

Review Article

Prolegomena to a True Integrative Medical Paradigm

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Abstract

When a paradigm starts to show signs of failure to cope with significant questions in any basic/applied branch of human knowledge, there come on the scene those who have perused the related literature enough to either answer those major questions according to the established paradigm or proffer a (wholly) new way of looking at things. In the latter case, the history of science tells us, a *paradigm shift* takes place. Modern medicine cannot be proven to be totally disconnected from its traditional roots. Where traditional medicine came to give its place to present-day conventional medicine, a number of humanistic aspects of healing in addition to some axioms of olden wisdom were actually lost. Employing a personalized strategy by taking into account the patient's specific conditions, Integrative Medicine (IM) endeavors to apply all appropriate interventions from a whole set of science branches to bring back health. However, this does not remain fully without its own challenges from almost all sides. Complementary and Alternative Medicine (CAM) on the one hand, and Evidence Based Medicine (EBM), on the other, have their own rightful say in the affair. Delving deep into the details of medical history's ups and downs, and examining—from the philosophy of medicine's and philosophy of science's standpoint—the pros and cons of integrative medicine, this present treatise makes a systemic, inter-disciplinary effort to put forward the best possible paradigmatology in a methodical way as far as the demands of society are concerned.

Keywords: *Complementary and Alternative Medicine, Evidence based medicine, Traditional persian medicine, Integrative medicine, Person-Centered care, Systems biology, Biostatistics, Paradigm shift*

Introduction

Is medical practice to be considered a pure branch of science or, possibly, more of a mode of an art? Is it interactively engaged with other departments of modern “basic” science or does it possess its own specific methodology of research and investigation? How can human beings as subjects be probably brought under magnifying scrutiny as far and as long as they are not precisely identical to other objects of modern-day science?

If we should get into the more traditional groove of thinking of patients as whole beings to be artistically pictured out through the skillful hands of physicians, then the shift of emphasis is duly to be put more on the human/humanitarian facets of clinical practice [1]. Otherwise, extended discussion has to be made on the philosophy of turning medical practice into a purely EBM-oriented corpus of knowledge [2].

One of the main questions confronting biomedical students and workers is whether medical practice uses science to provide health for human beings or it is itself a true division of science like any other scientific branch [3]. In case we do not regard medicine as a way of manipulating human bodies/minds much the same manner as physics and chemistry treat physical objects, then: finding, collecting, and making inferences from evidence (basically) differs from evidence-collecting in fields such as geology, physics, and chemistry.

Nowadays, the huge bulk of prestige is accorded to those with the largest number of scientific articles in a particular field, generally published in respected journals with some high impact factors. The clinical practice of the traditional healers is considered non-academic and even superstitious because they are not based on evidence-based

research. However, even according to some of the most optimistic estimates, not more than 20% of conventional medicine's literature is actually based on Evidence [4].

The truth of the matter is that nearly the majority of those practicing medicine know full well that not all remedies are totally based on scientifically objectively verified evidence [5]. Randomized Controlled Trials (RCTs), the main route of finding curing remedies for human ailments in modern-day medicine, are themselves replete with faults and defects [6].

Most of the time, a modern clinician is presently viewed as a programmed human technician rather than a care-giving professional healer [7]: limits and bounds are put on the range of diagnostic capabilities of a physician by restricting her to categorized (and sub-categorized) classes of diagnosis; repeated recourse has to be made to fairly expensive paraclinical lab tests only to be, later on, granted a specific list of medications prescribed [and “guaranteed”] by huge pharmaceutical corporations. Very little attention is paid, in the course, to the anguish feelings and concerns of patients themselves when it comes to decision-making for the future of their treating process.

Not scarcely are our academically-educated doctors (and nurses) finding themselves in more and more frequently appearing cases where they do not feel able to prescribe university-learned prescriptions for their patients: they simply do not answer to conventional medicine's

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cures [8,9]. This might well be the implicit result of the actuality that a large number of patients are (much) far away from the biological conditions of the “mean” in the RCTs, though there is little doubt that there are other causes for the abovementioned problem, too [2,10].

Evidence-based research in medicine

We are in a period that no new medical hypothesis can be accepted excepting that sufficient evidence-based studies confirm them [11]. The advent of the New Age deemed the inadequacy of evidence as a most significant shortcoming on the part of any “scientific” activity that would naturally have to with a rigorous paradigm. It is for this very reason that activity in academic medicine research contains a wide range of clinical and biomedical studies [12]. It was first Rhazes (in the 9th century) who gave out in relative detail the criteria necessary for what might be called essentially experiential medicine [13]. Later, in the 11th century, Avicenna put down the cornerstone of the famously written format of seven important criteria known by the majority of scholars to be the significant milestone of medicine based on evidence [14]. However, a group of Canadian physicians, at the McMaster University, quoted EBM in their article for the first time in modern era in 1992; and then Sackett et al defined EBM more precisely in 1996 [15].

EBR (Evidence-Based Research) has, now, turned out to be a scientific tool for validating the available evidences regarding the strength of methodology. The routine steps of EBR start with a research question and then designing methodology, pooling the accessible data and finally summarizing the process and the findings.

