abuse, and to be admitted was difficult. One needed allies among the masters of the guild. Nepotism was a rule. Each city a different guild, with different rules [2, 3].

Clinical research

Although medicine became a science in the 18th century, the History of Medicine demonstrates that clinical research has been a constant product of medical thought through the centuries.

For example in China, in 2500 BC, evidence had accumulated about the risk of excessive salt intake: "too much salt in the kitchen hardens the pulse" [4].

Herodotus, in turn, narrates in his *Histories* that in Babylon patients were accommodated along the streets so that they could ask to those passing nearby if they personally or others had experienced a disease identical to theirs. It is nice to learn that nobody refused to answer.

An experiment on a single person

In *Genesis* (2,16 and 3,6), we read: "Then Yaveh God gave the man this command, 'you are free to eat all the tree of the garden. But of the tree of the knowledge of good and evil you are not to eat, for, the day you eat of that, you are doomed to die'. She [The woman] took some of its fruits and ate it. She also gave some to her husband who was with her, and he ate it".

While the biblical narrative goes on to recount their punishment by the wrath of God, the fact is, she did not die, and having survived the experiment she could now recommend clinical research to the generations that were to come. If one accepts this analogy, Eve began the very tradition of search, the free play of curiosity which has evolved into research and this could have occurred only by the acquisition of wisdom from eating the fruit of the tree that imparted it [5].

The first clinical trial

Daniel 1,3-19 reads: 'After Nebuchadnezzar took Jerusalem he ordered to his chief eunuch Ashpenaz to recruit a group of young Hebrews suitable for family origin, studies, physical constitution, and knowledge in every branch of wisdom eventually suitable for service at the royal court, and to teach them the language of Chaldeans'. 'The king assigned them a daily allowance of fruit and wine from the royal table. They were to receive an education for three years, after which they would enter the royal service. Among them there were the Judaeans Daniel, Hananiah, Michael and Azariah Abed-Nego'. 'Daniel, who was determined not to incur pollution by food and wine from the royal table, begged the chief eunuch to spare him this defilement'. The eunuch warned him 'if he [my king] sees you thinner in the face than the other boys of your age, my head will be in danger with the King because of you'. Daniel then said 'please allow your servants a ten days trial, during which we are given only vegetables to eat and water to

drink. You can then compare our looks with those of the boys who eat the king's food; go by what you see, and treat your servants accordingly'. The man agreed to do what they asked and put them on ten days trial. When the ten days were over, they looked better and fatter than any of the boys who had eaten their allowance from the royal table, so the guard withdrew their allowance of food and the wine they had to drink". The Biblical story discloses that the king 'found none to equal Daniel, Ananiah, Mishael and Azariah. So they became members of the king's court'.

"Could this be considered the equivalent of the pilot phase of current clinical trial? Could Nebuchadenazzar be considered the equivalent of an editor accepting the results of the full study phase of a clinical trial for publication, after it had been subjected to peer review by the court of the King? This exceptional event records a clinical trial notwithstanding that much of the early clinical knowledge of Egypt and Babylon derived from direct observation without controlled clinical experimentation other than trial and error. Yet as sterile as the observation without experimentation may be considered by current standards, it is observation and its refinement that determines the practice of medicine for much of recorded history. For example in Edwin Surgical Papyrus (about 1600 BC) treatments are described, such as that for a dislocated jaw or the bandaging of wounds, that are considered acceptable practices to this day" [5].

Medicine turned into science

Medicine was turned into science [6-12] between the years 1761-1818. The year 1751 can be defined *annus mirabilis* since Morgagni published *De sedibus et causis morborum per anatomen indagatis, Cotugno published De acqueductibus auris humanae internae dissertatio, and Auenbrugger his Inventum novum ex percussione thoracis humani ut signo abstrusos interni pectoris morbos detegendi*, which received proper credit after it was translated by Corvisart in 1808. In 1776, Fourcroys read before the Royal Medical Society in Paris an introduction to Ramazzinis' *De Morbis Artificum* (a neglected original, innovative book, not read by Morgagni) which spread its originality. The decree of the 4th December 1794 introduced, , a curriculum centred on physiology, chemistry, dissection of cadavers and clinical training in the university of France [13]. This is a paradox since clinical education was established by a chemist. Finally, in 1818 Laennec wrote the *Traité de l'auscultatione médiate et des maladies des poumons et du coer*.

