
Herbological.com - Greatest Hits
1998-2008

Herbological.com

Greatest Hits (1998 - 2008)

Jonathan Treasure

Tech Support - Chris Atkinson; Life Support – Lissa Treasure

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JonathanTreasure.com

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My new educational and informational site for both herbalists and health-care professionals interested in botanical medicine for cancer, herb-drug interactions and Herbalism 3.0.

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Forward

I was born in the university town of Cambridge in England a couple of years after The War ended: Baby Boomer time. My single mum worked part-time as a tech assistant in the University Mathematical Laboratory, where the first operational computer known as EDSAC had just been built.

As a toddler, instead of day-care I used to hang out on the Mathematical Lab's new mezzanine floor, which had been installed to accommodate EDSAC's huge rack system of 3000+ tubes (valves). Looking back, I often wonder if EDSAC was responsible for my comfort and long-held fascination with computers.

EDSAC (Electronic Delay Storage Automatic Calculator) circa 1950

About 17 years later I returned to Cambridge, now as a scholar at King's College. I was totally drawn by the spell of new developments molecular biology, a path that eventually led me, via some detours, to herbal medicine.

Fast forward to 1994, the year I left the UK for the United States. That year I had given a seminar titled On-line Tools for Herbalists at the National Institute of Medical Herbalists' annual conference. At that time few British herbalists even had an internet connection; 14 k dial-up was progressive, and the NCSA's Mosaic web browser was a year old.

I was excited to share with herbal colleagues the possibilities promised by the emerging internet, such as telneting into Norman Farnsworth's NAPRALERT database in UIC for botanical research citations without leaving one's desk. In addition, using the Internet to form an on-line community of herbalists from far-flung corners of the world seemed like a perfect solution to the fact that herbalists typically chose to live in remote, rural or wild places far from one another and often avoided metropolitan settings. That idea later became partially realized when I met herbalist Howie Brounstein from Oregon on-line. Together with Rob Bidelman from Northern California, we founded the professional herbalists discussion group Herbal Hall, (named after Toad Hall from The Wind in the Willows). After nearly two decades, Herbal Hall still enjoys the lively participation of many professional herbalists from different traditions and countries around the world.

Cornus canadensis © Mimi Kamp

When I first arrived in the Pacific Northwest from England I was, like many Europeans, overwhelmed by the enormous size of the U.S. I landed in Oregon, a state far bigger than the whole United Kingdom yet with barely three million inhabitants. Inevitably I turned to the Internet for both community and communication. I started writing reviews of herbal medicine books, which I originally published under the title HerbalBookworm at a domain I registered as herbological.com- what would today be called a static

web site. The herbological logo was based on a line drawing of Cornus canadensis by Southwest botanist, artist & photographer Mimi Kamp, who is perhaps best known for her exquisite line art illustrations of Michael Moore's herb books.

After establishing HerbalBookworm reviews I started a series of articles called Herbal Hypotheses, which were intended to address more theoretical and philosophical issues. I had long contended that herbalists of the Western traditions were under-endowed in the departments of theory and philosophy since the turn of the previous century. The 1988 publication of Weiss's Herbal Medicine in English was really the only major contribution since Thurston's 1900 text Philosophy of Physiomedicalism. Herbal Hypotheses, as explained in more detail in its own introduction below, was a contribution to the attempt to redress the balance in favor of herbal theory.

After Y2K I became increasingly preoccupied with the poor quality and misdirection of much original scientific research into botanicals, as well as escalating attempts by mainstream medicine--faced by rapidly increasing public interest in herbs--to neutralize, subvert, or dismiss the positive potential of botanicals and herbal medicine. At the same time, public mistrust of the mainstream was fuelling another perennial American phenomenon, the cure-all-snake-oil-quack-alternative wonder cure, sold with hyperbolic claims and unverifiable testimonials, promoted via Internet rumor and forum chitchat. WordPress software was launched around 2003 and so began the blogosphere. I reformatted herbological.com into a dynamic site with a WordPress blog titled simply Herblog. For a good while, Herblog became a platform for deconstructing or debunking the worst of these scams; for example, the notorious zeolite cure for cancer (and everything else). At its height, a Google search for "zeolite scam" put Herblog at top of the search results and resulted in thousands of page views.

The effort of taking on both mainstream misinformation and scam merchants in a regular blog was demanding but rewarding; during that time, in addition to my clinical practice, I had been working on a major collaborative textbook on herb-drug interactions, which made blogging seemed like light relief. Once the textbook book was completed my blogging momentum flagged; HerbalBookworm and Herbal Hypotheses suffered from neglect and herbological.com began to lose its vitality. In retrospect, this process was part of a general maturation of the blogosphere, one that reflected the organic process of change and development that pervades the ecosystems of the web, which itself had already started undergoing exponential changes on its way to morphing into today's behemoth of social media & Web 2.0.

Meanwhile mainstream medicine had been implementing digital technologies across the board, from health administration (EMRs, or electronic medical records) to applying post genomic science to produce new diagnostics that generate a therapeutic approach of truly "personalized" medicine. The challenge for

herbal medicine is how to find its own unique way to harness digital technologies, networking, web & social media tools to move its project forward. In my view, herbalism has reached a historically unique juncture. In no small part the recent digital momentum in both the medical and life sciences has itself destroyed the narrow limits of the reductionist paradigm; this is what Eric Topol dubs the "creative destruction of medicine" in his book of the same name. In herbal medicine, parallel developments are leading to what I have elsewhere described as the emergence of Herbalism 3.0...but that's another story.

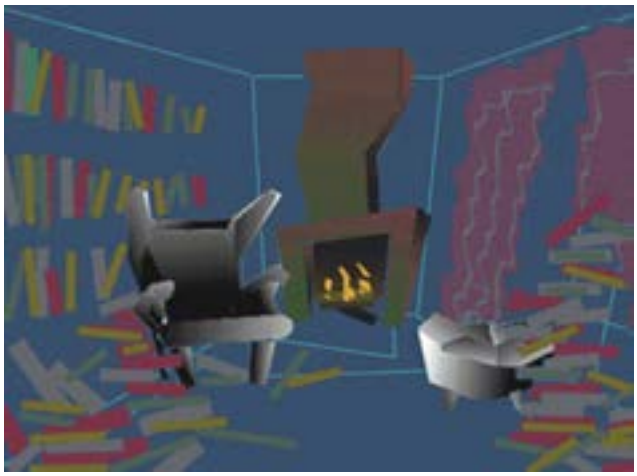
For my part, I have reconstructed my clinical practice into a virtual office using web tools, from secure online billing and appointment scheduling to a clinic "help desk" system for patients. This I've based on tech support approaches developed by software companies for tracking and solving client issues. Among its many benefits, this approach is opening time for me to return to writing, research and publications.

Googling oneself can be a scary exercise, as innumerable cyber-traces of past, long-abandoned, transcended or forgotten writing, rantings and ravings appear like ghostly digital cyphers of former selves. After attempting something of a "cyberhousecleaning"-–actively dismantling the old links to herbological.com content-–several people, including herbalists and herb students, wrote to ask me for copies of various articles they were searching for or had been referred to. This e-book offers a selection of some of my better-known articles and reviews from herbological.com. There was a lot more stuff there, but excepting this selection, it has hopefully evaporated into the cybersphere. Tomorrow is another day. Enjoy.

Our revels now are ended. These our actors,
As I foretold you, were all spirits and
Are melted into air, into thin air:
And, like the baseless fabric of this vision,
The cloud-capp'd towers, the gorgeous palaces,
The solemn temples, the great globe itself,
Yea, all which it inherit, shall dissolve
And, like this insubstantial pageant faded,
Leave not a rack behind. We are such stuff
As dreams are made on, and our little life
Is rounded with a sleep.

William Shakespeare
From The Tempest, Act 4 Scene 1

Herbal Bookworm



"The book of my enemy has been remaindered. And I rejoice.."

I launched HerbalBookworm in 1994 with the above graphic and quote by Australian anglophile critic Clive James. At that time the pendulum was swinging positively toward an "herbal resurgence"; this spawned large numbers of mediocre "me-too how-to" books on herbs and herbalism by journalists, opportunists and assorted self-proclaimed experts. the HerbalBookworm's initial mission was simply to help separate the wheat from chaff.