The triad of the best evidence, i.e. patients’ value and clinical expertise make the sides of EBM triangle [16]. Although EBM seems not to have been able to attain the precise standard(s) of all nuances of the patients’ preferences in medical practice, it continues to be the predominant motto amongst those willing to witness some sort of change in reciprocal handling of data and patients. Evidence-based medicine (EBM) has found an increasingly growing global accessibility. This may be due to electronically-mediated communications among researchers through the World Wide Web and the predominance of pharmaceutical industry to use evidence-based researches [17]. Evidence-based medicine and medicine based on evidence are two distinct entities with two distinct definitions: the first is a systematized scientific movement based on scientific studies whereas the latter is based on experiences in the past and gathering the pieces of medical evidence; of course, it has not the accuracy of evidence-based medicine regarding the application of new scientific instruments and methods [18]. Evidence-based practice is either making the right decision, or doing the right thing in the right time [19].

Over and above EBM and EBR have come on the stage the so-called systematic reviews [sometimes known to be meta-reviews as the “outcrop” of meta-analysis]. They will have presumed the appearances of a teleological, final judge if medical researchers apply statistical procedures to bring together the results of systematic reviews [20,21]. As a result, the accepted protocol would be that all evidences answering the clinical questions and do not mislead us to do something wrong about the patients should be considered evidence-based.

More specifically in biomedical research protocol, statistical analyses have protruded out much higher since the advent of biostatistics during 1960’s and 1970’s. At the very beginning of the period, only a few authorities put forward their works of research via exact statistical analysis [22]. Towards the end of 1970’s, however, much enthusiasm was attached to the tailored statistics for purposes of advancing sciences in general and biomedical (applied) branches of science in particular. This made the researchers then [and now] feel

much more of “scientists” [23,24]. Still, the echelon of rigor claimed to be extant within the body of research work conducted by proponents of EB medicine themselves did not appear then as it is supposed to now. A brief look at the history of dealing with bits and pieces of statistics in conventional medicine reveals the fact that clinicians have routinely been involved in taking measurements and making various observations on their patients, making attempts, at the same time, to take decisions on what disease the set of symptoms on the part of the patients are a clue to, and to what degree of severity. Since then, establishing the medical practice upon some firm basis of evidence(s) has been interwoven into the warp and woof of modern medicine, not disregarding the role played by the (generally frequentist) statistics [25]. In its own turn, such a manner of looking at semiology, diagnosis, and analyzing medical problems was “revolutionary”, much as it tried to bring in the double-edged mesh of evidence and statistics.

Scientific methods seek a rule among objects which are replicable and universal. Yet, unique realities do not fall in the realm of science. Individual cases cannot be analyzed by statistics [26]. Brands of statistics are already extant by means of which researchers can relatively facily skirt the intricacies of frequentist approach: according to frequentist statistics, students and workers must needs be in possession of a bulk of sufficiently provided N-number of samples of populations in order to be able to draw conclusions [on a significant basis] as to the (degree of) efficacy of a certain treatment [27]. This takes us far away from approaches whereby we would wish to draw conclusions on non-statistical probability bases, whereas the (true) gist of many of CAM branches is not precisely population-based [28].

The question remains open regarding not only defying frequentistic scientific procedures of validity establishment, but also going beyond even Bayesian data crunching for purposes of leaping into the darkness of realms such as connectionistic induction, single-rough-node deduction, mono-case generalizability, and a posteriori multi-phase digit comparison. All these are, now, vitally necessary if we are ever to be serious about removing most of the bias set against Traditional Persian Medicine (TPM) and other branches of CAM in the face of the hugely-felt impact of a priori suppositions not having firm roots in any mind liberal to whatever brand of medicine capable of bringing sickly people some acceptable level of health of body and peace of mind.

There is very little doubt that EBM has been able –in its relatively short history—to act as a helpful tool (somewhat strategically) for giving out the best possible service by physicians onto their patients [29]. Personal judgments and prejudices may, thus, be brushed aside to come down to the most relevant systematic reviews from the most trustworthy sources of treatment guidance.

EBM can act as a tool in the hands of the data-crunchers to gain their own benefits from the terms: EBM and EBR. EBM is, additionally, a good choice for some of the large pharmaceutical companies to fabricate EBR with the mere aim of promoting their products. It is, moreover, a good masquerade for governments to withhold their assignments because of the lack of EBR (14). Not few and scanty have been the cases when governments [in the developed/developing] world have actually decided not to turn to CAM simply because –according to their own ratiocination—enough weight has not been granted to Complementary and Alternative Medicine by EBM and EBR. While the accuracy of not applying CAM in a number of such decision-taking are not to be doubted, there are tabled many other cases when CAM has rashly been pushed aside simply for their claimed not having been re-affirmed by enough EBR literature [30].

The truth of the matter is that: although conventional medicine is in itself based upon so many measurements, measuring alone could not possibly rise to the occasion of deciding over such issues as

incidence, prevalence, risk, morbidity, mortality, and cause-and-effect relationships. (Much) more significant than the process of measuring, turns out to be the process of “interpreting” what have been measured, not, of course, to say anything of the degree of precision [accuracy] in measurements [31].

