REFLECTIONS ON THE SCIENTIFIC METHOD IN MEDICINE

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Summary

In the last 60 years, medical research has suffered a crisis of efficiency in its effort to achieve the humane goals of medicine. It has been disfavored the clinical ortho-investigation of high quality induced directly from lacunae inside the clinical sciences, originated-in-the-patient and investigator-driven. Clinical progress is being practically achieved through clinical meta-investigation, mostly induced from outside the clinics by the basic-sciences and technological-sophistication processes, and by the measuring of death-disease-risk indexes decline of the health-sciences. The aim of this article is to meditate on the concept of a comprehensive scientific method to make clinical medicine research more creative and fruitful, strengthening its internal logic of progress. Using scientific system analysis and intuition are made suggestions on the application of the scientific reasoning and method in clinical research, for the strengthening and completion of its scientific foundation, and the benefit of an advanced and integral clinical teaching and care of the patient. The article reflects on a better adjustment of the scientific method hypothesis-driven in clinical medicine, science of particularities and generalities too, now a huge empirical research domain but a too little theoretical research realm yet, between the more mature pre- and post-clinical dominions. It meditates on the complementarity of an integrative inductive-deductive theoretical-research strategy for discovery of new medical hypotheses; of two computerized knowledge- and data-driven systems: one, for discovery of "recombinant" hypotheses from knowledge-bases, and other, for optimization of

research design through human modeling-simulation-prediction from databases; and on the medical probabilistic and determinist systems of inference, as well as on the need to accelerate an empirical-theoretical solution for the medical body-mind problem. It concludes that a unified scientific methodology with a solid foundation could be created for medicine, through a trans-methodological model of clinical, basic and health sciences, re-unifying the clinical scientific method for practice and research.

1. Background

Working for more than 50 years with its very broad definition of health, World Health Organization policy has been unable to resolve the problem of finding a balance between the biological and disease paradigms of medicine, on the one hand, and public health, on the other. The explosion of medically-applicable knowledge and high technology has rendered a balance even more difficult to achieve. This situation has encouraged the biomedical model of world health policy that continues to demand increasing research to cure acute and chronic diseases, rather than focusing also on promoting – in the individual and the population – an optimum state of health in the most developed countries, and a good, or at least minimum state of health in the less developed countries. It is now argued that there is a need for a different kind of methodology in medicine that will lead to a different global health policy, yet also impact on clinical care.

The aim of this article is to meditate on the concept of a comprehensive scientific method to make clinical medicine research more creative and fruitful, strengthening its internal logic of progress. Using scientific system analysis and intuition are made suggestions on the application of the scientific reasoning and method in clinical research, for the strengthening and completion of its scientific foundation, and the benefit of an advanced and integral clinical teaching of the physicians and care of the patient.

1.1. The approach to a scientific method in clinical medicine

To achieve a realist view of the beginnings, advances, trends, limitations, and challenges of the scientific method in medicine in the 21st century, it is desirable to review the historical context of the practice of medicine, of science in general, and of the particular science of medicine with its three dimensions of medical sciences, of their allied sciences, and of scientific attitude, thought, objective and method.

The American economist Jeff Sachs writes, "human ignorance, poor health, brutish and short lifetimes have changed dramatically with economic development from prehistory up to ten millennia ago, when agriculture arose and practically all people had to survive unending epidemics, famines, miseries, local wars and political despotism with very primitive knowledge, technologies, sanitation, and natural medicine that did not help enough. From those times up to around the mid-1700s, there was a very slow change for the better but most people still lived with ignorance, ill health and poor quality of life, advancing from extreme poverty through moderate and mild poverty".

"However, from the world's 0.9 billion people around 1750 to the 2000s, merely 250 years, an extraordinary and sustainable global market-based international economic and social development has spread industrialization, wealth, democracy, technological-scientific progress, with an increasing middle class - coming from and reducing the poorest class. While these changes have also brought about global environmental degradation, wars, and terrorism during the 20th and beginnings of the 21st century, ignorance, ill health, hunger and poverty have been more than halved, life span and living standards have been more than doubled", although the need still remains for more social justice and attention to what people feel.

Nevertheless, these advances have come accompanied with global confusion bringing setbacks in economic and social matters as well as in science and medicine. As written in the American biologist Paul Gross's book, "in the 20th century, the whole spectrum of pre-scientific medicine: remedies and techniques coming from prehistory up to the 19th century: was once again re-established in the most developed countries. In USA alone, in the 1990s, the estimated number of visits to unconventional medical providers was 425 million/annum with an out-of-pocket cost of $10.3 billion/annum, whereas there were 388 million visits to US primary care physicians, whilst the cost of all US hospitalization was $12.8 billion".

Sachs resumes, "in 2005 one half of the world's 6.3 billion people still live in closely regulated centrally-controlled systems and 40% in poverty -- including one billion in extreme poverty". Like their ancestors in the 1750's, they still suffer ignorance, ill health, poor quality of life; they lack necessary education and essential health care, in spite of the existence of oceans of wide and deep knowledge, the highest technologies, advanced sanitation, and total or at least partially effective scientific medicine for most known illnesses.

The persistence of long-established infectious epidemics in the developing countries together with those lately emergent and re-emergent, is conspiring at the global level not only against the health of the world's poor population, but also against the best health of the affluent and middle classes in developing and transitional countries, and even of the most developed countries, in addition to their own specific burden of chronic non transmissible illnesses of affluence.

The clever option in facing this situation is not to go back to a previous socio-economic and techno-scientific period. It is not to retreat to all the primitive and pre-scientific medicine remedies and techniques of health care. Instead, the developed and developing countries, with the guidance and help of the most advanced countries, should seek the way to achieve auto-sustainable economic, educational, scientific, and health care growth, with reduced suffering of the whole population (and environment), using the vast potential of modern economic, educational, scientific and medical systems and of the material, energy, information and communication technologies. How is this to be achieved? A digression on the training of medical practitioners and researchers is instructive.

1.2. How the current situation developed

Usually in most world universities, when medical school undergraduates and residents learn the scientific method as a preparation for research in medicine, they first receive a short introduction to a universal, abstract scientific method. It starts with schemes for devising and writing a research design, a report, a presentation, and an article on empirical results. This is followed by a long, abstract, and detailed examination of mathematical statistics: from estimation and hypothesis testing, to the meaning and use of means, standard deviations, correlation and regression coefficients; non parametric statistics, tables, graphics, and statistical software to simplify procedures. Gaussian and Bayesian probability theories, analysis of variance, multivariate analysis, all have a part in the quest for medical certainty in the results of medical surveys and trials, but are often presented without a specific orientation towards medical science and research.

The scientific method as received by these students has self-contained form that seems to have existed indefinitely, as the scientific method in medicine. However, the origins, application and development of the scientific method in medicine and the scientific foundation of medicine are much more complex and by no means free of methodological complexities and flaws as yet incompletely understood. Scientific research in medicine is much more than the simple use of a universal and abstract scientific method assisted by statistical procedures and software because, unlike for example, agronomy and veterinary care, it involves the human being.

