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Continued overleaf

Clinical research with traditional herbal medicines

Evidence-based medicine (EBM) is the new nostrum, and the randomised controlled trial (RCT) is the chosen device for buttressing its evidence base. Evidence, in the context of decision-making about therapeutic interventions, serves one purpose: it is the medium of establishing their efficacy for clinicians involved in the care of patients' life and health, and their rightness for experts charged with the responsibility for taking decisions with regard to therapeutic guidelines, public health interventions and health care systems.

The long-standing dispute about the nature of science and scientific method, with respect to the inductive and deductive approaches to scientific knowledge, continues unabated. Recent attempts to stratify evidence into hierarchies based on 'levels' of sources and perceptions of quality have intensified the controversy pertaining to the relative merits of experimentation versus observation in the domain of modern therapeutics. The Scottish Intercollegiate Guideline Network (SIGN) is a typical example of a hierarchy of evidence [1]. All hierarchies place RCTs at the pinnacle, with observational studies languishing in the lower regions, and 'expert opinion' at the bottom. Hierarchies of evidence are now widely regarded as reliable measures of relative 'strength' of evidence in therapeutics, and used – particularly by committees that develop guidelines – to rank therapeutic interventions' merit, based on their perceived robustness. There is no gainsaying of course that popular acceptance of EBM has transformed medical practice and research preponderantly for the better, but the widespread and mechanical use of hierarchies of evidence has also raised many questions [2]. The findings of a single RCT or a systematic review of several will give evidence about the efficacy of an intervention (ie. 'the particular treatment has worked somewhere'), very often without supplying testimony regarding its clinical effectiveness in actual practice (ie. 'the treatment works extensively'), or its efficiency (ie. 'is it worth it?') [3,4,5].

Most RCTs test efficacy with carefully selected patients, numerous exclusion criteria, absence of co-morbidities, intensely supervised treatment, monitored patient compliance and careful follow up – ideal conditions rarely available in actual clinical practice in which effectiveness and efficiency are important considerations [3,5,6]. RCT evidence is often not generalisable to certain groups of people, individuals, or different settings. Often RCT evidence also fades with time. To choose one example from the many available, older antipsychotic medications have been shown in large well-designed trials to be as effective as the newer ones (eg. olanzepine, risperidone etc.), and cost much less, alas! after widespread prescription of the newer drugs had made fortunes for their manufacturers [2].

Among the large number of distinguished clinicians and scientists who have expressed serious misgivings about such hierarchies of evidence in

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general, and the enthronement of RCTs in particular, perhaps the most persuasive and exquisitely argued denouncement is The Harveian Oration of 2008 [7], delivered by Professor Sir Michael D Rawlins, Chairman of the National Institute for Health and Clinical Excellence (NICE), UK, since its inception in 1999. I make no apology for reproducing here three direct quotes from his Oration.

- "The notion that evidence can be reliably placed in hierarchies is illusory. Hierarchies place RCTs on an undeserved pedestal for, as I discuss later, although the technique has advantages it also has significant disadvantages. Observational studies too have defects but they also have merit. Decision makers need to assess and appraise all the available evidence irrespective as to whether it has been derived from RCTs or observational studies, and the strengths and weaknesses of each need to be understood if reasonable and reliable conclusions are to be drawn".
- "Experiment, observation and mathematics – individually and collectively – have a crucial role to play in providing the evidential basis for modern therapeutics. Arguments about the relative importance of each are an unnecessary distraction. Hierarchies of evidence should be replaced by accepting – indeed embracing – a diversity of approaches".
- "I am aware that those who develop and use hierarchies of evidence are attempting to replace judgments with what, in their eyes, is a more reliable and robust approach to assessing evidence. All my experience tells me they are wrong. It is scientific judgment – conditioned, of course, by the totality of the available evidence – that lies at the heart of making decisions about the benefits and harms of therapeutic interventions".

It is against the backdrop of these prefatory observations that a seminal publication put out jointly by UNICEF/UNDP/World Bank/WHO [8] titled, "Operational guidance: information needed to support clinical trials of herbal products" (CTHP), acquires cogency and immediacy, for we are now witnessing a burgeoning worldwide interest in, and consumer conversion to, herbal and other traditional remedies, that is tempting hordes of researchers to surf the crest of a massive wave of enthusiasm for research into herbal products.