Quantification, or rather: quantization has been the cornerstone of modern scientific revolution soon after renaissance. It is not imaginable for us—the present-day scientists—to visualize the fundamental paradigmatic change in the manner science is being conducted nowadays, without its concomitant wide application of mathematics in the format of quantizing secondary and even primary properties of objects of science. In point of fact, scientific method has well received measuring quantification as its foundation without which no more navigation in the field of basic/applied sciences could possibly go on [32].

So much so that even qualitative methodology of research again reverts itself back onto the numerical categorization of the qualitative properties under discussion, thus somehow decreasing its own value as being purely of “Quality” [33].

Now, as for the abovementioned activity of putting “correct” construction upon so many digits and data, there is not a single one approved methodology by all the different branches of medicine and all the offshoots of philosophy-of-science application thinking thereof [27,31]. Having a glance at the printed literature on ways and means of mathematico-statistical construing of numerical outcome of measurements, offers us a not-too-short list of “interpretation” schools and their stipulated faults and defaults whether a number of already defined prerequisites have been met or not.

If we consider RCTs as the accepted norm for either approval or rejection of null hypotheses in present modern medicine, the simplest excepting that can spring to the mind of many a medical student would naturally be: what judgment ought we to pass on a hypothesis that has been rejected by the 99% statistical rigidity criterion if the same hypothesis might well fall in the range of acceptance with some 95% statistical rigor? This matter-of-fact question is not remote from routine among many of our own younger students: it simply does not jump out of the established RCT rejection/approval semiology within the conventional medicine [34,35]; it only changes the “shaded” approved area of the modeled data from a-bit-higher standard to a-bit-lower one within the very same paradigm.

A relatively good example of yet more lucidly bringing out the complexity of Clinical Trials’ outcome construing would be the issue of “heterogeneity”. Treatment heterogeneity is one of individualizing clinical problems. Heterogeneity in RCTs is the outcome of different results emanating from the same treatment; it can sometimes be totally misleading. If we uniformly provide the treatment with a group of patients, still there are many individual differences that change the result of treatment in different individuals [36]. Under such circumstances, the success may be a reflection of a heterogeneous study result including harm and benefits, with the dominance of the benefits, of course [36]. The confounding effect of gearing up the individual effect’s interaction with the very treatment effect itself will give rise to an even yet higher risk of heterogeneity.

Good estimates of the average effects may be provided in Clinical trials. However, we may not apply averages to all. By attending to risk without treatment, responsiveness to treatment, vulnerability to adverse effects and utility for different outcomes, researchers can tailor studies that characterize the people who potentially benefit from the designed medical intervention. More likely outcome shall be arrived at by determining the risk without treatment, utility of different types of the outcomes, response of the patients to the specified treatment as well as their vulnerability to the adverse effects [36].

Hindrance and hampering are not remote from taking place as to HTE analysis [i.e., analyzing the Heterogeneity of Treatment Effects] when it comes to testing multiply (probably giving false positives) with experimental efficiency not being sufficient (likely to lead to false negatives) [37,38].

In the routine medical practice, RCTs are found to be helpfully guiding us whether a certain treatment is efficacious as for a grouping of average individuals [39].

Unfortunately, HTE analysis methods are not yet used by the practitioners notwithstanding the fact that it has been published since long before [40]. The outstanding conflict within the medical circles remains to be resolved: it is not true that a suitably chosen sample number (N) in an RCT would vividly reflect any other gathering results from other experimental subjects.

If we come across another grouping of subjects to the treatment having previously been conducted and registered in a separate RCT, then the evidence gathered from this other instance of imposing the same treatment might not necessarily reflect those of the first instance [41,42]. Not only this, but that: deviations are frequently seen to be made from the (most) suitable experimental design, specifically when more than one factor happens to be effective upon the treatment’s inner workings –this simply leads to some hike in the level of misconstruction put upon experimental results.

Sampling of RCTs by convenience cause narrowing of inclusion criteria and subsequently increase chance of heterogeneity of results [36]. One of the most natural consequences, therefore, would be erroneous analysis of HTE. In case we ever decide to obtain the data for purposes of ameliorating towards any “customized” solution within the boundaries of EBM, then we shall have to apply one of the confirmatory analyses cited in specialty texts (Confirmatory Analysis of Exploratively Obtained Factor Structures).

Since evidence-based medicine scarcely considers the preferences of patients in intricate situations [43], the misinterpretation(s) coming from the sheer HTE-misappropriation (or, say, maladjustment) acts as a barrier to the personalized medicine that is badly needed whenever the heterogeneity of treatment crops up even more grossly. It is for this reason that the evidence that EBM harms the patients less than interventions based on other philosophical schools seems scant.

While applying the results of a systematic review or a meta-analysis in medical practice, the amount of the heterogeneity among the evaluated clinical trials should be observed skeptically [21]. Despite the fact that mathematical quantification shows itself in many different guises while “science” is being “done”, these guises ranging from various systems of notation to equivalency expressions to differential calculus to interpretative mathematics, most probably the widest application has been made over the domain of statistics (and probability).