As the American historian of science Rosser Matthews writes, "the emphasis on abstract statistical inference began in the late 18th century. Then in 1946, after a century of debate, medical statistics was first accepted when the British physician-statistician Austin Bradford Hill made the first randomized, controlled clinical trial of streptomycin in tuberculosis" --beginning to move the pendulum to the other extreme. Since then, "the scientific credentials given by experimental physiology and bacteriology laboratory techniques to medical research from the 1840s to the 1940s, depended upon experimental statistical techniques applied to clinical and epidemiological research**,** all the rest being considered merely clinical art and technology". It seems that the just balance in clinical research will be achieved only when the pursuit of clinical results by a clinician, surgeon or psychiatrist investigator, using a more explicit creative and powerful method, retakes scientific leadership in clinical research, assisted where appropriate in statistical issues by a statistician who understands clinical medicine. This will be possible when the new generations of physicians includes full time theoretical clinical investigators to work, like clinical investigators two centuries ago, with the logic of facts again.

The scientific method in medicine must be studied more actively taking account of the great spectrum of empirical research methods, which use supplementary statistical techniques to handle factual data, and the no less important creative, rational research methods of the scientific medical hypothesis, theory, and law. (The concept of ‘medical laws’ has been very little handled by most medical researchers, with the exception of the French physician-physiologist Claude Bernard.) Thus the conceptual and operational framework needed in order to use the power of a comprehensive scientific method in clinical medicine, presupposes the existence of a minimal, very critical and, above all creative, attitude of thought, reasoning, goals, strategy, and procedure. So the first step in examination of a research problem, leading to a first hypothesis, should be the study and design of a complex matrix of facts and ideas, in such framework, without excluding either empirical or rational elements**.** The opportunity will arise subsequently for the guided selection and design of the clinical research, with its essential statistical procedures to handle the sets of variables and group(s) of patients.

But medical scientific research in the last 60 years continues to be subject to heated debates in the ethical, ontological, and epistemological fields throughout the world, in the task of trying to balance ambitious goals with limited means. One main discussion is about which research is the more human-oriented: high-technology research to cure disease and delay death, or low or non-technological research directed to care and palliative action for patients, to promote healthy persons and prevent them from becoming sick or disabled. Another major controversy is about which is more effective on a medium and long-term for human beings: conceptual, complex, and expensive research to explain disease mechanisms and to cure at least to some extent, or simpler and cheaper research to improve an individual's lifestyle and increase the preservation of health.

So today, methodological discussions in medical research continue, about measuring the partial research facts about the patient and establishing their reliability, on the one hand, and about the clinical understanding and judgment resulting from research on the patient as a whole. Regrettably, the growing fusion – and/or confusion -- of technology with science that has arisen**,** has originated acceptance of the randomized controlled double-blind clinical trials of industrial bio-pharmaceuticals, bio-devices, procedures and equipment, and more recently of natural and traditional remedies and techniques, as the only true and objective clinical research.

2. Essential methodological principles

This contribution is based on five main methodological principles:

1) Some scientific general problems still require scientific solutions that go beyond the limits of the present set of medical sciences and the simple articulation of their growing knowledge. This could be achieved through a broad integrative scientific research strategy. It would aim to complement the necessary, successful but insufficient research methodology of reducing complexity to its elements; it would need to employ a process of iterative induction. In this way, unifying principles within a general body of theory of a unified medical science might be obtained, and original hypotheses revealed.

2) Medical research and intervention (R&I) as well as medical research and development (R&D), have many areas of operation: the person and the family at home or in the community, the clinical office, the ward, surgical theatre, involving activities of a basic or an industrial laboratory, or a health service. R&I and R&D may utilize a medical knowledge base, a database or an internet virtual net-clinic or net-lab. These are all related fields or facilities and, taken together, offer opportunities for a unique creative process for solving scientific problems. If their scientific methodologies could be integrated, greater scientific efficacy would result than when they are used separately.

3) There could be a rapprochement and a linkage between existing medical research methodologies, including both empirical and quantitative methods, and the rational inductive and qualitative ones recommended here. This broader methodology could include more data-driven discovery support systems for extending and developing hypotheses. It could include pre-physical experimentation and prediction by modeling and computer simulation, and new ways of formulating scientific hypotheses, law-like generalization, and theory formation; this development would make medical scientific research enterprise more complete and coherent, and would allow the establishment of some scientific general methodological principles of clinical medicine first - and later - of the totality of medicine**.**

4) Tacit epistemological principles about the nature of knowledge in medical science could be identified explicitly in the conceptual framework composed of sub-disciplinary, inter-disciplinary and super-disciplinary paradigms governing current medical scientific research. These could be also taught in order to enhance scientific critical and creative thought, and the aims and methods of the clinical medical scientist. Learning concepts, hypotheses, laws, and theories in a practical way, but

with an abstract approach as well, would help practical and empirical clinical investigators to guide and enrich their own research, and that of more theoretically directed investigators.

5) Strengthening the internal logic of the methodology of clinical medicine research, mainly depends on the revitalizing the scientific method of clinical judgment. In practice this demands a more explicit algorithm of procedures for care, and a renewed creative and heuristic method for research. This should provide a powerful tool that would attract many more young students, generalists and specialists - giving them a better training in clinical research methods to face and solve the greatest scientific challenges still facing clinical medicine science, for the benefit of the individual patient and family.

The scientific method has evolved over millenniums. Mario Bunge, the Argentinean physicist-mathematician defined it well. The decisive breakthrough came with the British Isaac Newton's "Principles of Mathematics" in 1687. His hypothetical-deductive method has now come to be specified in terms of a heuristic series of steps. First, information is gathered by observation of the fact being studied. Second, based on that information a preliminary description or explanation conjecture or hypothesis is created by inductive reasoning. Third, this in turn leads by deductive logic to some consequences that must be tested logically and theoretically with the known knowledge. Fourth, ultimately these deductions are tested by further empirical observation and experiment. If the conclusions drawn from the original hypothesis successfully meet all these tests, the hypothesis become non rejected and accepted as a scientific theory or if sufficiently strong, as a law. If additional facts observed or experiments are in discrepancy with the hypothesis, it may be modified or discarded in favor of a new hypothesis, which is then subjected to further scientific tests. The capacity to predict or not new facts and data, is a key test of a scientific theory.

Thus we have the framework of a new coherent and comprehensive scientific methodology. It is intended to re-conceive, educate, and make clinical medicine research more creative and fruitful for the benefit of patients and healthy individuals, at the same time strengthening the internal logic of research progress with integrative strategies. The hope is, while recognizing the success of the reductionist approach (assuming that a system can be understood in terms of the operation of its constituent parts), to take greater account of the totality of the patient, his environment, family and social milieu.

3. Logical and methodological problems of clinical medicine science

Modern medical sciences can be divided, as in the times of the Greeks, into three main branches: the clinical medical-surgical sciences, which are the trunk or primary branch, and the laboratory and health sciences being the two derived branches. They correspond to clinical and experimental medical practices and public health activities. There is a consensus concerning the colossal amount of fragmentary results of investigations on disease assembled over the last two centuries, but specially by western medical and health sub-disciplines during the last 60 years.