The CTHP goes a long way in removing many of the shibboleths clinicians, researchers, their associations and regulatory bodies (such as Medical Councils and research ethics review committees) are likely to have harboured about herbal medicines as a consequence of the particular training they received according to modern allopathic clinical and research concepts. For example, the CTHP emphasises that, unlike conventional modern allopathic medicinal drugs containing a chemically-defined pharmaceutical ingredient, herbal products are, almost always, mixtures of partially or wholly uncharacterised constituents; and that being a mixture provides putative therapeutic advantages of one constituent enhancing the efficacy of one or more others in an additive or synergistic fashion, or of one constituent minimising the side-effects of others. Deriving from recognition of the postulated advantages of being polyherbal, the CTHP has asserted that assessing their efficacy does not require attempts to purify herbal medicines down to single constituents or chemical entities. Another game-changing declaration of the CTHP is that phase 1 studies in healthy volunteers are generally unnecessary for most herbal medicines if their substantial prior human use conveys reasonable confidence that these regimens can safely be administered to small numbers of carefully monitored clinical participants in phase 2 trials.

This assertion of the CTHP signals a formal acceptance of the value of historical observational evidence accumulated over a long period, regardless of any hierarchical grading [8]. The important proviso here is that the herbal medicine in question should be manufactured in accordance with procedures closely mimicking the traditionally used formulation. An additional crucial stipulation of the CTHP is that, notwithstanding historical evidence of safety, in both phase 2 clinical trials with small numbers of participants and large phase 3 trials (which include several hundred to several thousand), safety of participants should be assured by a comprehensive literature review as well as by specified protocol provisions [8].

Yet another example of the reservations many allopathic clinicians and researchers have had pertains to lack of data on the pharmacokinetics of herbal medicines and herbal substances. These reservations have often metamorphosed into an inhibition to undertake research, a reluctance (catalysed somewhat by a slavish subservience to hierarchies of evidence) to accept the cornucopia of findings currently available from a plethora of research, and even to an ideological rejection of herbal medicine as a whole. The CTHP recognises the technical difficulty of defining pharmacokinetics of herbal medicines and substances, as their active pharmaceutical ingredients (APIs) are often unknown, and a large number of APIs are likely to be present. Consequently, the CTHP recommends that dosing regimens for clinical studies be deduced from traditional methodology rather than from animal pharmacokinetics, and asserts that non-clinical pharmacokinetics is *not* a prerequisite for human clinical research [8].

There are available a multitude of publications ranging from anecdotal reports, oral tradition, case-control studies and case series, to monographs, compendiums (eg. national herbal pharmacopoeias) and RCTs that provide support for the principal recommendations of the CTHP, and concur with the more inclusive, rational and holistic approach to assessing evidence of efficacy, safety, effectiveness and efficiency of therapeutic interventions as envisioned by Professor Rawlins [7]. Some of these publications, for example, a Technical Report of the International Union of Pure and Applied Chemistry (IUPAC) [9], the WHO International Conference(s) on Drug Regulatory Authorities (ICDRA) of 1991 to 1999 [10-12], and the Joint Agency Model – Joint Tasman Project of the Australian Therapeutic Goods Administration [13] deserve special mention for their completeness, and balance concerning therapeutics, industry and regulation.

Moving beyond the territory of what clinicians, researchers, regulatory bodies and journal editors ought to regard as acceptable evidence in relation to herbal medicines and their clinical use, there are other key issues such as definitions (eg. of herbal medicine, herbal substance, herbal product), API, chemistry-manufacture-control (CPC), good manufacturing practices (GMP), contaminants (eg. bacterial, fungal, pesticides, fumigation agents, metals, radioactivity), willful substitution, misidentification, possible variation in therapeutic properties of different cultivars, and toxicity. These are comprehensively dealt with in the publications listed above [9-13], and interested readers and prospective researchers should consult them for details.

Herbal materials administered clinically are referred to as herbal products. Herbal medicines and herbal drugs are acceptable synonyms for herbal products. In developing countries it has been estimated that about 80% of the population depends on herbal products for their primary health care [8]. Examples of widely used traditional systems include Ayurveda in India and Sri Lanka, Kampo in Japan, Unani in the Middle East, and Chinese traditional medicine. Although the use of herbal medicines declined rapidly in the West with the advent and rapid advance of modern allopathic medicinal drugs, herbal medicine is now enjoying – for a variety of reasons – an astonishing resurgence in these affluent countries. For instance, annual global sales of herbal products and herbal medicines has already exceeded USD 100 billion, and will rise to USD 1000 billion in 20 years at the current growth rate [9]. In Australia there were at least 2.8×10^6 consultations for Chinese traditional medicines in 1995, representing a turnover of 84×10^6 Australian dollars in that country's health economy [14]. Herbal products such as cosmetics, fragrances, teas, health foods and nutraceuticals form a large proportion of the global herbal business. Examples of profusion in the consumption of herbals may be easily multiplied but would be superfluous. So vast untapped pastures are flourishing out there in which researchers looking for opportunities may profitably graze.