Person-Centered Care

PCC is a new entity, concerned about patient as a person not as a medical case. In PCC, the person substituting the patient has to be adapted to imposed conditions by medical settings, but he/she has the right to participate in the medical decisions by bringing up his/her own preferences to the clinician. It must not be confused with the term of personalized medicine that concerns genotypic or phenotypic characteristics of the patients in designing a medical plan. PCC cares about the person who is a human being with own feelings, needs and values, all earned throughout the lifetime [44]. For instance, Ekman et al found that using a full PCC program could shorten the duration of hospitalization in the patients with congestive heart failure [45]. Along with other causes prompting patients to intentionally prefer CAM could be the fairly famous three Ts that a complementary

therapist has the capacity to offer: Time, Talk, and Touch [46].

EBR in CAM

We know that the justification of a wide spectrum of medical therapies in CAM is not exactly fundamentally the same as those in conventional medicine. The proximity in between conventional medicine and evidence-based medicine (EBM) appears to be much more noticeable. CAM itself is a jump, and many a time a long leap, from the medicine as taught in present-day academies. This does not, however, spell that CAM is far less based on evidence vs. conventional medicine [47]. In point of fact, the very truth that some brands of CAM have a very long history of up to thousands of years makes them, in many practitioners' opinion, much more reliable as far as they are concerned with "evidence of proof".

Evidence-based practices help clinicians interested in CAM to have better justification in clinical decisions, and use more easily (and, more assuredly) the interdisciplinary practices [48]. There might very well arise the need for finding the proper application of ingenious experimental designs: even those designs that have traditionally been the point of emphasis in other applied sciences [fields such as agronomy, animal husbandry and plant viral/bacterial disease research] [49]. In point of fact, adapting and adopting many experimental designs into CAM (and even conventional medicine) research seem next to vital. When one comes to the details of experiment design in, say, agronomy established since 1920's [50], one wonders why and how designs such as Latin Square, Split-Plots, Sub-Plots, Confounding effects calculations, and so on and so forth have never come to be scrutinizingly re-shaped for almost exactly parallel phenomena both in conventional medicine and in CAM.

The scarcity of EBR in CAM is partly due to the lack of documents and scientific evidence in this field and partly because of insufficient funds to conduct methodologically strong clinical trials to prove CAM suggestions [51]. Resorting to CAM among people suffering from chronic diseases is not an irrational choice: rather, it shows an optimistic vision and a respectable hope for improving quality of life [52,53].

While the physician's aim—in the holistic approach—comprises of treating the patient as A PERSON, the major goal of conventional medicine is focused on treating the DISEASE, notwithstanding the highly marketed claim of the evidenced-based approach that the patient's preferences are considered in a triad of evidence-based research.

What is common in all CAM methods around the world is their intellectual foundation on a totality of body, mind and spirit [54]. Holistic medicine—which, many a time, is regarded equivalent to CAM—comprises of a number of healthcare practices not disregarding sides to human health other than those conventionally emphasized in modern medicine. This is targeted at obtaining physical, emotional, mental, social, nutritional, and spiritual aspects of health all at the same time (if gradually).

While not rejecting modern state-of-the-art modalities of diagnosis, prognosis, and treatment (including medications and even surgery, in the last resort), holistic CAM also gets involved with educating both at the personal and at the personnel level to achieve the highest goal of incorporating age-old wisdom of healing with the present-day procedural accomplishments [55].

Simplistic as the approach appears in categorizing a patient on but a few symptoms and laboratory tests, the holistic schools of medicine, e.g. TPM, delve into the whole background history of one's health based on a broader spectrum of natural variations such as: temperament of the patient, type and temperament of disease, severity of disease, age, sex, place of birth and/or place of living, occupation,

habits, season and climate, as well as physical stamina [56,57].

Manual practices such as dalk (Persian massage) need to establish defined parameters of the profession to avoid malpractice and provide a safety guard for customers [58]. However, the validation and standardization of manual alternative methods as an evidence-based practice is still a matter for debate [59]. It is, probably, more of "a matter for debate" since the structure of scientific methodology appears to be (much) more settled as for procedures like drug assay development, medication affinity measurement, drug production monitoring, active ingredient concentration checking, and pharmacovigilance. The very existence of organizations like FDA is good proof of the fact that how far from systematical (re-)examination remedies like acupressure, reflexology, shiatsu, and Persian dalk remain to be.

Just like any other scientific research, of course, designing a CAM study necessitates full concerns and overall care for the intention and the endpoint. If the endpoints do not parallel intentions, then we shall be wasting our resources [51]. It is not only in medical research of any type that the point to be investigated has not very well been set from the beginning in terms of researchers' intentionality. Offering alternative "mannerisms" as for improving patients' health just alongside testing its durability, has witnessed a fairly noticeable hike in recent years: these, of course, do not rigorously fall into the pre-defined guidelines put down by much of the scientific community. Nevertheless, the scientific community itself ought not to forget the facticity of the fact that the said rigorous guidelines themselves—for approving/rejecting any criteria of treatment—have once been supple offshoots of the then newly grown [mostly, often, trial-and-error routes] (sub-)disciplines of quasi-revolutionary paradigm shifts in pure and applied science.