There are many partial theories about different dysfunctions, diseases, and disabilities, even for aging and dying. Their causes, well known by doctors, are not well understood by patients, who need to be more aware of the procedures for their protection, diagnosis, palliation or possible cure. There are few integrative scientific theories that link function, health and survival with good quality of life, taking into account the whole person, the family, and the community. The causal webs have yet to be discovered, as well as are better means to promote, diagnose and recover health - means accepted by physicians and by the individuals they take care of**.**

There is an abundance of clinical, physiological, and pathological observations and confirmations in surveys and trials, with not all their biases yet entirely controlled, despite using placebo, elaborated blind and randomized statistical designs, analyses, and meta-analyses, powerful computers and information high technologies. But hidden variables mean that all these techniques cannot reach yet the rational level required to create, formulate and prove even partial scientific hypotheses and "laws". It can be noted that theory and practice of the traditional oriental and Arab medicine, with western complementary, alternative, and holistic medicine practice, tend to be intrinsically more integrative. Yet they have been poorly studied and tested with the methods of modern sciences, thereby losing the opportunity to unify a thorough body of medical scientific knowledge.

When results in the multi-causality field of diseases are reviewed, doubts remain about the accuracy, order and integrity of some causal chains or mosaics involving simultaneous nosological entities, which explains part of the still limited control achieved over them**.** For instance: is hypertension cause or effect of atherosclerosis, or are both effects of unknown causes? What relationships exist between the traditional risk factors of coronary artery disease, including C-reactive protein and the new homocysteine and Chlamydia pneumoniae factors? In atherosclerosis and cancer research, the old inflammation theory has been re-studied in the last two decades**.** Is helicobacter pylori the real cause of so many "degenerative diseases"? Is HIV a cause or an opportunistic infection in patients with AIDS due to other causes? Are the biophysical and biochemical abnormalities in the brain of the schizophrenic or depressed patient, all causes, or are some partly the consequences of other causes? Are the social contexts and psychological alterations in patients' behavior, all manifestations, or do some belong to their causes, and interact with other environmental and genetic conditions?

There are also hesitations regarding the efficacy of and even damage due to some diagnostic, therapeutic and protective methods used to deal with certain diseases. For example: Surgical treatment is not always effective because of the systemic nature of some cancers**.** Excessive radiation and chemotherapy may accelerate the death of the fragile elder cancer patient**.** Radical prostatectomy and external beam radiotherapy have not been shown conclusively to be better for quality of life than watchful waiting for the treatment of men with localized prostatic carcinoma. Prolonged survival is not ultimate proof of the effectiveness of early detection by screening for prostate cancer, because screening picks up proportionately many cases of slowly progressing disease -- or stabilizing or regressing disease. There is an increase in asthma patients and deaths, in spite of the development of new elaborated preventive and therapeutic measures -- vaccines and drugs**.**

Furthermore, much more research is needed on linear and nonlinear causal relationships of different health states or entities. Is cancer a physiological mechanism of natural selection, once genome deterioration is sensed? Is asymptomatic atherosclerosis really a disease in the advanced elderly? Is the structural progression-stabilization-regression process of atherosclerotic plaques, a physiologic and/or patho-physiological process? Has this microscopic process a nonlinear relation with the macroscopic functional manifestations and responses to the long-term pro-health lifestyle, lipid-lowering and antihypertensive methods? Which are healthy lipoprotein patterns? Are high-risk blood cholesterol levels (more than 5.1 mmol/L) associated to more atherosclerotic patients and deaths**,** whereas low concentrations achieved by therapy (less than 3.9 mmol/L) are related to more deaths by cancer, suicide, violence, among other causes? "Positive" or direct health causes, as well as the means to help strengthen their actions, have to be investigated within a more comprehensive notion of health**.**

There are not as many conceptual networks, models and methodological research, to describe, explain and predict human suffering, well being, health and life, as for disease and death**.** There is a lack of any unique general theory of scientific medical and health integrating and focusing all of them in the whole individual and in the population**.** Suffering is still neither well understood nor well handled**.** Currently, individual health is still seen as a physiological state (without disease) where each known clinical parameter value is within its normal range, less as a state of minimal happiness felt when the vital goals are achieved by second-order capacities or resources. Population health is still perceived mainly as a social state with low indexes of mortality, natality, morbidity, and disability, by age and sex, and high of life expectancy. Up-to-now, "health status" as a unique and integral "well-being state or ideal model", is not yet well described, in contradistinction to the thousands of partial diseases that are well described.

In short, few medical and health theories integrate the complex systems of cognitive levels that interact within the main object of that general medical and health sciences, which is the healthy and sick individual as a whole-system within a social organism, and not only the organic molecule, human gene, and cell**.** Frequently, the biological, psychological, anthropological, sociological and economic elements are excluded or only included as secondary or tertiary components of scientific explanations.

4. Suggestions to improve medical scientific methodology

4.1. Creation of an integrative medical scientific methodology

The rationale is proposed here of a methodological research strategy to establish a scientific foundation, on unifying scientific principles, leading to hypotheses that integrate biological, physical, environmental and social factors influencing individual and public health.

The viewpoint adopted is the following: in the clinically-oriented context of health and disease, an individual should be seen as part of an integrated, complex system. It involves not only his own ‘interior milieu’ but also the physical economic and psychosocial structure – including the home, the family and the community – within which he lives. This implies that while the findings of major projects such as that on the human genome must be taken fully into account, they should be taken in conjunction with the results of ethnological, bio-economic and psychosocial research. Complex systems exhibit behavior patterns and responses to disturbances that are dependent on the various operating sub-systems – hence the importance of understanding both, how these sub-systems affect the total system and how to make use of this understanding.

The ethical values, goals and frontiers of medicine have been internationally reconsidered, and the main medical and health problems throughout the world requiring more scientific research have been re-defined**.** Nevertheless, it is argued here that solutions must be selected with greater recognition of the mind-body dualism of man. The unified corpus of knowledge of medical science must, of course, be developed without leaving out or replacing the dominant existing paradigms governing today's research programs in the medical and health sciences. But isolated, they distort the humane nature of these sciences.

Research should be placed inside a framework of advanced concepts and models of the life and health of human beings within their physical, biological, cultural, economic, and social environments. All scientific theories and principles produced at every level of the clinic, laboratory, and health system, ought to be coordinated within broader theories and precepts, linking the more reducible biological subsystems of a whole and unique individual, and his less reducible economic and psychosocial supra-systems. This would guarantee filling in the empty interdisciplinary and supra-disciplinary spaces of the disciplinary matrix, now only full of increasing sub-disciplinary spaces.