My very first review was of David Hoffman's little-known (then and now) Information Sourcebook on Herbal Medicine (1994). Dave had been living on the West Coast of the United States for years; he was a fellow early adopter in recognizing the importance of the internet in herbal medicine. His little book was well ahead of its time and featured many on-line resources…

Making Sense of Commission E marked a turning point for HerbalBookworm and warrants a brief back story. While I was researching books on herbs for children by Aviva Romm, Mary Bove and Annie McIntyre. I came across a copy of Professor Schilcher's Phytotherapy in Pediatrics, (Medpharm 1997). Prof.

Schilcher had been a member of the Commission E, and his slender volume on pediatrics included as an appendix several dozen of the Commission E monographs translated into English for the first time. At that time the American Botanical Council (ABC) was heavily promoting its forthcoming translation of the Complete Commission E corpus. This was a large project for them, although arguably made larger than necessary or appropriate and required considerable funding; consequently the ABC engaged in a major publicity and promotional drive to reposition the Commission E as "the definitive role model for a scientific approach to the regulation of herbs in North America. Now, out of the blue, dozens of the previously unavailable monographs that had been endlessly "in press" at ABC were accessible in the appendix to Schilcher's book that cost a few dollars; at the same time, ABC's planned edition was pre-ordering at a discount of $189.00. (It's currently $242.00 on Amazon). Far from serving as a teaser, this "sneak peak" in Schilcher's book was really a serious spoiler for the ABC. My own view, based on reading the preview monographs in Schilcher' s book was that the Commission E herbal monographs were disappointingly trivial regulatory documents of negligible interest or relevance. Further, the ABC had completely misread and overstated the importance of Commission E's text to an absurd extent, but were over-committed and over-extended–hoisted by their own petard they obviously had no choice but to continue with their publication plans.

Not surprisingly, Making Sense of Commission E found little favor at ABC. My review charged that these translated monographs, rather than being the Holy Grail of herbalism implied by the ABC, were tied to the cultural, commercial and political landscape of Germany in the 1960s and were of no compelling interest to contemporary Anglo-American practitioners. By default, the thrust of my critique charged the publishers with misrepresenting the importance and relevance of what they had exhumed from the German original. In 2000, the ABC published an expanded edition as a separate book. This is perhaps what they should have done in the first place, providing context and correcting the obvious errors (many of which I pointed out in my review) as well as providing literature support .

From this point on, HerbalBookworm transformed from a benign book review service to a platform for in-depth critical analysis of published works that were either overtly or covertly creating or propagating misinformation about herbs and herbalism. In the case of Commission E, it was clearly a case of "the emperor wore no clothes." Subsequently, HerbalBookworm's notoriety increased dramatically. Here I have included three reviews, including the now somewhat infamous Making Sense of Commission E.

The second review presented here, Deconstructing Varro Tyler's Honest Herbal, is a prime example of an HerbalBookworm debunk. From today's vantage point these two related books by the late Professor Tyler might appear anachronistic for Tyler's risible ranting against "paraherbalism"; however, both titles have been posthumously updated and remain in print. At the time, Tyler's books were repeatedly quoted as authoritative texts by numerous secondary sources, including many mainstream publications and indexed articles,

presumably due to Tyler's credentials as Dean of the School of Pharmacy at Purdue University and his textbook on pharmacognosy (a subject that was intrinsically part of pharmacy in Tyler's day).

This review manages a tricky task: steering a line between the Scylla and Charybdis of justifiably accusing an author of committing fallacy by argument from authority, whilst avoiding the counter-charge of conducting an ad hominem attack on the same author whose authority is questioned. Herbalists might do well to reflect upon this issue, for argument by authority is a pervasive and generally unchallenged tendency in the U.S. herbal community.

Thieme is an a important international publishing house producing many alternative and complimentary healthcare books, as well as numerous journals including Planta Medica and Keith Block's Journal Integrative Oncology. My review of Thieme's revision of Rudolf Weiss's seminal text Herbal Medicine remains one of my personal favorites, largely because of Thieme's response. A small independent English publisher, Beaconsfield Press, produced the first translation of the 1965 Weiss text by Anna Meuss. Beaconsfield could not match Thieme's terms for a licensing a second impression and sadly had to abandon reprinting. Meanwhile Thieme had commissioned Professor Fintelmann (who was, ironically, an ex-Commission E member) to "update" Weiss's text. The result was at best a massacre of the original; my review Re-Weissing Weiss pulled no punches. Initially aggrieved, Thieme contacted me, first from its New York office, then from its German headquarters. After some correspondence Thieme decided to reprint the original Weiss text after all as the "Classic" version of the book alongside the updated Fintelmann edition. That a single reviewer's blog could lead to a policy change by an international publisher made the labor seem worthwhile. Kudos and respect to Thieme!

Not all HerbalBookworm reviews were debunks. Had I more space here I would have included reviews of several great books : Francis Brinker's Complex Herbs Complete Medicines, Bill Mitchell's Plant Medicine in Practice, Michael Moore's Constitutional Physiology, Mills and Bone's Principles and Practice of Phytotherapy, and Kerry Bone's Blending Liquid Herbs. Some of these reviews were regarded as controversial and often resulted in more or less amicable correspondence with the authors themselves (or their publishers). But rather like Anton Ego, the notorious restaurant reviewer in Disney's Ratatouille animation, the critic eventually turned author himself. Mosby Medical published the collaborative text Herb, Nutrient and Drug Interactions in 2008; this widely-acclaimed work received dozens of positive reviews. I waited in vain for a ruthlessly critical analysis and detailed review. It never came. I sometimes wonder what HerbalBookworm would have said about it.

MAKING SENSE OF THE COMMISSION E MONOGRAPHS

An essay reviewing *"The Complete German Commission E Monographs, Therapeutic Guide to Herbal Medicines"*

Edited by Blumenthal M, et al., published by The American Botanical Council, Austin, Texas, 1998.

A review of the ABC's English translation of The German Commission E Monographs. The essay critically examines the monographs, the publisher's extensive additions to the volume, and touches on relevant historiographic and sociological considerations. The author disputes the publisher's claims of scientific accuracy and contemporary therapeutic relevance of the Commission E Monographs. The evaluation concludes that healthcare professionals in North America needing accurate information regarding safety, efficacy and administration of herbal medicines will not find this book to be an appropriate or useful resource, and that it may in fact be misleading. It is further suggested that the US regulatory context regarding herbal medicines has influenced the publisher's inappropriate representation of the text as a definitive and authoritative publication.

MAKING SENSE OF THE COMMISSION E MONOGRAPHS

> ***"No publisher should ever express an opinion of the value of what he publishes. That is a matter entirely for the literary critic to decide... A publisher is simply a useful middleman. It is not for him to anticipate the verdict of criticism."***
>
> *- Oscar Wilde (letter in St James's Gazette, 28 June 1898.)*

The much heralded English translation of The Commission E Monographs from The American Botanical Council (ABC) boasts some lofty claims on its back cover. Professor Varro Tyler asserts that the "Commission E Monographs represent the most accurate information in the entire world on the safety and efficacy of phyto medicines," while Dr. Andrew Weil adds "here is a reference book on botanical medicine that physicians can trust… Accurate, responsible and authoritative, it is a must for every health professional interested in practicing natural medicine. It is also a model I hope will be used for the review and evaluation of herbs in the US."[1]

This essay will argue the case that Commission E Monographs as found in *The Complete German Commission E Monographs* (1998), are not, in fact, either accurate or reliable in any definitive sense. They require considerable experience and understanding to assess and interpret. They are limited in range, content and depth by cultural,

1 In fact , Dr. Weil has recently revised his opinions of the usefulness Commission E, stating on his web site 'Ask Dr. Weill' stating that they are "dated" and "unfortunately they are not very useful to physicians…and omit some of the most important herbs used in this country" (http://cgi.pathfinder.com/drweil/qa_print/0,3008,1546,00.html: dated 6/23/99)

historical and political constraints that hamper any simple application to the contemporary North American context. It is quite arguable that the entire volume may generate more confusion than clarity for those without prior familiarity with modern herbal therapeutics. Moreover, it is hard to see how physicians and health care professionals in the USA seeking accessible and straightforward therapeutic information about herbal medicines today could benefit from them at all.

The addition to the text of eight therapeutic indexes, four chemical and taxonomic indexes, extensive excerpts from European regulatory literature, eleven appendices and an extremely lengthy introduction only serve to make the whole package bewilderingly less accessible. The Commission E Monographs could easily have been presented in less than 200 pages. Prof. Schilcher's *Phytotherapy in Paediatrics* (1) reproduces 100 of them quite legibly in 40 pocket size pages, yet the present edition weighs in at the coffee table heavyweight category of over 650 pages, without a single illustration. There is a distinct impression that some other agenda may lie behind the overinflated presentation of this collection of dated and seriously flawed German government official documents as if they were the Lost Ark of all herbal wisdom itself. This essay will also attempt to both untangle the product from the packaging, and in the process offer some suggestions as to how to make sense of the Commission E Monographs.