It is for this reason that we might venture to exemplify the functionality of such hybrid modes of clinical data gathering as those conducted in many points of, for example, Nordic countries where methodology has "regressed" [according to some authorities] into square curve clinical research paradigm [51]. In those same Nordic countries, there are others who firmly believe that the mushrooming of CAM manners of therapy has "advanced" into brand-new methodology for paralleling endpoints with the conscious intentions of both patients and therapists.

If and when some systematic optional view is to be offered to a [relatively] wide range of patients who are, themselves, not unfamiliar with (at least) one specific branch of CAM, and not that unfamiliar with one major symptom of their own illness, then anecdotal evidence can possibly turn into more fundamentally historic-scientific procedures of treatment [60]. In case such patients have had a minimal degree of acquaintance with their own trajectory of disease, endurance, non-conventional interventions on the part of CAM practitioners, relief, relapse, or even probable paroxysm of their own ailment, let alone their full recovery from the harrowing experience they had undergone, conventional physicians might easily follow the trend of their single-case disease remedy into some combinatorial meta-analysis. Such meta-analysis would most likely arise from longitudinally following the quasi-collective data, mirroring not exactly the cause-and-effect nature of the paradigmatology of meta-analyses, instead: giving (sort of) all but simultaneous involution of causes and effects being not rigorously disparate from one another [61].

While the clinical practice of many CAM healers is deemed non-academic and non-scientific, the kernel of the debate goes so harsh between the modern medicine school and the EBMists. Much critique had already been loaded onto CAM specialists even before the idea of EBM started to come on the scene. Yet much more of it was showered upon the CAM schools when EBM found its own fervent proponents. There are many onlookers who do not (want to) realize that not only EBMists have their own clashes with the mainstream modern medicine, but also that it is just a couple of decades since

EBM began to strike roots in addition to the fact that, according to some estimates, not more than twenty percent of our conventional medical college graduates are for EBM.

The repercussions of the very word “EBM” play an extremely significant role in how to settle the dust of dispute not only between advocates of EBM and the mainstream modern medicine, but also between promoters of EBM and practitioners of CAM. To start with the not-so-friendly discourse between “EBMists” and the conservative academicians of medicine, it should be made clear that the latter group attack the core thesis of EBM demanding narrowest vision of what constitutes “evidence” and how the things ought to be arranged among theory, evidence, statistics, and clinical practice. A fundamental re-scaffolding of the medical science, as demanded by promulgators of EBM, does not go very easy with old professors of various medical colleges’ departments.

EBM & CAM: Reconciliation

Accuracy of diagnosis will be increased if an evidence-based guideline is processed and developed by a multidisciplinary teamwork [62]. Arrogance on the part of many physicians who simply prefer to forget about all the basic science assistance delivered into the hands of medicine is just one cause of shortage and/or total lack of teamwork. The economics of the matter is yet another causative parameter. Other in-work factors remain to be discussed.

Reprimanding other philosophies that they are not evidence-based does not seem a constructive argument [43]. Rather, ways and means are to be sought after in order to combinatorially see into the effect of CAM wherever the multiplicity of conventional cause-and-effect mannerism peculiar to the majority of CAM remedies works much better.

Thence, EBM might not be considered a blind circle of clinical trials, meta-analysis and systematic reviews [20]. For instance, Pharmacogenomics is a new approach in conventional medicine that considers individual patients for determination of drug response and drug dose adjustment based on patients’ genotype [63].

As for the initiation of both the interaction, and: the cooperation between conventional medicine (research) and CAM (research), there is no denial that it is not something to be just a castle in the clouds. In fact, it has already got underway in some parts of the world for many years [64]. The appearance of many hospitals offering CAM treatments, the coming on the stage of quite a few physicians who do not frown upon CAM therapies, and yet: many more who actually go to the length of including CAM in their own methods of treatments, in addition to the ever-growing linking establishment in between academic centers and health organizations where CAM remedies are on the offer, are all hallmarks of the union taking place between the two [65].

Such union must need to be of foundations that are, on the one hand, of (more) qualitative nature –such as:

- How, where, when, and: why does a certain CAM remedy happen to be embraced by the conventional medicine establishment?
- Who can be in a position to make it ideal for obstacles to be removed on the way of CAM-Conventional integration?
- How effective should any CAM practice prove to be to raise enthusiasm on the part of the conventional physician?
- What role does mere “plausibility” play for public opinion to speedily accept the advantages derived from alternative treatments?