The formalization required to achieve this unity should be different from the first attempts of axiomatization made for classical --and even relativistic-- mechanics. John Brown with the very rudimentary empirical knowledge obtained prior to 1770 attempted to provide medicine with a unitary structure of knowledge about physics. Brown's system in "The Elements of Medicine" was supported by some scientists and philosophers of science such as Kant and Schelling, but criticized as empty formalism and metaphysical speculation by others, such as Hegel, but within the context of non-intelligent animals. However, Hegel made a useful logical speculation beyond that limited basis --not yet tried. But this could now be achieved through an integrative scientific research strategy, using an iterative induction method as follows: In a first phase, the specific theories and principles obtained from scientific facts drawn from the different medical sciences (using their usual reductionist research approach) could be synthesized and generalized by high-level inductive reasoning. Thus, unifying principles within a general body of theory of a unified medical science might be obtained. In a second phase, original hypotheses might be revealed by a novel process of deductive inference from the guiding principles - structuring and concluding them, along with the induction of accepted theories and facts, using the insuperable hypothetical-deductive method**.**

4.2. Use of a "recombinant" hypothesis-discovery support system

The 20th Century saw the arrival of personal computers and the emergence of the internet. These allowed the development of an important breakthrough on discovery support systems: the "Arrowsmith" created by the American Don Swanson (information specialist) and Neil Smalheiser (psychiatrist). This is an aid to the process of generating and assessing novel scientific hypotheses, using the structure of cross-specialty knowledge - information and data - contained in a multiplicity of computer data bases. Initially it used the Medline database, then PubMed, through the internet. The application of interactive software and database search strategies, using the internet, made it possible, in principle, for anyone to perceive implicit relationships and connections not previously recognized. Using the sub-categories of medicine, it could allow identification of possible new causes, treatments or preventive measures involving intrinsic factors such as genetic components or extrinsic factors such as deficiency states, dietary or toxic factors and pharmacological agents. In addition to the etio-pathogenic, therapeutic or preventative approaches, "Arrowsmith" could anticipate adverse drug reactions, identify mechanisms by which agents modulate cellular or organism responses and identify potential animal models for various human conditions.

This brilliant idea originating in the 19th century was re-captured in non-automated form in 1986. It extended the power of PubMed searches, on the premise that results in one area of research can be of value in another, even when not previously recognized. It could be used, singly or jointly, with other

Internet databases such as Biosis, Embase or Scisearch. The system worked with a probabilistic correlation data-driven methodology in a search for new "recombinant" hypotheses, as an aid to the classical hypothesis-driven scientific method. Subsequently an automated data mining technique has been used with the enormous data bases of genomics, proteomics, capable also of utilizing imaging data sets. However, further development of target search-strategies will be required.

4.3. Use of a modeling and simulation research design optimizer

The American surgeon Richard Satava writes, "the process of a new scientific method has been alluded to by scientific savant Stephen Wolfram in his book "A New Kind of Science". The author repeatedly refers to the power of modeling and simulation and the importance of an iterative optimization of the model. "Build the computer model, add the data from real world experiment, see if the results match real world expectations, change the model to more closely approximate the input real world data, and run the next iteration, and so on. This is continued until there is concurrence with the evidence of real world results. Stefan Thomke also emphasized this process of iterative optimization, as carried out by Thomas Edison, in his book "Experimentation Matters: Unlocking the Potential of New Technologies for Innovation". The thesis is not only the importance of the creativity of new technologic ideas, but also the iterative proof of the scientific method to gain acceptance by the scientific community and public at large. The result is that world of science has come to change the scientific method to include an additional step between the design of the experiment (or trial) and the conduct of it. This step is: Modeling, Simulation and Prediction – by repeated iteration to optimize the design of the experiment– and only then to conduct the experiment. This appears to be, in effect, a new scientific method, perhaps designated the (or a) simulation method of science. This idea can be extended".

"The military has a research project, the Virtual Soldier, which is taking the first steps toward creating such a computerize patient (or soldier). This computer model, called a holographic medical electronic representation or holomer, actually exists in the computer (and on the soldier's electronic dog tag) as an information surrogate for the soldier. The holomer is also a visual electronic health record. Of course, healthcare has no computer representation of its "product", the patient, although the emergence of total body scanning offers a first step into this area of "computer representation of our patients". Once it is learned how to approach our patients from this radically new perspective (that is, viewing their holomer representation in 'information space' on a computer), it will be possible to catch up with the rest of the scientific community and extend the traditional scientific method to the new simulation method - and rapidly expand our capabilities".

"In the context of patient care, if each person had their own holomer, it would be possible to simulate a treatment option before prescribing a medication – for example a patient with an arrhythmia could be given a virtual dose of an appropriate agent to see if the arrhythmia would resolve, and if not, the dose could be adjusted until arrhythmia within the holomer ceased. Or again, before a complicated surgical procedure, the surgeon could rehearse the simulated surgical procedure on the patient's holomer before operating upon the patient. Any errors in drug dosage or surgical technique would occur upon the holomer, not on the actual patient. Today, in clinical trials of chronic diseases (of a new drug, device, procedure, etc) hundreds and thousands of patients are subjected to a new, unproven treatment (and compared to controls) over a fixed period (usually from months to 10 years). By analogy to other disciplines like weather, aviation, manufacturing, one might envisage creating a database of anonymous models (holomers) of a million different patients and conduct a clinical trial over 50 years of time – and simulate the results rapidly on a supercomputer, with no risk to any patient. The purpose of such a suggestion is not to eliminate clinical trials or basic scientific research, but rather to dramatically decrease the resources and time to conducting numerous experiments on the road to the final experiment that provides the conclusive results. The principles of the established scientific method have served us well for long periods of time; however, the new technology and methodology that exists today (already being used by others in the scientific community) can extend the traditional scientific method to the simulation method and elevate scientific inquiry to an even more productive plateau. If the remainder of the scientific community embraces modeling and simulation, so too should medicine, whether in daily clinical practice or in rigorous clinical research".

4.4. Enhancement of clinical scientific hypothesis creativity

Today many clinical physicians and investigators are well versed in the "state of the art" of the several and diverse fields of clinical practice knowledge and technology, through textbooks, journal reviews, task forces, and guidelines for clinical practice and education. However, when it comes to clinical research and the formulation and testing of hypotheses, there is scope for confusion between clinical research hypotheses and those on which statistical testing is structured. They may be concerned about the statistical design of their clinical research and of good clinical practice in the research. The fact is that all the statistical methods were created by non-physicians and non-clinical physicians not all of whom know the "state of the art" of clinical medicine. Not surprisingly, clinical physicians and investigators frequently start a research from an intuitive empirical hypothesis having a very low level of theoretical abstraction, very near to the practicalities of prevention, diagnosis, prognosis, therapeutic or rehabilitation technologies, but with limited theoretical support. They may confuse the concept of clinical hypothesis with the null (H_0) and alternative (H_1) auxiliary statistical hypotheses, leaving all these issues to the clinical biostatistician or the statistical mathematician, perhaps simplifying to the extreme the creative part these experts could contribute to the whole design and performance of the clinical study, trial or survey. This confusion of the scientific theoretical method of the hypothesis formation and deduction of the testable research model, on the one hand, with the supplementary statistical hypothesis testing on the other is not exclusive to medical science; it happens in other sciences too**.** Indeed, half a century ago, Bunge wrote a powerful book of one thousand pages to demonstrate that the scientific method (in physics), was much more than statistical methods; this modest work offers significant indications about how to develop a more comprehensive medical scientific methodology.