QUANTITY VERSUS QUALITY

The figure of "three hundred and eighty monographs" is misleading. Around eighty of the Commission E Monographs are devoted to so called Fixed Combinations that relate specifically to German commercial combination products, many of which are nearly identical. Repetition is a feature in the single herb monographs, with the inclusion of duplicate and triplicate monographs - for example Hawthorn has no less than four monographs: flower, leaf, flower and leaf, and berry. Predictably, the herbs included are largely drawn from the established North European and North East American materia medica. Even for those familiar with these traditions, there are some surprises in the roll call – the inclusion of remedies such as Loofa, Uzara Root, Haronga bark, and Sanicle may pique the curiosity of some herbalists, and might be interesting additions were it not for numerous major omissions. Several important herbs in common usage today are not covered, including *Astragalus, Centella, Schizandra, Ganoderma, Pygeum* and *Withania.* The list of absentees from the traditional Euro-american materia medica is lengthy and belies any claim to comprehensiveness; missing entirely are standards such as the *Asclepias, Baptisia, Bellis, Chelone, Chionanthus, Daucus, Eupatorium spp., Geum, Hydrangea, Hydrastis, Lactuca, Leptandra, Lobelia, Medicago, Mitchella, Parietaria, Phytolacca, Piscidia, Prunella, Prunus (serotina), Rumex, Scrophularia, Stachys, Trifolium, Viburnum spp., Xanthoxylum* and *Zea,* to name but a few.

The monographs themselves follow the same general format, with minor changes over the years. A herb is either "Approved" or "Unapproved". There is also a curious limbo category (where herbs otherwise Unapproved may pop-up) called "Approved Component Characteristic", as well as the "Fixed Combinations". In Germany, only the 191 herbs with Appproved status are (or will eventually become) legally available. The monograph

structure changed somewhat over the years and additional sub-categories appear in some monographs without much rhyme or reason, while the monographs themselves are strangely terse and truncated, and unsatisfyingly lacking in depth. They contain no information on botany, constituents, pharmacognosy, pharmacology, or pharmacopoeial standards - these categories are largely absent, some being covered up to a point in other German official publications such as the *DAB* (German Pharmacoepia). Since the monographs are described as therapeutic guides, the absence of standard categories such as differential therapeutics, Specific Indications (the outstanding indication of a particular herb in terms of unique symptomology), or useful combinations and formulae is more serious for prospective clinical use. Such information is always helpful in the process of remedy selection.

LACK OF CUTATIONS AND PROOF OF SCIENTIFIC METHODOLOGY

The brevity of the monographs is compounded by the complete absence of any citations or references to the sources that formed the basis of the Commissioners deliberations on the herbs. These are apparently only accessible when legal cases are brought under the German Medicines Act. **The failure to include verifiable scientific primary sources necessarily places the entire Commission E Monograph corpus irredeemably outside the most elementary accepted standards of academic requirements for rigorous scientific publications.** The uninformed reader is thus obliged to accept as an article of faith the veracity of the information in the text. The fact that Professor Varro Tyler assures us that safety data were reviewed by the Commission according to a "doctrine of absolute proof" (p.33) and efficacy according to a "doctrine of reasonable certainty" (p.x) may do little to convert skeptics, especially those who have found serious errors in Professor Tyler's own publications (2). Better perhaps would be to examine selected Commission E Monographs for well-known herbs with a solid record of safety and established therapeutic efficacy to test the claims of supreme accuracy and reliability - the approach that will be taken here.

Presumably anticipating criticism of obvious errors in several key monographs, the Introduction includes several lengthy caveats regarding the monograph entries for chamomile, echinacea, eleutherococcus (siberian ginseng), ginger, ginkgo, hawthorn, horse chestnut, sarsaparilla and valerian. The alert reader may wonder that if the monographs on such well known and much studied herbs require extensive editorial commentary and correction, then what of the rest? Be that as it may, a brief comment on the commentaries is in order to highlight the disorienting quagmire of contradictions and non-sequiturs that characterize the whole volume.

Chamomile for example has two Monograph entries, one for German chamomile (*Matricaria recutita*), which is Approved for gastro-intestinal spasms and inflammatory disease of the GI tract but not for its well known sedative effects, and one Unapproved entry for Roman chamomile (*Anthemis nobilis*). From the point of view of traditional Western herbal medicine, these two remedies are virtually identical and interchangeable. The *Anthemis* monograph describes the risks of *Asteraceae* allergenicity, but the Matricaria monograph does not.

Anaphylactic reaction to daisies, including chamomile, has been reported, but is not a major medical problem, although one much quoted by scientific reviewers. Such reviews are presumably unaware that chamomile, due to its well documented anti-allergenic and anti-inflammatory activities, is more likely to be a useful treatment for eczema and dermatitis than a cause of it. The point is that both remedies have similar activities and minimal toxicity, yet Commission E equivocally describes one as safe/effective and the other as unsafe/ineffective. This sort of contradiction is a recurrent feature of the monographs. The editorial speculates that the reason *Matricaria* was not approved for its sedative qualities was perhaps lack of available studies at the time of evaluation (1990) by the Commission, and continues by suggesting that recent pharmacological studies on apigenin binding to benzodiazepine receptors (BDZ-R) may now justify the sedative effect of *Matricaria*. However, the editorial adds that the Commission would, in any event, not have approved it since these studies were not human clinical trials. Given that hundreds of thousands of people are daily using Chamomile tea as a mild relaxing nervine (presumably without hospitalization due to anaphylaxis), the real question here is: *Precisely how were the actions and uses of herbs established by the Commission?*

Without citations we are left with an interlocking series of conundrums. Although we are assured that between 100-200 references were reviewed for each herb, it is a well-known fact that of the hundreds of medicinal herbs in the materia medica, clinical trials are unavailable for the vast majority. It seems that many well established traditional herb actions, and actions with significant supportive pharmacological data are omitted, overlooked, or Unapproved, despite the fact that the Commission apparently considered traditional usage. But on the other hand, an action of some description is always given for each Approved herb, most of which *de facto* cannot have been supported by human clinical trials - the stated Commission E gold standard.

Dandelion leaf (*Taraxacum officinale),* for example, is known by every neophyte herb student (and all who consume it) to be a highly effective diuretic remedy. Early pharmacological studies confirmed the diuretic activity of *Taraxacum* leaf, and one animal study in the 1970's compared its diuretic and saluretic efficacy to that of furosemide (3). However, dandelion leaf is not Approved as a diuretic by the Commission, but only as a bitter remedy for loss of appetite and dyspepsia. The dandelion leaf monograph has an additional section (not in most of the monographs) entitled *Pharmacological Properties*, which are listed as None Known. Ironically, the very next monograph (still in the single herb section) is for Dandelion Herb and Root combination for which the action is given (therefore approved) as - diuresis. It is emphatically the leaf that is considered by herbalists to be far more more diuretic than the root, and is also designated as diuretic by various authoritative sources (4). Pharmacological studies have also confirmed anti-inflammatory (5), hypoglycemic (6), and anti-tumor actions (7) for dandelion extracts, which are also ignored by the Commission. All this begs the question of why the approved dandelion leaf use disregarded both established traditional use and putative pharmacological evidence, and how the anti-dyspeptic activity but not the diuretic action of dandelion leaf was approved given that clinical trials on *Taraxacum*

leaf are unavailable in any event. The action of diuresis given for *herb and root* combination as opposed to *herb* is inexplicable, and unfortunately there is no separate monograph for dandelion root alone. One possible solution that seems to check out after a closer reading of several monographs is that that herb actions were often simply derived "theoretically" from the properties of the constituents listed under Composition of the Drug.

Most revealing in this connection are the candid personal communications from Professor Heinz Schilcher, who was the Vice-president of the Commission, quoted in the introduction. In response to a query regarding the apparent lack of scientific reports supporting the Commissions' alleged Risks of Sarsaparilla use, Prof. Schilcher states that the cautions made by the Commission were actually based on "a theoretical standpoint and we have in Germany little experience with Sarsaparilla" (p. 64). This extraordinary admission leaves one wondering how many other conclusions the Commission made based on pure speculation and lack of experience, let alone intrigues one as to how Professor Tyler might square this confession with his "doctrine of absolute proof" (p.33).