The crisis of clinical research

Edward H. Ahrens, a lipid specialist,and dean at Rockfeller institute, was the first to discuss in 1992 the inattentiveness to bedside research. He gave four fundamental reasons leading to the death of patient oriented research: 1. the growth of biomedical scientists who have surpassed clinical scientists in competition for grants, 2. the advance in molecular biology, 3. the peer review systems at the National Institute of Health composed of experts with no or hardly any experience in bedside research, and who have even stopped financing whole animal research, 4. the complexities of the costs of health care delivery which affect the life of the whole body of 125 academic centres in the USA where teaching and research play a secondary role to income-generation [14].

This was the first look into a relevant problem which evidenced the risk that even in the United States there was a loss of attractiveness of health science as a career. A quest was addressed to promote a new type of physician-scientist capable of translating fundamental laboratory discoveries into clinical practice. Drastic measures were foreseen: 1. recruiting undergraduate students into health sciences, 2. increasing the interest of minority groups, 3. enhancing support, 4. improving training and devoting attention to the needs of young scientists [15].

By reviewing issues on career pathways of clinical investigators, a Committee of the National Academy of Sciences [16] answered seminal questions: i). What is clinical research, ii). how can individuals be stimulated to pursue careers in clinical investigation, iii). what is the most appropriate curriculum, iiii). how can the gap between basic and clinical research be bridged, iv) how can funding of clinical research occur, v) how can clinical investigators be protected, vi) how can clinical researchers be retained.

The appeal for clinical research

In 1997 The Italian Institute for Philosophical Studies promoted an international conference on Human Clinical Research. Ethics and Economics generated an *Appeal for Clinical Research*, through the contribution of various experts in related fields coming from both sides of the Atlantic Ocean [17].

"Health care has improved markedly over the past five decades because of advances made in patient directed clinical research. The study of the whole human being, which has proceeded extremely fruitfully heretofore, is now threatened by its own success by the advent of technological

developments from studies in molecular biology. The profound shift over the past decade from patient oriented clinical research to research at the cellular and molecular level has not only created new ethical and religious dilemmas, but just as importantly has caused a shift of financial support to the more expedient studies at cellular level. As a result the study of the whole human being is languishing at a time that this kind of research is absolutely essential in furthering human health and transferring laboratory research to the clinical arena.

While the new technologies can be relied upon to provide basic solutions, patient-oriented clinical research is essential – now more than ever in the past – in order to translate the advances made in molecular biology into the practical and functional terms applicable to the whole human physiology and metabolism. to attain a better understanding of human biology, to improve the cure of human illnesses, and to deliver a better health to all mankind. It is fair to say that if both modes of research – molecular and clinical – are to prosper in the future, as they must, then patient-oriented research must receive stronger institutional and governmental support to do research and to provide answers to the ethical and moral problems raised by the advancing frontiers of cellular research.

We appeal to all concerned and responsible, public, private and governmental authorities to lend their support to this initiative".

One might notice that although in the fall of 1997 the genome had not yet been sequenced, even without reference to the volume of studies on the double helix in clinical research, the appeal has not lost neither its moral authority nor its analytical value.

Physician scientists: endangered and essential

D. Rosenfeld pointed out in *Science* [18], that because of the shortage of physician scientists the link between laboratory research and bed-side research will probably disappear. The very question concerns the education of physician- scientists needed by the pharmacological industry to plan, direct and explain clinical trials. Clinical investigators can easily interact with biomedical scientists. There is a need to act immediately, to educate a new calibre of physician- scientist capable of responding with success to modern challenges.

Survival is not enough

In 2004-2006, the scientific council of the Italian Institute for Philosophical Studies hypothesised, structured and promoted an International Conference on *Survival is not enough* in 2007. The conference takes place every year in different universities, in Italy and Europe, in the second week of March and coincides with World Kidney Day. The failing kidney is used as a model since it is the only organ which can be substituted by a machine for decades. The conference highlights the point that patients need more than cures, and that the health care system should not governed on the basis of either reducing the availability of services or by increasing waiting lists for services. The conference invites philosophers (as third parties) to act as patients' warrantors, and to discuss with economists, and other health care specialists involved , the possibility of a health care system based on patients' needs rather than on a reduction of services. The conference supports prevention, the promotion of clinical research, innovative cures for all and a new kind of economist capable of outlining a health planet that originates from patients and their needs [19-24]. It should be noted that in Italy we invest 8.4% of the gross domestic product on health which is below the European mean (9.5%), and the National Council for Economy and Labour (CNEL) has asked the Italian Government to increase the expenditure by an additional 2% of the GDP. A total of 3 conferences have been organized, the fourth is scheduled for 2010. Various monographs and Journal Supplements have been dedicated to this event with the goal of promoting a system not only compatible with resources, but also one that is just, efficient and immediately accessible.