The formation of scientific hypotheses and the design of statistical hypotheses are essential to modern clinical, surgical and psychiatric research. In fact, the design of statistical hypotheses depends upon the previous formation of a scientific hypothesis, which must be based on deduced facts coherent with clinical theory and logic. In order to advance clinical creative thought more effectively, prior hypothesis formation must be achieved before the step of designing the statistical analysis in clinical research

Over the past 60 years, the application of efficient experimental, quantitative, epidemiological and computing algorithmic methods has furthered the progress of large applied empirical screening and confirmatory randomized and blind clinical trials: therapeutic, diagnostic, and preventive**.** At the same time, however, the development of the very scientifically creative initial observational, qualitative, and pre-computing heuristic methods for exploratory, descriptive, explanatory, and interventionist small clinical discovery trials and surveys have remained virtually stationary. Several factors could explain this situation:

Clinical judgment is primarily used to discover routinely operational hypotheses about a particular state or process of an individual patient during clinical care. But it has lost any real appreciation of its potential value in the discovery of more creative conceptual hypotheses: about particular and more general states or processes in one or few more patients - hypotheses that could be useful in a broader clinical scientific sense. Although part-time and full-time clinical investigators have now better abstract scientific operational training, most of them lack an adequate conceptual background in scientific method and logic of clinical medicine research; in brief, they do not know how much they can expect of the techniques of statistics and informatics. But if these clinical investigators fail to do their own basic clinical research work, they will lose the scientific skills necessary to perform the rigorous clinical trials and surveys suggested from outside the clinic, most of all on the scientific hypotheses developed by the full-time experimental, industrial, and epidemiological investigators. This is where the data-driven computerized systems mentioned above could be a powerful aid – in the search for general scientific hypotheses inside the clinic, and pre-testing them in a virtual way before beginning a formal investigation.

Other suggestions can be offered to support this approach: 1) heuristic rules about clinical judgment have to be more closely studied and made more explicit; 2) programs for clinical research training must offer a more thorough conceptual background in logic and the scientific method in clinical medicine, clinical medical statistics and informatics; and 3) more part- and full-time clinical investigators should be dedicated to the theoretical formulation and testing the evidence for new scientific hypotheses - factual deductions that aim at improving basic clinical scientific knowledge, and not only clinical technology, in the clinical sciences.

Each of these suggestions could help the method of clinical judgment to regain an appreciation of being able to discover new, general, scientific hypotheses. To improve the efficiency of clinical research projects and programs, the clinical biostatistician, laboratory experimentalist, and field epidemiologist, must work together with the clinician, surgeon and psychiatrist researchers, to help the development of fully scientific, heuristic and creative rules by which to formulate general scientific hypotheses - starting with sound clinical judgment. By drawing on progress in the basic research in clinical sciences, the procedures used to discover new general scientific hypotheses, now implicit, will become explicit, and their future formalization and computerization will become easier and quicker. More imagination, more intuition will be needed to create new rules and algorithms of clinical scientific creativity and to develop heuristic and scientific methods for generating clinical hypotheses and for empirical hypothesis formation. These improvements are needed also in the design of clinical trials to provide evidence in test of hypotheses.

Hitherto, the work of the clinical investigator in making precise observations working with the individual patient at the bedside or in the clinic or community, exchanging and studying the work of other investigators, has not been seen as a part of the scientific method in medicine. Yet here is where the first empirical hypotheses could arise. It is in this point in the whole scientific process that the research can succeed or fail in producing theoretical developments, and when the first factual implications of the hypothesis can suggest further detailed investigations. In short, the key for the discovery of new causal physiological and etio-pathological knowledge is the observational investigation of single case studies and groups of small number of patients, correspondent to phases I and IIa of the clinical trials, following up the pre-clinical research together with non-clinical scientists.

However, medical scientists have to be much better prepared in medical research. First, they must be trained in the methodology and logic of in-depth research on medical systems, factors and relationships concerning medical and health scientific problems, and subsequently, in medical statistics, informatics, and other sciences. In recent decades, a focus on experimental design and data analysis using statistical techniques has been dominant. But while these are important aids, they have, to a degree, distracted clinical physicians from their primary responsibility in clinical investigations: to generate hypotheses by the intensive study of patients. This raises a notoriously difficult subject: "the incomplete application and adjustment of the scientific method to the clinical medicine reality of the individual patient and group of patients, and the incomplete foundation of the clinical medicine science", and how this deficiency could be solved.

5. Underlying theoretical and philosophical problems of medical science

First, a very interesting statement of the Greek medical oncologist Dennis Razis needs to be mentioned. Writing in 1988 on how medical progress has been achieved, he pointed out: "In theory and methodology the change has been from determinism to indeterminism in all sciences from microscopic physics to biology. Now, statistical association is almost never one hundred or zero percent".

However, the determinism of physics could scarcely have been achieved without mathematical formulation, but this is lacking in even macroscopic medicine. Few medical laws have been structured in a determinist form even in physiology, although they must exist in all medical phenomena too. Medicine has passed directly from the phase of pre-scientific statements with little supporting evidence through the phase of statistical techniques applied to most scientific statements with much stronger evidence and typical probability values of confidence between 0.001 and 0.05. The embryo of determinism that could have been developed more in medicine between the 18th and 20th centuries was diverted by Pierre Laplace's powerful suggestion of indeterminism in medical therapeutic decisions --afterwards applied also in most biomedicine and epidemiology.

As Matthews writes, Pierre Laplace in his "Philosophical Essay on Probabilities" had stated, concerning determinism that probabilities lead to rational inferences in situations of incomplete knowledge. He explicitly cited medical therapy as a possible domain for applying the calculus of probability. He said, "Different levels of analysis must be distinguished. Our knowledge is incomplete, and we have to live with that. That is why probabilistic reasoning is extraordinarily successful in practice, but when it works; this is due to our partial knowledge". This is true and probability has helped and must continue to help clinical medicine in decision-making in conditions of partial knowledge. However, decisions on therapeutics were not in the 18th century, and are not even today, the only and main objective of scientific research in clinical medicine science. But the completion of scientific knowledge in all aspects of medical systems, included therapeutics, should be precisely the major labor of science in clinical medicine.

Karl Pearson lacked Francis Galton's originality… but it was his zeal… that created the statistical methodology and sold it to the world. Galton had a thought: "In science credit goes to the man who convinces the world, not the man to whom the idea first occurs"**.** This happened with Galton's correlation coefficient, which has passed to history as of Pearson. However, Pearson, a mathematician "who did not study medicine", wrote in the "Grammar of Science" a thought crucial to understanding one of the major hurdles still faced in medicine. As Matthews writes, Pearson said, "The very statement of the law of causation involves antecedents –sameness of causes-- which are purely conceptual and never actual. Permanence and absence of individuality in the bricks of the physical universe are only demonstrated in the same way than the bricks of a building are for many statistical purposes without individuality. The exact repetition of any antecedents is never possible, and all we can do is to classify things into like within a certain degree of observation, and record whether we note as following from them are like within another degree of observation. Whenever we do this in physics, in zoology, in botany, in sociology, in medicine, or in any other branch of science, we really form a contingency table, and the causation of the physicist solely results from the fact --not that the contingency coefficient of everything physical is unity-- but that he has so far worked to most profit in the field, where his contingency is so near unity that he could conceptualize his relationships as mathematical functions"**.**

At this stage of the examination of the evolution of the modern scientific method and its foundation in clinical medicine, it would be interesting to examine the theoretical homologues that could exist with the theoretical, methodological and philosophical problems in the 20th century quantum mechanics. This will be done to see if it is possible to extract some valid and useful experiences and suggestions that could help clinical investigators, to use all the potentiality of the scientific method and give a more comprehensive scientific foundation to clinical medicine, surgery, psychiatry, all increasingly depending from external statistical techniques and epidemiological approaches since the last century. Reference should be made to three discussions on the foundations of physics in the Gross' book: "Quantum Philosophy" by Sheldon Goldstein of Rutgers; "Physics and Common Nonsense" by Daniel Kleppner of MIT; and "Science of Chaos or Chaos in Science" by Jean Bricmont of Belgium.