Still, there are more quantitative-scientific questions to be discussed when it comes to any smooth interactive communicability

between the two aforesaid trends of medicine –such as:

- What level of acceptability is to be deemed “standard” when it comes to reducing any one of the complex of multi-factorial interrelations either in vivo or in vitro? Is it, say, the cytological plane, the organic level, or the eco-epidemiological grade where the integrative practice of modern medicine has to be justified with its CAM counterpart?
- Where does the economics of the matter arrive when it comes to setting up any faculty fellowship as for the design and conducting of research and investigation for a holistic service delivery model?
- To what extent ought the observations to be tolerant of so-called “statistical” chop and change? Where (precisely) does the boundary lie between the flexibility of hinging data crunching and, for example, sample size?
- A little bit more mathematically speaking, what “gap” coefficient is to be regarded as acceptable for cases when Evidence-Based-driven research does not exactly correspond with the actualization of clinical practice?
 - A. What percentage of clinical vs. evidence-based differentiation in conventional medicine goes to either of the two?
 - B. How much distinction is to be attributed to intra-CAM conflicting evidence(s) when it comes to integrative medicine?
 - C. Which (approximate) percentage of intra-conventional-medicine conflicting evidence(s) is at work when integrative medicine probably/partially fails?

No doubt, these are just a limited bundle of questions to be answered as specimens for bringing together CAM and conventional medicine OR for erasing discrepancies that arise partly from the statistical methodology applied and partly from the very nature of reporting non-confirmatory pieces of research [observations].

In designing a research in holistic medicine, we are supposed to choose the final result of intervention as the main endpoint, regardless of underlying theory and mechanism of proposed intervention [51]. This is because it is an arduous task to prove the exact mechanism of effectiveness of a CAM method with tools of a totally different school. In case EBM or CAM or, for that matter, conventional medicine is to be in search of finding the mechanisms behind diseases, or rather: causes, which focus of research should naturally be in any of the above-mentioned, then the “politics” of finding causes are not exactly the same in all the three. It is only through such comparative methodology that some Meta-view could possibly be grasped as to the precise workings of a certain CAM remedy’s efficacy. After confirming the effectiveness of a CAM method, the second step would simply be to clarify the scientific basis of this effectiveness. It is only then that a scientifically established theory could be hypothesized. Without understanding the scientific basis, a traditional method rarely finds acceptance by the present medical communities [51].

A common intervention in both conventional and non-conventional medicine is pharmacotherapy with side effects potentially present in both of them [66]. In traditional medicine, contrary to conventional medicine, suggested herbal medications have generally not passed through the scientific crucible of randomized clinical trials. In some cases, nonetheless, the efficacy of recommended herbal remedies by CAM healers have been proved by clinical trials; however, the active ingredients in bringing about the healing “chemistry” may be identified or it may not be [at least, at present] well known [67].

Herbal drugs contain many active ingredients that are able

to interact with other herbal or synthetic drugs [68,69]. Lack of knowledge about these interactions may threaten the health of users. Some of these drug interactions are identified, such as interactions between, say, Ginkgo biloba and warfarin and/or aspirin [67]. There are, yet, other interactions that have remained –among a relatively large portion of scholars of the field– to be re-examined in much more detail. This cannot possibly be an Achilles heel attributed to Traditional Persian Medicine, and: there is much controversy surrounding similar weak points being fundamentally attached to other schools of CAM [70]. All the more, the investigation into the working nature of CAM over the issue of pharmacotherapy remains to be well ploughed.

Systems biology

Systems biology simply tells us that there is some principle of fundamental organizational robustness by means of which things do not go contrary to each other at the cell level [71]. The stunning diversity of biological organs, organisms, and systems –not to mention ecosystems– is, in the most normal sense of the word, built upon a not-very-large number of underlying operating attributes [72]. The factorial matrix of extensive systems of human knowledge is, in its own order, derived from the tendency to ignore fluctuation among systems: to focus on their appropriate similarities and, only then, take into consideration the diversification thereof [73]. This becomes somewhat of an absolute need to see through applied practices in biology (such as medicine, agronomy, nutritional science, medicinal chemistry, etc.) how they occur to be synthesized with their own differences approach in each branch alongside controlling cellular dynamics that are not far from “universal”.

Systems biology has apparently come on the scene to not see biology other than at the systems level. Despite the fact that there were (and there still are) theoretical biologists who asseverate that the origin of systems biology must necessarily be an adapted/adoptive version of “systems theory” [74], it later proved to be the case that systems biology was more of a masterpiece being given birth to by gargantuan leaps and bounds attained at such levels as: genetics, molecular biology, computer science, and organic chemistry [75]. This most likely means that because of the fact that systems biology stems from a (more than) additive combination of the abovementioned branches of science, we cannot simply rely on it as the best possible source when we come to paradoxes in more applied branches of biological science like medicine and veterinary medicine.

Inside the realm of medicine itself, there is an irremovable need for paying much more attention to systems biology with its more “universal” worldview when it comes to either comparing or integrating any one of CAM branches with conventional medicine. Notwithstanding such ignored rules on the part of medical practitioners, systems biology itself proved not to be the measuring stick for acting as an adjudicator (which it was supposed to be) when differences of advised practice appear in the remit of medical sciences: systems biology does not “feel” holistic enough [at least from a theoretical point of view] to register modalities of treatment with their appropriate explanation.