Constituent compounds are not detailed in any depth by Commission E and are mostly confined to generic classes such as tannins, bitters, and saponins. Almost every herb that has a bitter content is simply assigned the action of antidyspeptic. Similarly almost all the herbs containing tannins are listed as having astringent action. Well tannins do astringe, and bitters are anti-dyspeptic in the widest sense of that word but such dissimilar *remedies as* bogbean, sage, dandelion, ginger, horehound, iceland moss, devil's claw, yarrow and many others are all reduced by the Commission E to the same lowest common denominator. It could be argued that this reductionist approach does not, strictly speaking, violate the claims of accuracy and reliability since it is based upon general constituent data, but reducing the complexity, variety and number of herb activities and uses to these categories is the logically inevitable result of applying what might be called a "doctrine of absolute oversimplification". At the very least it results in a misleadingly monochromatic picture of the many herbs so categorized, and is of no conceivable help to those seeking accurate information on their differential therapeutic usage.

TENDENCY TOWARDS COMMERCIAL BIAS

A few monographs are much longer than most, and with apparent inconsistency, include considerable pharmacological information. Closer examination reveals that these particular monographs relate to best selling German phytopharmaceutical products such as *Ginkgo, St John's Wort, Hawthorn* and Echinacea preparations. Commercial pressures seem to be at least a plausible explanation Why else is the *two paragraph* monograph on *brewers yeast* (not generally considered by herbalists to be a herb at all) immediately followed by a two *page* monograph on a proprietary strain - *yeast, brewers/Hansen CBS 5926* specifically sold for prophylaxis and symptomatic treatment of diarrhea eg while tube feeding? Proprietary data from manufacturers was apparently made available to the Commision - but as with the other source material of the Commission's deliberations, this data is not available for

examination. The topic of commercial bias re-emerges in the Commission E monographs on Echinacea.

ECHINACEA: A MONOGRAPH DISSECTED

Considered as a whole, the Commission E characterization of Echinacea species is extraordinarily confusing, containing errors of omission and logic, unsubstantiated therapeutic speculations, and is further biased by domestic German market considerations. Of the three species of Echinacea commonly used in herbal medicine, *E. angustifolia*, *E. purpurea*, and *E.pallida*, the Commission Approves only the aerial parts of *E purpurea* and the roots *of E pallida*. *E.purpurea* root is an Unapproved Component Characteristic, while *E. angustifolia* herb and root is Unapproved in the single herb section but the actual Monograph is titled "Echinacea Angustifolia herb and root/Pallida herb"! It is hard to know what a North American reader is expected to make of this muddle, particularly since the only two Approved Monographs refer to those preparations least available in the USA, and where popular usage centers on *E.angustifolia* and *E.purpurea* root.

Now it is true that the triangular rift between scientific research, popular usage, and the professional herbalist community is probably greater for Echinacea than any other single herb, and it is beyond the scope of this essay to detail this ongoing debate - let's just say that the jury is still out. It is clear however that Commission E was obliged by its own criteria to approve only aerial *E.purpurea* (historically favored in Germany for economic and horticultural reasons and hence the only preparation that has been extensively studied there). But it is patently not true that *E. angustifolia* root is ineffective or unsafe, and logically absurd to maintain that only the aerial parts of *E.purpurea* are safe and efficacious as opposed to the root of the same species. It is equally obscure to claim that *E. pallida*, generally regarded by Western herbalists as the minor player of the Echinacea trio, is the only acceptable root preparation in opposition to *E. purpurea* and *E. angustifolia*. The information on therapeutics is similarly misleading. For a start, confusion is compounded by the fact that parenteral preparations of *E. purpurea* were available in Germany at the time of monograph publication. Hence we are warned about side effects due to intravenous use of the herb which do not apply even in Germany today since this use is now illegal there also - although presumably this does explain why the pharmacological action of Echinacea in the appendix is bizarrely listed as "temperature elevation".

The Duration of Administration is given as "not to exceed eight weeks. This much repeated fallacy, often reproduced by "expert" publications on herbs (8), appears to have its origins in a misinterpretation of a single study - critically reviewed by Bone (9) - and is unfortunately now gaining currency amongst orthodox physicians citing the authority of the Commission E position. Echinacea use is also stated to be contraindicated in "progressive systemic diseases" (*E.purpurea*) and autoimmune conditions (*E.angustifolia*); examples given being "collagenosis" (ie the connective tissue disorders or CTD's - such as lupus and rheumatoid arthritis), multiple sclerosis and tuberculosis.. The contraindication of Echinacea with autoimmune conditions has absolutely no published basis in the medical literature nor in databases of pharmacovigilence or in adverse

reaction reports. This situation was emphasized by leading Echinacea researchers, including Dr Rudi Bauer, at two recent Echinacea conferences in the USA. (10). It is presumably deduced from a simplistic conception of CTD's resulting from "hyperactivity" of the immune system which therefore should not be further "stimulated". In fact Echinacea is used for extended periods with great effect in many long term chronic and autoimmune conditions by professional herbalists. To a clinician, it is not hard to see why this might be so - if SLE is taken as an archetypal collagen disease - the primary pathology results from the deposition of immune-vasculitic complexes (eg in the renal glomeruli). These are cleared by phagocytic activity of the cell-mediated immune system. It is precisely this activity that *in vitro* studies suggest is promoted by Echinacea. (11) Whether there will emerge in future specific instances in which certain immune mediated conditions might be contraindications for Echinacea is unknown - the current status of medical literature and clinical experience to date overwhelmingly suggests the opposite is true (9). The contraindication in tuberculosis is also unjustifiable. Echinacea was an established effective treatment for tuberculosis used by both the Eclectics and "regular physicians" prior to the discovery of streptomycin. Ellingwood's "monograph" on Echinacea (12) runs to nine pages of dense clinical detail - the Eclectic physicians were meticulous clinical observers and they would have documented any problems if they had seen them. Finally, and of more contemporary relevance, the Commission E suggestion that Echinacea is contraindicated in HIV and AIDS is also without published foundation. Echinacea has been used by practitioners for both opportunistic infections and the primary pathology in HIV although published clinical studies are limited (13). Overall, the Commission E limitations of use for Echinacea are without foundation, based on errors which decisively undermine any claim to accuracy or authoritativeness. It would be easy but fruitless to continue analyzing each monograph in the same vein - the same issues recur throughout. The essential point remains that the Commission E Monographs simply do not measure up to the extravagant claims of validity and therapeutic relevance.

THE PROBLEM OF DOSAGE

Dosage (or posology in the wider sense) is a crucial matter in administering herbal medicines effectively. The Approved monographs contain dosage information, which, in line with German practice, is mostly given in terms of dried herb for aqueous infusions or decoctions - generally in the range of 2-10 gms daily. For certain herbs with more potent drug-like constituents (such as *Ephedra*) maximum daily doses are given appropriately in terms of mg calculated "as mg active constituent", such as "total ephedrine alkaloid". The problem for potential users of the Commission E dosage information is that in North America hydroethanolic extracts, (usually tinctures, or solid preparations derived from such extracts) and often of **fresh** rather than dried herb material, are the form of herbal remedies preferred in clinical practice - not dried herb teas. Unfortunately conversion between dried herb infusion and fresh plant tincture data is far from straightforward, indeed debates on the subject are perennial among professional herbalists and ethnopharmacologists. Equally, the contemporary trend in North America toward use of standardized herbal material is not easily related to the infusion based dose

data in the monographs. Additionally, where figures are occasionally given in Commission E for tinctures and fluid extracts, they do not always correlate. For example the single dose for valerian tincture (herb/menstruum ratio not stated, but usually 1:5 in Europe) is given as 1-3ml, but the single dose for a fluid extract (Fluid extracts are 1:1) is 2-3ml. This is a complex area, but the main point is that once again one can only question the claimed usefulness and applicability of the Commission E information to North American physicians and healthcare professionals unfamiliar with the complexities of dosage in herb prescribing.