Some theoretical and philosophical problems arisen after the foundation of quantum mechanics in the 20th century, based on the "randomness" and "indeterminism" to reality, conducted to the creation of a "quantum philosophy", and to a long discussion among the greatest physicists and mathematicians. The clear constructive response of the Austrian physicist-mathematician Albert Einstein was as follows: "I am, in fact, firmly convinced that the statistical character of contemporary quantum theory is solely to be ascribed to the fact that this (theory) operates with an incomplete description of physical systems…. [In] a complete physical description, the statistical quantum theory would… take an approximately analogous position to the statistical mechanics within the framework of classical mechanics". Part of what Einstein was saying here was that (much of) the apparent peculiarity of quantum theory, and in particular its randomness, arise from mistaking an incomplete description for a complete one**.**

Afterwards, John von Neumann, one of the greatest mathematicians of the 20th century said: "Einstein's dream, of a deterministic completion or reinterpretation of quantum theory, is mathematically impossible", and von Neumann claim was almost universally accepted, and followed by most of the world scientists. However, in 1952 David Bohm, through a refinement of de Broglie's "pilot wave model" of 1927, found just a reformulation of quantum theory. Bohmian mechanics was precise, objective, and deterministic—not at all congenial with quantum philosophy and a counterexample to the claims of von Neumann. Nonetheless, the "Bohmian theory" and the "hidden variables theory" continued both in doubt for more that a quarter of century.

Based on recent experience with the quantum theory, it could be deduced that medical theory has been operating with an incomplete description of medical systems. The deterministic completion or reinterpretation of medical theory could be made with or without mathematics at the moment. With the medical theory and factual information already discovered in the last 200 years, some clinical medicine theory could be reformulated in a more precise, broader and deterministic central corpus of theory; crucially it would be applicable in diagnosis, therapy and prevention of diseases scientific matters, continue being applied branches with the most practical and direct consequences.

The core of creative clinical research in all its forms, as well as in the basic sciences, and in epidemiological-health sciences, should be the discovery of the hidden factors and hierarchization of the variables and their inter-relations operative in clinical, pre-clinical, and post-clinical systems. In the medical systems under study, when most key variables come to be discovered, the important contingency coefficients could be so near unity as will render unnecessary the probabilistic statement. Randomness could be greatly reduced and the systems could then be explained scientifically with deterministic statements and mathematical functions, as is usual in physics and other hard sciences. The discovery of the hidden variables must be done by clinical investigators with a keen interest in the clinical exploration not only of the whole patient but also of the whole natural and social environments in which the patient lives. It must take into account all direct objective and subjective evidence as well as all the interventions experienced by and carried out on the patient and his/her detailed responses, as well as all indirect evidence originating with all the methods and instruments of diagnosis and of biological, economic, and psychosocial evaluation.

Unsurprisingly, in the absence of enough empirical evidence in the human sciences and of a scientific method of clinical judgment in medicine, the Queteletian and Laplacian scientific approaches to physiological data and to clinical judgment with probabilistic mathematical precision have produced very important advances in medicine up to the 21st century. However, medicine advanced much more in etio-pathogenesis and preventive knowledge, in diagnostic and therapeutic technologies of disease, than in the knowledge of the complete system of the causal physiological human being and in methods to maintain it entirely healthy in body and mind at the same time. Thus, the task of the full application and adjustment of the scientific method and foundation of medicine stays unfinished. The body-mind unity problem is not solved yet, and its solution is also a need of the external logic of clinical medicine to satisfy the demands of public health, by focusing much more on the quality of the biological, economic, mental and social health, especially as life-expectancy increases.

A way forward for the scientific hypothesis-driven method and logic of medical facts and systems can be seen in randomized clinical trials and surveys and more recently, and powerfully, in data-driven discovery and modeling-simulation systems. But physicians and neuro-scientists will have to discover new ways to solve the body-mind duality stated by Descartes in the 17th century, centering also their attention in the mind, in order to be able to describe better the human health system, finding in the human physiological system the hidden variables, whose absence has led most physicians and mathematicians between the 18th and 21st centuries to believe that all human health phenomena in medicine had an "irreducible randomness". The corollary of this concept of irreducible randomness was that health phenomena could only be handled indirectly by statistical inference, and not directly by clinical inference or by mathematical equations as in the hard sciences.

Informatics data-driven discovery support systems could help to find those hidden variables of the human physiological system. However, at the moment nothing seems able fully to replace the basic hypothesis-driven method of clinical judgment, if used by a well trained clinical investigator seeking to discover the hidden variables of the whole diverse system of the human being and its subsystems - in his/her patients on the ward, in the office, and in the home with the family. Nevertheless, the scenario is opened also for mathematical investigators to develop, together with the theoretical clinical investigators, newer human and clinical mathematical models and techniques to characterize, describe, simulate, explain and predict the systems behavior of the complex human being by computer simulation and other means.

6. Unified methodological system for investigation in medicine

6.1. A trans-methodological model of clinical, basic and health sciences

To understand how to develop a unified methodological system of medical scientific research, the first thing is to place this matter briefly in its historical and logical context. Medical sciences were born as a result of the use for a long time on the patients of the clinical medicine judgment method, which from its very beginnings has been as the American physicians Alvan R. Feinstein and H. Tristram Engelhardt has stated is more qualitative than quantitative method. Subsequently, the later differentiation of that first, general medical science into clinical, laboratory and health sciences began with their respective scientific investigations and methods. To date medical sciences have been developed as more theoretical on the one hand or as more practical sciences on the other, with the important assistance of many mature sciences like physics, chemistry, biology and even the so called "immature" sciences as psychology and sociology. The union of physicians with physicists, chemists, biologists, psychologists, sociologists, mathematicians, economists, and so forth, has made crucial contributions to medical science progress at opportune moments.

This help has given scientific methods to medical sciences to create, for medical facts, the theory they needed with a measure of certainty, aiding through medical education to achieve the goals of medical and health care: less suffering, solace, illness, and handicap, and more health and well-being, as the American physician Dan Callahan stated. However, the first medical science was divided into dozens of clinical and derived laboratory and public health sciences. Most of the medical sciences of today study and measure the body and its diseases through its parts, as clinical cardiology and cardiovascular surgery, clinical neurology and neurosurgery, and so forth, and the etio-pathogenesis mechanisms, as microbiology and virologist, molecular biochemistry, genetics and immunology, and so on. Only psychiatry, studies exclusively the mind and its illnesses with big difficulties to measure the functional ones yet, but not so much as its health and well-being. Bio-epidemiology and social epidemiology study the entire communities and populations, with their mutual biological and social environmental interactions. Only general and family medicine are trying to study the patient and his family and community as entire body-mind units, each one with their specific distresses, ill health and disabilities, and also their health and well-being, in their own environment.