A plan for prevention and clinical research in France

In 2008 Jacques Attali and 41 intellectuals in writing the *Rapport pour la liberation de la croissance française* [25] departed from the general tenet that "Health care expenditure is considered harmful for economy. It is usually suggested to reduce the availability of services for patients. However where such manoeuvres have been attempted like in Ireland, Denmark, Finland, they have failed".

For Attali et al. it was evident that "health care expenditure grows because of chronic long-lasting diseases. In France it is foreseen that the fraction of gross domestic product utilized for health care will increase in 2030 from 15% to 20%". Therefore, France has to promote prevention and research in the field of pharmaceuticals: "we need to develop *les essays clinique* since only 3 out 29 university hospitals have the capability to do clinical research. There are reasons for the inadequate development of clinical research

which is crucial for producing new drugs. We need to concentrate on the best hospitals and to provide education in methodology of research. We need to integrate public and private efforts. Health protection is an opportunity, a motor for economic growth". Accordingly, an interesting group of decisions has been foreseen and are outlined in Table 1.

A medicine attentive to prevention

According to Luc Montagnier, formerly Director of the Pasteur Institute in Paris and now, because of forced retirement from the National Research Council, a life-long jet professor of the City University of New York, it is time for a new medicine, one that is more attentive to prevention since the human life span has increased significantly in the last century due to the progresses of hygiene and the improved quality of available food. In fact, this has increased the costs because of the high prevalence of chronic disease that increase in an aging population. "Actually 20% of the patients use 80% of resources. In the long run there is only one possible way both for the society and the single individual. We need to act on causes of diseases by promoting a policy of prevention. Nowadays we invest only 2% of the health care budget on prevention . We have to act upon risk factors and the causes of diseases. Some factors are environmental and cannot be abolished unless we plan collective actions on a planetary scale. This is the case of particles dispersed in the air. There is a need for a new science aimed at slowing the course of a serious disease or to prevent it. This might well represent the profile of a healthy strategy where medicine instead of care of near invalidating lethal cases – a disaster also for the society – plays the role of prevention" [26].

There is a need for a triple strategy. First of all we need "a change in medical education based on new diagnostic technologies and on continuous dialogue with the patient, seen not as a container of organs but in its physical and psychological unity". Secondly, "patients will learn to consult the physicians when they are healthy, that is to take care of his health not of his diseases". Of course ,patients must be ready to reduce their risks by modifying their lifestyle and by visiting practitioners at regular intervals, as we do with our cars, where coupons for checking ones' health must be used timely. This represents a call to proper use of "personal responsibility, that represents the essential step". The third element of the preventive strategy is political in nature. It can be achieved if we are able to transmit to politicians that prevention – apparently very expensive – is the only road in the future" . This strategy, in the long run, will allow a reduction of costs related to the treatment of chronic diseases and will produce a coherent social welfare that can keep costs under control. There is no question that we cannot impose prevention, but we have to stimulate interest in this manoeuvre. The concept must emerge that the attitude to have the car checked every ten thousand kilometres fits in with personal and societal health demands. Most probably, the pharmaceutical industry will change and will also concentrate "on drugs to be used for prevention". As one might expect from the curriculum of this Nobel Laureate, for him "progresses in science are a value only if they are of benefit to the whole of mankind".

Table 1. Characterization of measures described in Sarkozy's plan for prevention and clinical research [25].