INACCESSIBLE AND DIFFICULT TO USE

Finally, some mention should be made of the numerous cross-referenced appendices added by the publishers apparently "to make this publication as useful as possible, particularly to health professionals and researchers". In so far as the information in the appendices is compiled directly from the monographs, they merely serve to summarize how inappropriate the book really is for health professionals. For instance, a search under pharmacological actions for something useful like, say, Prostaglandin Synthesis Inhibitors - would yield the sole entry of nutmeg! Nutmeg, however, is Unapproved due to side effects of "psychic disturbances". In another example, if one conducted a search for high blood pressure, the only herbs listed as Approved anti-hypertensives are *onion* and two cardiac glycoside containing remedies, *lily of the valley* and *squills*. Even disregarding the contentious (to say the least) implication that cardiac glycosides are indicated for hypertension, we may acknowledge that there is indeed a time honored tradition of using "kitchen remedies" in herbal medicine. One could conceivably do worse than use onion and nutmeg to treat a hypertensive headache- but one could do a whole lot better as well. The point remains that this sort of data hardly qualifies as authoritative scientific information on herbal therapeutics for modern health professionals.

More disturbing is the Appendix of interactions of herbs with conventional drugs. The information here omits numerous interactions including some potentially important ones such as concurrent use of PAF interactors and fibrinolytic herbs like garlic and ginkgo with warfarin/coumadin. Yet it includes the nonsensical warning that antimycotics may interfere with the activity of brewers yeast, which we learn is also apparently contraindicated with MAO Inhibitors. The index of chemical constituents is *de facto* uninformative since the monographs only contain rudimentary constituent information in the first place. The general glossary, including medical terms, provides some relief for the healthcare professional presumably by now disoriented by grappling with the book. There they will discover that antifungal means "destroying or combating fungi", or that a laxative is an "agent having the property of loosening the bowels." The final addition is a section of excerpts from the European Regulatory literature. While these may in fact be of some interest to a minority of herbalists, they are hardly relevant to busy clinicians who are usually more preoccupied with treating the patient in front of them than in studying comparative regulatory bureaucratics.

IN CONCLUSION

What does all this mean? Ultimately, the monographs produced decades ago by the now

defunct German Commission E are, by any considered judgement, a marginal contribution to western herbal therapeutic literature. They add little to our knowledge and understanding, and also contain errors, omissions and speculations. The monographs are systematically colored by historical and cultural factors that arguably render them the least useful of any of the monograph collections currently proliferating in the international literature. Official herbal monographs are invariably produced for political reasons, usually as a result of regulatory pressures by governments and related agencies interacting with scientific authorities, industrial manufacturers, relevant professional associations, often with a wary regard to the groundswell of popular public support for the right to use herbal medicines: The German Commission E was no exception.

In the USA, the situation is very different. Interested parties are jockeying for position in a regulatory flux dominated by untrammeled pursuit of profit by manufacturers large and small in the current Klondike like explosion of the herbal market place. The absence of a coherent and effective professional herbalist practitioner lobby in the situation is conspicuous. Meanwhile mainstream orthodox medicine intensifies its attacks on the dangers of popular herbalism whilst ersatz sub-factions such as pharmacists are arrogating their own "scientific" version of herbs as pharmaceuticals. The American Botanical Council clearly considers it has a role to play as an authoritative "independent" pro-herb voice in this scenario, acting as a mediator between the industry, regulatory authorities and sections of the medical community, whilst assuming an authoritative "educational" stance to its members and the general public.

It is hard not to conclude that the presentation and packaging of The Commission E Monographs in this ABC edition has much to do with the agenda of lending credibility to their self-appointed role. The introduction to the book concludes that the "Commission E system can provide an excellent model for regulatory reform, in the United States and possibly other countries, by providing a rational process for reviewing herbs and phytomedicines for their safety and efficacy". Let us hope not. Unfortunately some physicians and particularly pharmacists are already beginning to cite Commission E myths as immutable truths (14); the specter of the monographs being used to justify malpractice litigation may yet materialize. But the real problem already facing herbal medicine will be the capacity to retain its core philosophical principles in the face of mainstream attempts to incorporate its materia medica and theraputics within a reductionist biomedical framework. The charge has to be laid against the publishers that despite their best intentions their elaborate representation of the Commission E Monographs as the last word on safety and efficacy of herbal therapeutics may well do more harm than good to the cause of promoting herbal medicine. Time will tell.

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DECONSTRUCTING VARRO TYLER'S HONEST HERBAL

An essay reviewing *"The Honest Herbal"*

Prof. Varro E. Tyler, PhD

Jonathan Treasure

A critical review of *The Honest Herbal* (1995) and sections of *Herbs of Choice* (1994) by Prof. Varro Tyler in which the reviewer analyzes the many errors of fact, logic and bias present in these books. Following further evaluation of Tyler's commentaries, the reviewer concludes that *The Honest Herbal* was written from a position of subjective bias against and ignorance of the basic principles and practice of phytotherapy (herbal medicine). The historical and cultural reasons for the misrepresentation of these books as authoritative sources for healthcare professionals and interested lay persons in North America needing accurate information regarding safety, efficacy and administration of herbal medicines are examined. The bibliography of Professor Tyler is discussed from the perspective of the appropriateness of the publishers and others claims of his authority and expertise in the field of clinical use of medicinal herbs.

DECONSTRUCTING VARRO TYLER'S HONEST HERBAL

Tyler's books claim to present objective scientific evaluations of medicinal herbs, their therapeutic uses, safety and efficacy to interested readers, including medical professionals. This claim is buttressed by the presentation of Tyler himself as a highly qualified authority on the subject and appears to have been successfully promoted with *The Honest Herbal* (1995) a best seller in its third edition, and a perennial favorite in the *HerbalGram* Top Ten herbal book chart. Popular articles reconfirm this image of Tyler and his books on a regular basis - for example *Health Magazine* recently discussing "Alternative Approaches to Cancer" (1998)) exhorts its readers to: "before using any herb, check a reliable reference such as Varro Tyler's, *The Honest Herbal"* (p. 69).

Tyler in fact has a low opinion of herbal medicine: "you are less likely to receive value for money spent in the field of herbal medicine than in almost any other" (Tyler HH p.7).

This view is not shared by the World Health Organization which endorses the use of traditional medicines as safe and *cost-effective*. Nor has this view been shared by the American public whose number of annual visits to obtain treatment with "alternative therapies" has long since overtaken the number of visits to regular primary care physicians in the USA - and at an average cost of less than $27.00 per visit (Eisenberg et al., 1993).

In addition to having a low opinion of the field of herbal medicine, Tyler also has a low

opinion of herbalists: "To understand plant drugs completely, we need to know their botany, chemistry and pharmacology. Few modern herbalists possess such a comprehensive background" (Tyler, HH, p.2).

In fact, as we shall see below, Tyler considers "modern herbalists" to be a subspecies of countercultural drug peddler, and reviews of Tyler's books within the professional herbal literature have understandably tended to be brief and dismissive. But the continuing promotion of his books as a benchmark of scientific integrity for the assessment of herbal medicine means that an in depth review from an informed herbalist perspective for readers outside the profession is overdue.

We shall also see that Tyler's claim to be an authoritative source of objective information about medicinal herbs is lacking in both substance and merit. However, both Tyler and his books have been enlisted to support an ideological view in an emerging discourse concerning the scientific validity of herbal medicine. This view seeks to make herbalism scientifically respectable by portraying it as an ersatz version of reductionist biomedicine, whilst denying its historical, philosophical and practical origins in vitalistic philosophy and empirical therapeutics. These latter are in fact the great strengths of herbal medicine that ultimately underlie its current resurgence. This essay will therefore examine Tyler's book *The Honest Herbal* with some reference to the later "Herbs of Choice", and deal with some of the contextual issues in the current debate around the scientific validity of herbal medicine.

The Honest Herbal and *Herbs of Choice* are philosophically and logically flawed, riddled with errors of both omission and commission. They are based on a limited and partial selection of secondary sources and systematically omit coverage of primary studies. In *The Honest Herbal,* conservative opinions replace useful information about therapeutic actions; ominous but unsubstantiated warnings replace accurate data on safety and toxicity; it contains no useful facts about dosage; misleading polemic and prejudice rather than references and reliable information mean that far from being "honest", or *objective* at all, the book is quite the opposite - overwhelmingly *subjective*.

In *The Honest Herbal* Tyler employs techniques of tabloid journalism such as denigration by association and innuendo. He selectively quotes dubious and dated sources like old *High Times* articles and obscure, out of print 1970's "counterculture" books on recreational drugs, which are portrayed as representing what "modern herbalists" practice and promote. The agenda is presumably one of discrediting herbal practitioners, who by implication are half witted yet potentially dangerous drug pushers. A typical example of this "druggie" smear tactic is shown in this passage on *Cytisus scoparius* ...