So far, in their major solutions to the scientific problems of the different parts of the human being, each science - isolated or associated - has contributed many pieces of medical scientific theories and methods, but have not well achieved the goals of medicine, as stated Callahan. Paradoxically, they have increased the conceptual and methodological problems, because as poorly-integrated contributions, they have not been suitable to deal comprehensively with the complex medical facts of the entire human being**.** For all these reasons the methodology of medical scientific research still has not its own body of knowledge. It has not gone beyond the accurate and successful application of the general scientific hypothetic-deductive and statistical-computing methods; it has not been extended to inductive methodologies applied to factual, observational research in the laboratory, the health system and above all in the clinic. This less than eclectic status is limiting the enormous potential for progress that medicine has today**.**

This compartmentalizing situation disintegrates the harmony of the unique creation process of medical research. The process should be complete, dynamic, continuous, basic and applied. It begins with creative (i.e., sensitive to significant observations) medical practice in any research field – physical or virtual clinic, laboratory, or health system -- and finishes generally in clinical medicine and public health practices, only to restart, improving theory and practice iteratively. And medical investigations in the specific subsystems must integrate multilaterally their methodologies.

Medical scientific research requires at least four conditions to be integrated methodologically: First, acceptance of the general methods of scientific investigations in the clinic, laboratory, and health system; Second, the synthesis of the specific norms and skills of good common medical practice (this includes the set of auxiliary and specific scientific tools, technological and non-technological and particularly, relations: physician-patient, physician-family, and physician-community relations); Third, the assimilation of models and methods of health and economic organization and management, and the production of a suitable climate to encourage creativity and the active support of good ideas, hypotheses, protocols, research data, scientific outcomes, as well as rapid application of the results into current medical practice, taking account of cost-effectiveness criteria; Fourth, the development of clinical judgment and recognition of its importance in clinical research, in addition to new methods for modeling, experimentation and prediction by computer simulation for investigating etiology, diagnostics, therapeutics, rehabilitation and prevention. Finally, of course, formulation of scientific medical hypotheses, law-like generalizations, theory formation and systematization should maintain close contact with the conceptual framework of medical sciences and also with all levels of medical education and care.

6.2. Re-unification of clinical scientific method for practice and research

The potential of clinical medicine research to generate firsthand new scientific hypotheses must be urgently reanimated, supported by the essential methods of verification. To successfully achieve multilateral integration, careful research must be done on the logic and methodological system of clinical research. The complex link between the two current methods of scientific clinical, surgical and psychiatric investigations should be examined: 1) research on a specific diagnosis and prognosis, with preventive and/or therapeutic interventions (R&I) in clinical care, individualized in a sick or healthy person and/or in a family of a community - through the current procedures of clinical judgment and decision-making in common medical and health care -- but using more quantitative research methods; and 2) general research, starting from the one-case study, then to an initial study of a few cases -- applying more qualitative research methods at this initial step --, up to the pilot study or trial in large numbers of patients. Further, while also studying the theoretical problems, a search should be undertaken for new concepts, causes and methods of research and development (R&D) of clinical care, in patients affected by one or more diseases or risks and/or in healthy individuals --

through a revitalizing of clinical judgment as the basis for a scientific method for the discovery of generalities. The aim is not to oppose the practice of clinical to research on clinical care**,** or clinical research to laboratory or public health research, empirical methods to theoretical and interpretative methods, qualitative to measuring or quantitative methods; the aim is to reconcile all of them. This could be achieved by studying the relationships between theories and methods among researches in the clinic, laboratory, and health system, and the interactions and exchanges among their outcomes, coordinated by the principles of clinical R&I and R&D because only clinical research focuses and works on the whole individual.

Thus, non-mathematical deduction-like inferences could be achieved from empirical or low- and medium- theoretical levels by intuition and induction; in addition to being analytic as with all deductions, these could also address new ways to suggest high and low level particular hypotheses, at the empirical level, arising from the facts. Through these unfamiliar analytical inferences, the general principles of clinical medical knowledge could activate the generation of new testable hypotheses while the general principles of clinical practice could lead to devising new technical hypotheses to improve the quality of care of an individual patient in clinical medicine R&I. Such heuristic and creative methods in clinical science and clinical practice employed to generate original hypotheses could probably be more easily computerized than the ones developed to date without these general principles**.**

These ideas about unifying clinical R&I and R&D could be extended to epidemiological and public health scientific tasks, which work with partial and whole populations of individuals. The point would be to harmonize epidemiological and health programs and management with epidemiological and health research.

Somewhat more than a decade ago, "The Goals of Medicine", an international theoretical research project of the US Hastings Center and thirteen countries, in cooperation with the World Health Organization, coordinated by Callahan, established priorities for its long-term progress, and planned to undertake reforms in medical research. The first reform, which is to improve medical research using both medical research paradigms, has generated, since 1994, an international theoretical project, the complementary emergentist research strategy in the bibliography. Concerning the second reform, to increase research in clinical medicine, epidemiological and public health, in addition to the extraordinary laboratory research "Human Genome Project" designed at the end of the 1980’s, and also the "Human Brain Project", something else has been lacking: such as a "Human Health Project"**,** as well as a "Human Development Project", and a "Human Behavior Project". These would employ the new Sachs’s method of clinical economics**,** specially in poorest villages and slums, and those of classical and clinical psychology and clinical sociology, into the framework of a new "bioeconomic-psychosocial" paradigm.

Nevertheless, such efforts will not be enough to satisfy the present and future needs of national, regional, and global medical research, education and care worldwide. This is because laboratory and health researchers cannot do the indispensable research that could be undertaken by the huge mass of clinicians, surgeons, and psychiatrists; they cannot therefore, personally solve the disease and health problems of the entire person. The clinic is the critical research field. In this sense, the unity of the health of the human being could only be approached through a "Human Medicine Project"**.** This could develop a "Clinical Medicine Interface" subproject to rigorously validate and translate those biological, economic, and psychosocial results from the basic and public health jumbo projects into practice. It could also interface to other projects such as the Digital Human, Medical Simulation and Training, Virtual Autopsy, the Virtual Soldier, etc, as Satava stated**.** However, the following clinical medicine subprojects: "Basic Clinical Medicine", "Conception of New Clinical Medicine, Surgery, and Psychiatry Research Spaces", "Creation of New Family Medicine Research Spaces"**,** and "Patho-Physiological and Dynamic Health Classification" should be planned, - the latter two for use in primary general medical care and family medicine**.**

7. Conclusions and Recommendations

Clinical medicine is the heart of humanitarian and scientific practice, research, and science of medicine with the individual human patient. It has advanced greatly in two centuries of scientific research. However, scientific knowledge and systems in clinical medicine are yet incomplete, with many hidden key variables still to be discovered by clinical investigators - through the old and often-criticized scientific method of clinical judgment. No other clinical method seems able to substitute this basic hypothesis-driven method, although many others can and will complement it. The still factual and theoretical lacunae in clinical medicine systems are the reason why, currently, the clinical researcher cannot investigate anything without the help of probabilistic techniques and statements. But new degrees of observation and levels of analysis must be employed for the completion and re-interpretation of medical systems theory in deterministic statements and also in mathematical formulas. In future research, clinical investigators must make use of all the modern theoretical and empirical methods, and utilize all the modern technological instruments of diagnosis and research developed, and have the collaboration of all the derived pre-clinical and post-clinical sciences and scientists, and of all the contemporary hard and soft sciences. It is fair to say that this huge scientific research program was impossible to do two centuries ago.