On the other hand, reference has also been made to BPS i.e., biopsychosocial model, as the even better integrator of psychic aspects of disease (or, rather: a diseased person) with its social matrix as interwoven with the biomedical facets of treatment [76]. Here the mentality of looking at diseases as having detectable certain “causes” with specific recognizable “remedies” is replaced with bringing in a new paradigm originally adopted from psychiatry [77]. When psychiatry –with its entangled complex of etiology– was put to acid test by the relatively famous experiment of Rosenham in 1973 in the United States, it was revealed that there is much more misdiagnosis in current psychiatry than it was thought before [78]. This study showed

the urgent need for revision in fundamentals of psychiatric diagnosis, which might even be generalized onto other branches of medicine. However, no considerable diagnostic paradigm shift has happened yet.

An interbreed of systems biology principles and theories with the medically [not necessarily psychiatrically] tailored Adolf-Meyer-style diagnosis and treatment does seem necessitated [79]. Thereby, no dismissal would have possibly been made of the relevance of biology and basic sciences such as: anatomy, embryology, physiology, histology, and pathology; however, questioned is a rule-bound, mechanistic [-algorithmic] approach to diagnosis which had its origin in the Diagnostic and Statistical Manual [D.S.M.] (and suchlike) system(s). Adolf Meyer and many others had/have come to realize that some multi-factorial standpoint might have well been urgent if medicine is ever to catch at any holistic approach at all [80]. This, in its own turn, requires some of the most meticulously designed set of experiments prior to highly rigorous manner of data analysis [81,82]. It was exactly this point that demonstrated itself as ONE of the blind spots of Mayer et al.’s work. Mayer and his followers did not know precisely how to not leap over from one paradigm of medicine onto another with the exact aim of bringing “humanistic” and “scientific” together [80,81].

The motto of antireductionism which is most often taken for granted in works of those students who have been confronting the faults and deficiencies of both EBM and conventional medicine, has actually swamped them in problem-oriented contingencies whereby omission is made of what actually this present treatise is putting forward: the question ought, according to writers of this article, to be how immanent medical paradigm shifts from epoch to epoch are to be. The allying of the gist of medical paradigms in such a manner as to lead to the kind of practical results intended by those aiming at integrative medicine, must necessarily “invite in” some doctrinal phenomenalism of the Immanence present in (all) those medical traditions that might be on the agenda to be integrated. In some way or other, we consider the immanence of all the routine remedies–be they in conventional medicine, CAM, and EBM–as intrinsic parameters in our comparative paradigmatology of olden and modern medicine.

We believe that the idea of causation which lies at the bottom of any pure/applied scientific endeavor, has its roots in the interactive observations usually deemed disparately separate modules. One cannot simply gather together prescriptive cures and remedies from many different medical lineages in an additive style. Thence, the authors of this present treatise do not suppose that borderlines among, say, TCM, Naturopathy, TPM, Chiropractic, Ayurveda, Aromatherapy etc. are illusory and/or imaginary. On the contrary, they are quite real. Still, the mutuality of their targeting for treating human diseases would unavoidably push us in the direction of searching the said Immanence among various medical traditions.

We are not here talking of archaic concepts such as “leading” entelechies, *elan vital* and/or formal/final causes. We three are, hereby, speaking about the notion of communal immanence to be derived from whatever amount of good sense plus good science that exist in the modern worldview of any physician. It is for this reason that the fixed one-to-one relation in between cause and effect [as considered to be extant, especially by EBMists [83]] vanishes to give its place to the more elaborately defensible idea of interacting styles of medicine. Eventually, this may even end in the historical event of clinically trying the evidence immanence in medicine.

We three do not regard the split between subject and object to be no longer precise or definite. If worked on enough, the division between the two is still valid: they do not incorporate into a single whole. Instead, the doctrine of immanence –as we are propounding it– gives occasion to some view of interaction as singularly present in

(at least) all recent trends of medical research.

Conclusion

When the road was first paved by John Graunt in England and Charles Clermont in Wales for establishing the primordial archetype of medical statistics between 1662 and 1672 [84,85], the medical community took relatively long to get accustomed to the idea of mathematically analyzing data from clinical observations. They may not have regarded it as absolutely vital to see things statistically in the practice of medicine as far as they were, then, concerned with many other branches of research and investigation that were to open in the eighteenth century and thereafter [86,87]. There were already-established data of births, deaths, some epidemics, etc. However, the numeralization of aspects of clinical work with patients did not appear to the then medical establishment as bearing true guidelines for furtherance of the science of medicine [88].

The history of setting up experimental stations for research in agronomy in England in early twentieth century brought forward ideal types for designing and executing experiments in one of the applied branches of biology [50]. These were to be, later, copied by other practical branches of biological sciences as the results in agriculture turned out to be profusely helpful in advancing agronomy itself [89,90]. What came to be of greatest value for modern medicine were the set of fully randomized experiments whereby subjects of experiment were randomly “dispersed” in batches of treatment so that every single unit of the experiment would ordinarily receive treatment/control without bias as to gender, age, race, weight, height, etc.