> *A counterculture publication recommends.... the moldy dried blossoms are then pulverised and rolled in a cigarette paper and smoked like marihuana. One such cigarette is said to produce a feeling of relaxation and euphoria lasting about two hours. But the greatest potential danger in smoking moldy broom flowers probably lies not in the flowers, but in the fungus infecting them. Studies have shown that almost all samples of illegally obtained marihuana tested were contaminated with pathogenic inhalable Aspergillus species..... Broom flowers purposely allowed to become*

moldy would almost certainly be similarly contaminated with such pathogenic organisms and would thus present an appreciable risk to the user (Tyler, HH, p 59).

It is unclear why these concerns should comprise the major part of a discussion about a herb that is used in modern phytotherapy to treat cardiac arrhythmias (a pharmacological effect to which Tyler devotes only one line followed by the incorrect comment that it is no longer used for that purpose). This "recreational drug" innuendo is used throughout *The Honest Herbal*, although it is somewhat unclear whether the herb, herbalists, or some version of "counterculture" is the target...

HOPS

Hops are closely related to marihuana and some writers advocate smoking the plant material to obtain a mild euphoria (p.176).

LOBELIA

Members of the counterculture smoke Lobelia to obtain a mild legal "high", analogous to that produced by smoking marihuana (p.206).

Stretching to include *Hydrangea* in his list of marijuana substitutes requires Tyler to refer to both to the incorrect species as well as the wrong plant part (the medicinal species is *H. arborescens* and the part used for herbal medicine is the root bark).

HYDRANGEA

Hydrangea paniliculata v grandiflora *leaves have been smoked in a fashion analogous to marihuana to produce a kind of euphoria or high (p.181, underlining added).*

When *The Honest Herbal* was first published in 1982, herbal medicine was far less established in the US than it is even today. In the 1970's herbs and herbalism were certainly minority interests, and to some extent associated with people adopting "alternative" lifestyles. Tyler's prejudices are commensurate with the propagandistic backlash of Congress against decriminalization of marihuana (which had actually been proposed by Nixon's Drug commission in the 1970's) and they may at least be historically understandable in that context. Attempts to banalize the "hippie" movement of the sixties invariably miss the point, and in any event those *High Times* readers and graduates of the "Leary School" are now more likely to be found at ethnobotany conferences, giving scholarly papers (or writing books) on ethnopharmacology and ethnobotany. In comparison, *The Honest Herbal's* dated anti-drug propagandizing betrays a lack of academic rigour that would now be unacceptable in an undergraduate essay. Tyler may once have considered himself a knight saviour protecting the naive consumer from drug-pushing herbalists, but as the slick marketeers of the OTC supplement industry move into top gear for the next century, his script reads more like the archaic ramblings of a Don Quixote, tilting against fantasy windmills. Neither Tyler nor his publishers appear to have taken advantage of the opportunity of later editions of *The Honest Herbal* to correct these embarrassing tirades.

A related tactic in *The Honest Herbal* is to ridicule a herb, by emphasizing some incidental non-medicinal aspects about it:

MYRICA

Since the root bark has no proven medicinal value anyway, it seems best to restrict the use

of the plant to its berries, whose wax does make nice smelling candles (p.42).

Traditional or folk uses that have not been confirmed by studies also come in for ridicule, rather than a simple observation or comment that they remain to date unsupported by available research....

BORAGE

Borage no more stimulates real courage than the potion in the square green bottle, which the Wizard fed to the cowardly Lion in the Wizard of Oz (p.52).

A little circumspection might be more appropriate here as modern research has more often than not confirmed traditional usage of medicinal herbs. Despite the inaccuracies which litter *The Honest Herbal*, Tyler seems immune to embarrassment. His opinions are not only contrary to widely accepted facts of traditional usage and contemporary therapeutics, but also to published research. Dismissal of empirical clinical results and historical usage may be a predictable part of Tyler's criteria of being "scientific". His disregard of the relevant primary pharmacological and clinical studies, as well as the lack of familiarity with or reference to respected authors in western medical herbal science or to commentators known for extensive reviews and surveys of the technical literature is incomprehensible and inevitably leads him to make repeated false claims and draw erroneous conclusions.

Some typical examples from *The Honest Herbal* follow...

TARAXACUM

In summary no significant benefits should be expected from the use of any Dandelion products (p.110).

[In contrast, in Daniel Mowrey's (PhD) *Scientific Validation of Herbal Medicine (1986)*, dandelion root heads the list of excellent medicinal foods for the liver, and related organs and glands (p.177). This high position is supported by the available research. Likewise, in *Herbal Drugs and Phytopharmaceuticals (1994)*, from Prof. Max Wichtl PhD one learns that dandelion fluid extracts have been shown to have a diuretic and saluretic effect equal to that of furosemide (p.598). In the *ESCOP Monographs* (1996) the reader will find that dandelion root is effective in restoration of hepatic and biliary function, dyspepsia and loss of appetite.]

CIMICIFUGA

Although black cohosh does appear to exert some physiological effects, none of them have been clinically verified in human beings (p.46).

[However, in *Women, Hormones and The Menstrual Cycle* (1998), Dr. Ruth Trickey explains that numerous clinical trials in Germany have attested to the efficacy of Cimicifuga for menopausal complaints.]

GINSENG

Unfortunately Ginseng remains an enigma with no proven efficacy for human beings (p.158).

[To cover all the data on Ginseng would require at least one book...several European clinical studies have produced interesting

results-- among them a shortening of reaction time to visual and auditory stimuli, increased respiratory output, increased alertness and power of concentration, a better grasp of abstract concepts, and increases in visual and motor co-ordination (Foster & Chongxi, 1992). Clinical studies have demonstrated that therapeutic effects against antineoplastic medicine side effects, particularly normalization of leukopenia; lowering of blood sugar in diabetics, lowering of HDL cholesterol, improvement in post surgical recovery, elimination of menopausal symptoms, and increase in sperm production (Bone, 1996).]

DONG QUAI

There is little reason to utilise it as a therapeutic agent (p.113).

[However, Dr Christiane Northrup notes in her book Women's Bodies Women's Wisdom (1994) that various herbal preparations such as Siberian Ginseng, Dong Quai, Black Cohosh and Wild Yam have helped many women with menopausal and other symptoms.]

ALL PLANTS ARE NOT DRUGS

The later work *Herbs of Choice* is marginally less opinionated than *The Honest Herbal*. Here Tyler expounds his philosophical views (in a chapter entitled "Basic Principles"). This "mission statement" is useful because it spells out both Tyler's agenda and the foundation of his arguments upon logical inaccuracies.

Consider for example the following logical fallacy...

All cats have hair
All dogs have hair
Therefore all cats are dogs

This is of course absurd - obviously all cats are not dogs. The fallacy is that two objects are held identical because they share some characteristics in common. Tyler employs this fallacy in the form...

All plants contain chemical compounds
All drugs are chemical compounds
Therefore all plants are drugs

For Professor Tyler, cats are dogs and plants are drugs. Plant remedies are thus removed from the messy realm of herbalists, herbal science and phytotherapy and made the object of pure scientific pharmacological understanding by redefining them as single active drug compounds. Ironically Tyler proclaims that he believes *he* is the one who has uncovered a fallacy precisely as he falls prey to this one ....

...the dogma that whole drugs, that is leaves or roots or seeds or the like - have physiological properties different from the active constituents isolated from the same plant parts. ***This is of course a fallacy.*** *.....herbs and other drugs exhibit the same activity as the active principles isolated from them (Tyler, HH, p.3).*

Tyler supports this argument with the predictable example of *Digitalis* (Foxglove). *Digitalis* is just the perfect example, paraded like a super model on the catwalk, familiar but never accessible, the star of every show, from pharmacology text books to popular paperbacks on herbal

medicine; quoted by all, used by none. *Digitalis* **is** arguably unique amongst plant remedies - in that it is a single plant remedy entirely capable of restoring weakened organic function of the failing heart to normal - an indication that may be narrow yet one of tremendous importance. This uniqueness is however an exception, and one that proves no rule.