Clinical investigators will have to discover new ways to solve the body-mind problem, centering their attention much more on the mind. They will have to find, with much more research in the human physiological and pathological, healthy and sick systems, the key hidden variables, the failure to recognize which has given the mistaken idea to most physicians and scientists since the 17^{th} century: that all human phenomena in medicine had an "irreducible randomness", which can only be handled indirectly by statistical inference, and not directly by the clinical medicine inference or even by mathematical equations as in any hard science.

Specifically, five key proposals are presented.

1. Clinical medicine and clinical health research should concern themselves with the whole human patient, his family and home, his community and the physical and social environment in which he lives. This shows, amongst other matters, that the mind-body problem cannot be disregarded. Research techniques in the social and environmental sciences may well be needed.

2. Clinical basic science and research should study more, apart of therapeutics and prevention of disease, the restoration of health status, capacities and resources, and health promotion in the patient, creating a more patho-physiological and dynamic health classification system for the third era of health.

3. It is necessary to establish a hard core of scientific theories. law-like generalizations and high-

level, well-developed hypotheses in clinical and health sciences, these all to be protected by formal methodological rules in order to direct attention to positive rather than fruitless research paths.

4. Full use should be made of the "Arrowsmith" approach for the purpose of searching data-bases for significant correlations and relationships not otherwise recognized.

5. Modeling and simulation should be used in medical research. If the remainder of the scientific community embraces modeling and simulation as an important research tool, so should clinical practice and rigorous clinical research. When optimizing a model by iterative adjustments and repeated trials leads to a satisfactory representation of its object, the likely outcome, in the real world, of a selected intervention can be pre-tested by a simulation on the model.

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Related Chapters

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Medicine, Science, Basic, Clinical, and Public Health Sciences, Physiological Sciences, Physical and Biological Sciences, Economic, Psychological, and Social Sciences, Philosophy of Science, Theory of Science, Logic of Science, Positivism and Post-Positivism.

Glossary

Acceptability **:** Term that is judged in terms of the degree to which observations and experimentations can be reproduced.

Axiomatic method	**:** In logic, a procedure by which an entire system (e.g., a science) is generated in accordance with specified rules by logical deduction from certain basic propositions (axioms or postulates), which in turn are constructed from a few terms taken as primitive. These terms and axioms may either be arbitrarily defined and constructed or else be conceived according to a model.
Biomedicine	**:** It is medicine based on the application of the principles of the natural sciences and especially biology and biochemistry.
Hypothetic-deductive method	**:** Procedure for the construction of a scientific theory that will account for results obtained through direct observation and experimentation and that will, through inference, predict further effects that can then be verified or disproved by empirical evidence derived from other experiments.
Mathematics	**:** It is the science of numbers and their operations, interrelations, combinations, generalizations, and abstractions and of space configurations and their structure, measurement, transformations, and generalizations.
Medical Technology	**:** The term technology began to define well the double essence of the practice of medicine in its progress, first as an applied art, and at the same time later as an applied science too, using knowledge, materials, tools, techniques, and becoming further dependent of the advances of applied medical and allied sciences, to increase the efficiency of medical work.
Medicine	**:** The science concerned with the maintenance of health and the prevention, alleviation, or cure of disease.
Method	**:** It is a discipline that deals with the principles and techniques of scientific inquiry.
Objectivity	**:** Term that indicates the attempt to observe things as they are, without falsifying observations to accord with some preconceived world view.
Paradigm	**:** It is a philosophical and theoretical framework of a scientific school or discipline within which theories, laws, and generalizations and the experiments performed in support of them are formulated.
Philosophy of science	**:** The study, from a philosophical perspective, of the elements of scientific inquiry and of their validity. Taken broadly as the progressive improvement of the understanding of nature, the intellectual enterprise of science originally formed an integral part of philosophy, and the two areas of inquiry have never finally separated.
Physics	**:** The science that deals with matter and energy and their interactions
Public health	**:** It is the art and science dealing with the protection and improvement of community health by organized community effort and including preventive medicine and sanitary and social science.
Science	**:** It is system of knowledge that is concerned with the physical world and its phenomena and that entails unbiased observations and systematic experimentation. In general, a science involves a pursuit of knowledge covering general truths or the operations of fundamental laws.

Scientific method **:** Term denoting the principles that guide scientific research and experimentation, and also the philosophic bases of those principles. Definitions of scientific method use such concepts as objectivity of approach to and acceptability of the results of scientific study. Scientific method also involves the interplay of inductive reasoning (reasoning from specific observations and experiments to more general hypotheses and theories) and deductive reasoning (reasoning from theories to account for specific experimental results). By such reasoning processes, science attempts to develop the broad laws that become part of our understanding of the natural world. Science has tremendous scope, however, and its many separate disciplines can differ greatly in terms of subject matter and the possible ways of studying that subject matter.

Surgery **:** Branch of medicine that is concerned with the treatment of injuries, diseases, and other disorders by manual and instrumental means. Surgery basically involves the management of acute injuries and illnesses as differentiated from chronic, slowly progressing diseases, except when patients with the latter type of disease must be operated upon.

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Biographical Sketch

Dr. Rodolfo-Javier Stusser is a physician trained since 44 years ago as researcher-professor on top basic science labs, on internal-general medicine practice in urban/rural centers, and on public health, biostatistics/ informatics in Havana University (HU), who founded the HU Basic Sciences Institute (1962) and Scientific Research Center (1968), Health Development Institute -MOPH- (1976), Clinical Research Center (1992) of West-Havana Scientific Pole, and assisted the Plaza- (1990-) and Vedado Community-Polyclinics to become Science-Technology Units. He has 38-year studies on the logic, forecast, policy/program of clinical/ population research/trials, health services research, on infant and maternal, cancer, myocardial infarction and stroke preventable mortality, global health research, among other matters, in Cuba, Nicaragua, and East Europe Comecon 1969-1989, PAHO/WHO 1988-2006, and 43-year teaching students/residents, researchers/ professors in neuro-physiology, semiology, research method/statistics, epidemiology/informatics. He designed and founded the laboratories of medical research methodology for 15 Cuban institutes of health in 1977, and was teaching pioneer in Cuba at the Cancer Institute of the logic of clinical and epidemiological research/trial at HU 1977-2006, as well as at Managua University and PAHO/WHO Office 1988-1990. His Ph.D. degree-thesis results: "Five unified-scenarios for cancer research and prevention for Cuba 1985-2000" (first in Iberian America), were applied in the planning of three-MOPH-programs: "Anti-Cancer Struggle" and "Oncology-Specialty" 1987-2000, and "National Health System's Objectives, Goals and Directives 1992-2000".
Dr. Stusser is the first Cuban International Member of the American Academy of Family Physicians, member of the International Societies of Clinical Biostatistics and Internet in Medicine, and founding Partner of the WHO-Alliance for Health Policy/System Research. Since 2000, he is Adviser/Lecturer at Havana to US People-to-People Ambassadors-Professional Program, Sam Nunn School of Foreign Affairs-Georgia Tech Institute, doing lobby work to restore the US-Cuban scientific research collaboration initiated 250 years ago. In 2006, he retired from his state physician job to make personal travels and studies.

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