Decision (no.)	*Goals*
66	Prevention
67	Regulation of drugs for which prescription is facultative
68	Clinical research
69	Competitiveness between biotechnological companies
70	Development of at least of two bio-clusters
71	Improve medical education
72	Rationalization of hospital admission and development of home care
73	Development of non-hospital medical centres
74	Assistance for the disabled
75	Externalization of peripheral services
76	Attraction of patients from other countries
77	Funding private and public research in neuroscience and psychology
78	New university courses to federate isolated disciplines

Translational research

Without basic research everything collapses including humanistic research. However without clinical research, very little falls back on patients of the enormous discoveries made by fundamental investigators. François Becker, in a book dedicated to fundamental research, appropriately pointed out " that there is no research without fundamental research since it answers to mans' innate expectations, to his basic need to provide his own contributions to the development of knowledge, which is a constitutive element of human culture. However one cannot perform fundamental research without applied research since the former generates applications whereas the latter , in association with technology, fertilizes fundamental research" [27].

How should basic research be turned into cure? The problems still lacks a definite answer, though various models have been advanced. For example at Stanford since 1997 a program on "Translational medicine and Clinical research" was started under the responsibility of an *ad hoc* vice-president. That event was considered so relevant that it was felt appropriate to announce in the Journal of Clinical investigation that "a unification of basic and clinical programs and the whole institution by putting to work side to side basic and clinical investigators". However now, 14 years later, The National Institutes of Health at Bethesda still lack an Institute for Translational Medicine and the discoveries made through basic research go mouldy in scientific journals and are not translated into cures often because there is a lack of people capable of completing the process. There are still insurmountable barriers to move before the discoveries of fundamental research from the bench of laboratories arrive at the bedside.

Specialists call "the valley of death" the time needed to translate a product of basic research into a cure. As pointed out by Sharon Begley [28], patients ask why, after having paid taxes to support research, do investigators' findings remain in the pages of the scientific journals and are not translated into cures? Patients also want to understand why, despite a doubling of the funding made available to the National Institutes of Health in the United Sates in the period 1996-2006, the number of new drugs has declined from 52 to 18. The reason is to be found in the inability of basic scientists to translate their discoveries into bedside cures, and also in the fact that curing diseases is not a primary goal for the NIH, an institution which appears to be the pride of Americans. This seems a good reason to promote a new centre at the NIH, a Centre for Cure. However, basic scientists do not favour this solution which may divert funds away from basic to translational research. On the other hand, tax payers should not have to repay a second time for making a basic discovery meet patients' expectations.

A doctors' vision of the future of medicine

Recently, Leroy Hood, inventor of the genome sequencing technology and founder of the Institute for System Biology in Seattle in Washington [29], has published *A doctor's vision of the future of medicine*. He is convinced that over the "next two decades, medicine will change from its current reactive mode, in which doctors wait for people to get sick, to a mode that is far preventive and rational". He called this P4 Medicine, that stands for "predictive, personalized, preventive and participatory".

The driving force for such changes are identified in the "new powerful measurement technologies and the so-called system approach to medicine. No more studies on one gene but analyzing all genes at once. The focus of medicine will be placed on individual patients. The focus of health care will shift away from dealing with disease towards maintaining wellness. Research will have to change since many diseases such as diabetes, cancer, heart disease, obesity, and Alzheimers are so complex, that traditional approaches have had marginal results". Of course, Leroy also clarifies that profound changes will occur in medical education and curriculums, since the present approach is based on a classification of diseases and on few measurements. "Tomorrows' physicians will need to be familiar with the complexity of the human biological system as never before".

The role of behavioural sciences in future medical activities

Neither Luc Montagnier nor Leroy Hood mention the need for behavioural sciences to be integrated into future medicine. Why? Both scientists are the last terminal of a science born with Claude Bernard which has completed its trajectory with cybernetics. They like to neglect that medicine, although aiming to become a science, it is far from that goal. As Gadamer stressed, health is not only a social fact but also a psychological-moral result which is well beyond what we consider as an objective fact like those described by natural sciences. In addition, the sick patient is left alone with his solitude, anxiety, fears, depression and the society around him has a modest quantity of time at his disposal. So more and more patients

seek help for a specific condition which other professionals can provide. This quest is one of the reasons for the development of behavioural sciences nowadays.

Conclusions

Health care expenditure is a relevant problem for governments worldwide and for any health system [30]. There is a need to explore new strategies to reduce costs if we want to continue to provide health care to everyone. With this in mind, it is feels appropriate to 1. switch the focus of health systems away from cures towards prevention and 2. to promote translational research. Both measures promise to be successful in the long run. This approach has been adopted by the French Government in 2008.

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