Foxglove leaf and purified digitoxin do indeed have similar cardiac actions. Ergo says Tyler, plants are drugs. This argument is false on two counts. Firstly, while the two are very similar in terms of pharmacodynamics, there are significant differences in terms of pharmacokinetics. This may be of little interest to a pharmacognosist but to a clinician it is crucial. Both *D. purpurea* and *D. lanata* contain a complex mixture of cardiac glycosides, each of which has small variations in molecular structure which confer different properties on the compound. The pharmacokinetics of different combinations of different glycosides will determine whether a particular preparation is most suitable for tachycardic or bradycardic arrhythmias, for advanced or moderate decompensation in congestive heart failure and so on. Tyler incorrectly suggests that all cardiac glycosides are equally toxic, and lists a number of plants that contain them (incorrectly including *Selenicereus grandiflorus* in his list, a plant whose cardiac activity depends on alkaloids not cardiac glycosides). However the differences in pharmacokinetics, especially in absorption and renal clearance, mean that in practice various cardiac glycoside containing plants such as *Convallaria* (Lily of the Valley) have a fraction of the cumulative toxicity of digitalis or strophanthin. Weiss calls these plants "digitaloid" - precisely because they are safe for use in mild to moderate congestive heart failure. *Convallaria* remains a mainstay of modern phyto-therapeutic treatment of heart failure despite the "toxicity" of convallotoxin.

Secondly, and more importantly there is a perfectly valid distinction made in herbal medicine by herbalists of all persuasions between strong - *drug like* - herbs, and the majority of medicinal plants, which are intermediate or milder acting herbs. As Rudolf Weiss MD, (one of the founding figures of modern German phytotherapy, a clinician with decades of experience and a long time university chair holder in herbal medicine) writes in his book *Herbal Medicine* (1998)**:**

> *Phytotherapy covers everything from medicinal plants with powerful actions, such as Digitalis and Belladonna, to those with very gentle action , such as chamomile, mint and many others....Gentle action...does not mean they are more or less ineffective, but rather that one would not expect these plants to produce instant and powerful effects like those seen after an injection of digitalis or strophanthin. ...Gentle action also means that as a rule these plants do not have any appreciable toxic effects and may therefore be safely taken over an extended period of time (p. 1).*

In other words, powerful *drug like* plants such as *Digitalis* do indeed have physiological actions dominated by one or two active chemical constituents, but these are an exceptional and small minority of herbal medicines, most of which fall into the gentle or intermediate categories. In these cases, contrary to Tyler's assertion, the whole herb cannot be reduced

to an active principle with defined drug like activity... again as Weiss says:

> *It is nevertheless true, with most gentle phytopharmaceuticals, that there is no standardised active principle that solely or largely determines the drug action...the gentle phytopharmaceuticals demonstrate in particular that with plant remedies one very often has a comprehensive complex of active principles, with individual components interacting with others, so that only the complex as a whole will produce the therapeutic action (p.1).*

Or as South West herbalist Michael Moore puts it with characteristic clarity: "The active principle is the whole plant*".* Herbalists have long viewed the multiple constituents of whole plant preparations as having synergistic properties that exceed the sum of the single constituents. In clinical practice real herbal prescriptions, whether time honoured elixirs or modern phytotherapeutic formulae are often compounded from many herbs, each with its innumerable active constituents, taking us into a world of polypharmaceutical complexity that is even further removed from the reductionist single constituent drug model of herb action. Tyler once again disregards both the empirical facts and the scientific evidence: For example, Tyler's false tenet 3 of paraherbalism is that *"*whole herbs are more effective than their isolated constituents*" (* HC p.8).

However, Onawunmi, Yisak, & Ogunlana (1984) found that:

> *While the geraniol and neral components individually elicit antibacterial action on gram-negative and gram-positive organisms, the third component myrcene did not show antibacterial activity on its own. However myrcene provided enhanced activities when mixed with either of the other two main constituents.*

Combined formulations of herbs in fact can increase activity: "...moreover a mixture of these extracts at 200mg/Kg was more active than the plants administered separately; this indicates that both plants may act in synergy*"* (Fleurentin, Hoefler, Lexa, Mortier, & Pelt, 1986) and bioavailability:

> *Piper longum increased the blood levels of Vasocine by nearly 233%...The results suggest that the Trikatu drugs (Long Pepper, Black pepper and Ginger) increase bioavailability either by promoting rapid absorption from the gastro-intestinal tract, or by protecting the drug form being metabolized in the first pass through the liver, or by a combination of these effects (Atal, Zutshi, & Rao, 1981).*

Tyler also states: "This ignorance still exists today: there is no difference in Vitamin C for example obtained from natural biosynthetic processes in rose hips or by synthetic processes in the laboratory of a chemical manufacturer" (HH, p.5). Or is there? This article in the American Journal of Clinical Nutrition found that: "Ascorbate in the citrus extract was found to be more bioavailable than ascorbic acid alone in human subjects*"* (Vinson & Bose, 1988).

For Tyler however, neither logic, studies, nor the viewpoint of phytotherapy are relevant. His insistence that plants are drugs (or as he also calls them "diluted drugs" referring to natures

tiresome intrusion of supposedly inert ballast of other constituents) is doubly ironic in view of his preoccupation with attacking "New Age-ism" and its alleged influence on "paraherbalism". Tyler does not see that his saying something is so, purely because *he* believes it to be so, implies that psychology determines reality - a viewpoint quite compatible with "New Age-ism". Ignoring the historical and philosophical bases of scientific knowledge, Tyler demonstrates the purely religious view of science as objective truth shared by that dwindling number of scientists unaware of the theory-laden and relativistic nature of "facts". The "mission statement" in *Herbs of Choice* attempts to distinguish the scientifically valid use of medicinal herbs which he calls "*rational herbal medicine*".... from what he dubs "*paraherbalism"* (that is Tyler's parody of herbalism as practised by professional herbalists) which involves adherence to a range of deviancies including irrational belief in the superiority of natural medicines, eating organic produce, reading Culpeper, opposition to animal experimentation, promoting consumption of poisonous herbs, recreational drug abuse etc. Tyler declares: "**Rational herbal medicine IS conventional medicine.** It is merely the application of diluted drugs to the prevention and cure of disease*"* (Tyler, HC, p.10 emphasis Tyler's).

At last, everything is solved ! Herbal medicine is nothing other than conventional medicine!

CIRCULAR REASONING

Tyler's logical errors also include circular reasoning. Having defined the activity of medicinal herbs as dependent on the presence of an active constituent, active constituents in turn being defined by scientific study, it necessarily follows for Tyler that herbs lacking studies are inactive and cannot be recommended by him. Repeatedly, *The Honest Herbal* defines herbs with empirically established therapeutic efficacy as inactive because research into their activity is lacking. The book lists 108 herbs in its summary tables. Less than half (49 herbs) are classified by Tyler as having "apparent efficac*y*", while a mere one third, (35 herbs) are considered to be both "probably safe" and "apparently effective." It has already been pointed out that since Tyler does not generally attempt to review the primary research in the first place, he inevitably dismisses a number of herbs with positive pharmacological and clinical studies. But Tyler also dismisses herbs for which he acknowledges positive studies do exist: in these cases he hedges by saying that a few positive studies are **not sufficient** cause for recommending the herb--the goal posts are simply moved when they get in the way:

> *It must be emphasized that these claims are based on studies carried out primarily on small animals or on small numbers of human subjects. Extensive clinical studies in human beings are required to verify these findings before the herb (Bilberry) can be recommended for these purposes" (Tyler, HC, p.54).*

Tyler is not alone in this use of circular reasoning about scientific studies as the validation of medicinal herb activity. It is actually one of the causes of the current emergence of a "super-league" of around a dozen herbs that have gained general acceptance because of the research into their pharmacology and clinical effectiveness (Echinacea, Garlic, Hawthorn, St. John's Wort

etc). The more research is published, the more that herb is accepted. By positive feedback, the "studied" herbs become progressively more established, while at the same time the lesser known plants in the materia medica become progressively ignored.

Of course, such circular reasoning is absurd. Garlic and Hawthorn and other "super league" herbs were Garlic and Hawthorn prior to any pharmacologist researching them or journal publishing studies. Their therapeutic actions were established before any constituent was identified or standardised product became available. It was precisely the empirical knowledge of their traditional use that led anyone to "study" them in the first place. And the hundreds of other medicinal herbs in the materia medica remain as effective as they always have been despite any lack of studies. Not only is it logically absurd to believe that a study makes a herb active, but there is here a crucial point in the whole debate about the scientific basis of herbal medicine. Of course herbalists value constituent studies, but it is also true that *the presence of constituent "studies" almost never significantly changes the way a medicinal plant is used therapeutically.* There are a few interesting exceptions to this, but much as one cannot discuss the strange case of the hyena with someone who believes all cats are dogs, one cannot begin to grasp the rich diversity of herbal remedies if their nature is essentially defined by the pharmacology of their constituents.