Sri Lanka is blessed with at least four extant systems that use herbal products in a variety of ways in clinical practice: Ayurveda, the rich and uniquely native Desheeya Chikitsa, Siddha and Unani. Physicians clinically experienced in the prescription of herbal medicines are available for consultation by people who are willing to seek their advice. Many of them have vast collections of hitherto unchronicled ola manuscripts describing herbs, herbal products and their clinical indications. The Department of Ayurveda of Sri Lanka is the legally authorised body [15] that oversees, among its other functions, the registration of all Ayurveda medicinal herbal products moving in commerce in Sri Lanka, Ayurveda institutions including ones that wish to manufacture, store and dispense herbal products, and Ayurveda practitioners. The Department has also published an extensive Ayurveda Pharmacopoeia [16]. In terms of the Act, registered Ayurveda practitioners may manufacture or prepare extemporaneously any traditional herbal medication for clinical use. Registered Ayurveda hospitals or manufacturing firms too may do so, provided that the formulation is according to the pharmacopoieal specifications. However, if a manufacturing firm registered by the Department wishes to make a herbal product having a new formulation not given in the official pharmacopoiea,

for purposes of sale or clinical research, a separate registration of the product with the Department of Ayurveda is mandatory. An application for such registration should be supported by extensive documentary evidence and express opinions of senior Ayurveda practitioners regarding efficacy and safety of the proposed formulation. In the case of clinical trials with registered or unregistered herbal products in which registered Ayurveda practitioners are collaborating with Western allopathic practitioners, it would be prudent to obtain permission for the trial from an ethical review committee of the Institute of Indigenous Medicine (of the University of Colombo), Gampaha Wickramarachchi Institute (of the University of Kelaniya), or the Department of Ayurveda, in addition to permission from an ethical review committee recognised by the Ministry of Health for Western allopathic therapeutic interventions.

In general, clinical studies on the therapeutic efficacy and safety of a single plant formulation or a single herbal constituent are of limited import, compared to a study using a formulation documented in the Ayurveda Pharmacopoiea, or of a registered new herbal formulation manufactured by a registered firm. Consider for example, the numerous studies done in Sri Lanka on sperm motility, or the hypoglycaemic effects of *Momordica charantia* (Karavila) [17,18]. Although useful in themselves they do not appear to have led to the formulation of therapeutically useful clinical products for diminishing sperm motility or for management of diabetes. In contrast, a polyherbal manufactured formulation using *Salacia reticulata* (Kothala himbutu) has been tested in an RCT and found to be useful in type 2 diabetes as an adjunct to glibenclamide and metformin in standard dosage [19]. However, this formulation had not been registered as a herbal medicine by the Department of Ayurveda at the time of the RCT or its publication, as far as I have been able to ascertain. More recently two other RCTs, one with a genuinely herbal toothpaste [20], and another with a new formulation for colds and catarrh [21] have been published. The former significantly reduced salivary anaerobic bacterial counts, plaque index, and gingival bleeding in regular users, and the latter significantly reduced the incidence of 15 previously validated [22] and common upper respiratory symptoms, their incidence over time, and severity in healthy volunteers. Both these are landmark RCTs insofar as they tested commercially widely used branded products registered by the Department as Ayurveda medicinal products, and have been manufactured according new formulations not listed in any Ayurvedic pharmacopoeia. The latter is also exported to several countries with approval from the appropriate authority in the relevant countries.

In summary, the consumption of herbal medicines and other herbal products (such as teas, health foods, nutraceuticals, and cosmetics) is expanding exponentially globally. This has major implications for public health policy, clinical care of people's life and health, health politics and macroeconomics, and the roles of regulatory bodies such as review committees for research ethics, Medical Councils, and medical science journals. It would be appropriate here to recall that a large number of effective modern allopathic medicinal drugs (eg. aspirin, digoxin, atropine, quinine, artesunate, artemether/lumefantrene, vincristine, vinblastine, and penicillin) have come from plant or fungal sources. Traditional medicines have been described "as a rich source of potentially attractive therapies", that are likely to have a "favourable risk-benefit ratio" [8]. Hence clinical research with traditional medicines, unrestricted by inflexible hierarchical distinctions, affords vast opportunities. Medical journals and researchers looking for research material ought to welcome it.

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