Later formally registered and recognized as RCTs, such experiments were dubbed the backbone of biomedical statistics to the extent that modern-day Evidence-Based Medicine is axially pivoted around a large number of RCTs. Such a position was accorded RCT at a time when probably “better” experimental designs might have worked for at least some of the testing carried out through RCTs [49,91]. The dark side of this whole procedure of RCTizing modern medicine was that many False-Positives were drawn, whence Over-Flexibility generally led to analyses and/or data-crunching easily permitting almost anything as significant [92,93].

Modern medicine which is sometimes (not completely erroneously) called Western Medicine, is deemed to be the mainstream medicine nowadays [94]. The patho-aetiology of such medicine, naturally depending upon a huge number of symptoms, comes across the type of semiology in which many symptoms [stinging pain, shooting pain, common pain, numbness, tingling, itchiness, etc.] may not be fully explained since they can well appear as common denominators of a corps of diseases that were formerly categorized minutely delicately as, for example, by TPM practitioners who did have enough theories about the nature of both ailments and persons [57,95].

This has generally led to enhancement of legions of medical gadgetry, machines, utensils, testing chemicals, and electrical devices for detecting and tracing diseases, commonly promoting an already long list of nominalistic [sometimes: disease-engendering] International Classification of Diseases (ICD) [96]. The notion of making CAM a partner to conventional medicine has finally led to the idea of Integrative Medicine which is supposed to remove undesired theoretical/practical disadvantages of modern medicine, simply to combine it with probable advantages of traditional medicine by means of comparison, collation, investigation, and application [67,97]: here theoretical science is to be incorporated into practical concerns.

In case Integrative Medicine is to shoulder the responsibility of combining effective treatments from traditional and Western medicine, then it has no way but to set down the rules for procreating a blue print [more likely: in a “complex” way] for diagnosing, shunning

misdiagnoses, recognizing side effects, offering unilateral/multi-lateral treatments, and enhancing quality of life. More could probably be added on to the abovementioned inventory of Integrative medicine while no attempt ought to be made to make it more “lean” [98].

The aforesaid blueprint cannot possibly be a patchwork of mechanically putting traditional and modern medicine together. It is not like a simple linear algebraic addition. The appearances push us into the direction of judging integrative medicine as overly simply bringing together branches of traditional medicine and modern medicine: whenever and wherever “they” find it more likely to remove the said symptoms by grafting one specific remedy of a certain brand of traditional medicine onto another treatment of Western medicine, they scarcely hesitate to do that [99]. This, in itself, is not bringing any peculiar harm to the patient: as it brings relief to her in the midst of all her pain as a diseased person. However, it lacks the theoretical basis that is absolutely necessary to science/practice of any genus of medicine [100].

We are in dire need of starting to build up a methodology for finding out and establishing some ubiquitous immanence of presently having at hand the THEORETICAL foundation of how to arrive at the “common denominator” of various “medicines”. This may drive us into the extended discussion of how to overlap brands of medicine one onto the other so that by, so to speak, looking at one type of medicine, we may be able to see through other types of medicine. This is not unlike making the infrastructure for the twenty-first century medicine, at least from a theoretical point of view. The ideal would be to perfect a serial chain of transcendental/de-cendental moves back and forth –down and up–out of one specific paradigm of medicine into another by positing their “wanting” essence together. It is the ideal which is vitally necessary for the world of medicine at its present state: it is not bombasting, turgid, pompous words to fill out the void of lack of cohesiveness in medical paradigm shift in the height of its happening.

We are not to straitjacket TPM, Traditional Chinese Medicine (TCM), Homeopathy, Ayurveda, EBM, etc. etc. all jam-packed into one magic “pill” of cure-all. We are not to try to atomize holistic attitudes of many brands of traditional medicine into their building blocks. Desired, here, is the rigorous methodology of creating the reconciling univocity in the midst of tumultuous disharmony of presently existing traditional and modern brands of medicine. This task is not an insurmountable one: something which had better be held over to generations to come. There IS enough evidence on which to base the theoretical framework of an all-embracing, really new paradigm of the science of human body and its treatment. There is also enough theoretical tradition in the very long history of medicine from which to derive models for thought [101, 102]. The jigsaw puzzle of putting together admirable fruits of modern Western medicine with equally appreciable centuries-old achievements of traditional medicine is itself One of Multiplicity.

Any transitional paradigm can well be proffered while coming to the resultant medical paradigm which is to be aimed at. In fact, many such transitional paradigms maybe put forward as far and as long as they are not simply integrative medicine. They have to have the characteristics of possessing the essence of scaffolding on which further theories of remedy could be put [or: from which unnecessary joints might be removed].

When any additional or extrinsic-to-the-nature paragon appears in the midst of such series of ideal types, one leading to the other, then: we may realize how differential categories of ideal types in any one branch of medicine (psychiatry, gynecology, ophthalmology, geriatrics, etc.) has had its own specific historiography whereby a whole view of medicine appears on the horizon not as still again a corpus of differences, but as a body of transparent extensities. Such a

work is going on in the Traditional Persian Medicine department of Shiraz University of Medical Sciences.

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