THE PROBLEM OF STANDARDIZATION

A related misconception that also flows from the view that plants are drugs is the erroneous belief that "standardization" somehow guarantees" quality" of a herb product. Standardised extracts involve the selection of one or more 'active' or 'marker' compounds which may then be assayed and if necessary manipulated in the production process to meet a minimum titre - usually stated as a percentage of that compound (or class of compounds). There are various problems associated with standardization, both technical and theoretical as well as clinical, and by an large the issues are too complex to discuss here in detail. However, since the vast majority of herbs do not have single active principles, the concentration of a compound that is selected for standardizing an extract guarantees precisely nothing - other than the presence of that amount of that compound in the product, and probably a degree of degradation in the manufacture of the product as well. Standardised herbals are yet one step further from the original plant.

For a current example that neatly expresses some of the problems, consider Hypericum. By convention, St. John's Wort is commercially standardised to no less than 0.3% of the chemical compound hypericin. Hypericin is demonstrably NOT responsible for the antidepressant effects for which this herb is currently so popular (administering isolated hypericin to depressed patients does not improve their condition). Recent research suggests that another compound - Hyperforin - is the most likely a candidate for the active anti-depressant principle. And this says nothing about the compounds responsible for the many other actions of St. John's Wort, which is far more than a "herbal anti-depressant". Yet intelligent consumers concerned about health and diet, (who may have long ago switched from Wonderbread to artisan baked organic whole grain loaves) will insist on ingesting Hypericum pills standardised to hypericin, despite their Wonder bread character, (ie that they are

industrially processed products that need constituents adding back to compensate for the degradation involved in their manufacture). And to cap it all hypericin is not even the active anti-depressant principle!

The idea that standardization per se can guarantee quality is a myth, albeit an attractive one in a culture where the confusion of quantity with quality is commonplace. The marketing hype spread by some well known US herbal product companies that standardised extracts are "safer" and more effective", is not only untrue, it is unproven, and the weight of evidence would tend to suggest that the opposite is more probably the case. There are several instances where reports of side effects of herbs coincided with their standardised extracts (as opposed to traditional galenical tinctures) becoming commonly available - for example Ginkgo and orbital headaches. Claims for the clinical superiority of standardised products are unethical commercial attempts to dupe the public in the name of science. The starting quality of the herbal material used in the extraction process is far more relevant to quality of the final product than any laboratory manipulation or "correction" during manufacture. Most companies offering standardised product start with crude herb purchased by third party brokers in the international marketplace - the provenance and quality of which is inevitably beyond their direct control. Alas, Tyler has in recent months lent his name and personal endorsement to precisely such claims on prominent product literature.

The concerned physician or informed consumer might ask well how then can quality of a herbal product be guaranteed if standardization does not assure reliable quality? The answer is - know the herb. The reductionist drug paradigm does not apply. Once more Weiss puts it well:

> *In the first place it is important that physicians once again develop a special, almost 'personal' relationship to the medicinal plants they prescribe, very much as it was in the past.....*
>
> *....Another aspect is that physicians should be able to make up their own formulations, plant drugs being particularly suitable for this. Finally the aim must be to link every proprietary product and every formulation with a definite concept of the plant on which it is based, not only as regards its actions, but also its appearance and the parts used, whether leaf, flower, root and so on. Where a chemical product has its structural formula, the medicinal plant has a specific image, and knowledge is required of the plant drug and its uses (Weiss, 1988, p.6-7).*

SAFETY AND TOXICITY

Safety and toxicity issues are major concerns in the use of herbal medicines, and a significant reason why healthcare professionals and educated lay readers need reliable sources of information. Tyler does not review safety and toxicity studies, does not present information on potential herb-drug interactions, and does not give reliable information on safe dose ranges or distinguish between therapeutic and toxic doses. Tyler classes only 57 of the 108 herbs covered in *The Honest Herbal* as being only "probably safe", several common herbs are suggested to be dangerous and possibly life threatening in excess. For example, Tyler subscribes to the traditional but discredited bad press given to herbs such as Licorice and Lobelia.

Consider the logic of this analysis of the "toxicity" of Licorice from *The Honest Herbal*: Firstly, Tyler points out that Licorice candy contains no Licorice, but is flavoured with aniseed. Then he warns that excessive consumption of Licorice candy causes terrible side effects. Following this we are given a case history (note that physicians' reports of single cases are always called *case histories,* while herbalists' reports of single cases are dismissed as *anecdotal evidence*) of Licorice toxicity requiring hospitalization - an elderly man chewed 36 ounces of tobacco (not candy) daily, swallowing it all. The tobacco was flavoured with 8% solid extract of Licorice (equivalent to a daily dose of around 85 grams of whole Licorice root) And thus concludes Tyler, Licorice root, used by hundreds of thousands of people world wide on a daily basis, is a herb toxic enough to be considered life threatening - it will allegedly even cause cardiac arrest (although that did not happen in the tobacco case and the only supporting 'citation' of this fatality is an anonymous letter, un-confirmed in the literature).

This progression of self contradictory statements unravels when we understand that there is not one single report of toxicity or side effect in the medical literature arising from the oral ingestion of whole Licorice root extract as used in herbal medicine. Every single medical report of side effects attributed to Licorice root come from abuse of industrially processed extracts, flavorings and additives in food, candy, tobacco products, never the form used in herbal medicine. The side effects from industrial products using Licorice concentrates are real, but have nothing to do with the medicinal herb taken in therapeutic doses. Nowhere in his Licorice "monograph" does Tyler cover the use of Licorice root by orthodox medicine to successfully treat Addison's Disease in the 1950's prior to the development of cortisol therapy, let alone the substantial volume of contemporary research confirming the hepatoprotective, anti viral, anti inflammatory, expectorant and anti-ulcer activity of Licorice root by *in vitro, in vivo* and clinical trial studies. Instead we are simply told that Licorice

> *…does have a flavor pleasing to many, and may have some utility in treating coughs as well as a number of other conditions (not specified) but it must be remembered that it is a potent drug, large doses over extended periods of time are quite toxic (Tyler HH p.199).*

The reader is also not informed about what the toxic or normal therapeutic dose of Licorice root may be. The same omission of detail on therapeutic and toxic dose data applies throughout *The Honest Herbal* for all the herbs covered, as do the frequent assertions of life threatening toxicity. For example, Lobelia, having already been 'rubbished' as a marihuana substitute is said, in excess, to result in a host of undesirable side effects including "sweating, rapid heart beat, low blood pressure, even coma, followed by death. Large doses may cause convulsions" (Tyler HH p.205).

The reference here is to a secondary source – *Martindale,* 1977 edition. The case referred to there was reported in the *British Medical Journal* in 1968 and in fact involved a middle aged asthma patient who was concurrently medicating with a sympathomimetic inhaler (orciprenaline sulphate) and who also smoked *Datura stramonium* leaves (containing the powerful anti-cholinergic hyoscyamine and hyoscine)

mixed with Lobelia. She had previously been taking the smoking mixture for twenty years, and collapsed after taking two prescription drug inhalations followed by smoking the mix for five to ten minutes. Lobelia, a very mild alpha-adrenergic agonist, is the least culpable element of this cocktail - and the case was dropped from later editions of Martindales monograph on Lobelia. As a lesson in herb drug interaction it of course remains relevant. Paul Bergner, Editor of the journal *Medical Herbalism,* concludes in his exhaustive survey of the origins of the Lobelia toxicity myth:

> *Despite the widespread use of large doses of lobelia in domestic medicine for much of the nineteenth century, there is no primary reference in the medical literature showing harm to any individual from the use of this plant. Secondary references occur to several politically- charged court trials of herbal practitioners in North America and London (the North American practitioner was acquitted) but no medical case report can be located listing any fatality or major injury by lobelia, with details such as the course or treatment or the toxic dose. In fact, the supposed toxic dose in the court trials is identical with the dose that was recommended for asthma in the U.S. Pharmacopoeia from 1820 until 1920, and lobelia tincture and several other lobelia products were sold without warnings of toxicity by the Eli Lilly pharmaceutical company as late as 1941 (Bergner, 1998, personal communication).*

The combination of lack of information and misinformation in *The Honest Herbal* is quite incomprehensible in a book purporting to inform its readers, but the irrational polemics against empirical and traditional use that replace them emphasise for once and for all the philosophical divide between Tyler and the science of herbal medicine. The latter recognizes the rich profundity of its historical origins, the validity of the individual patient's experience, *as well as* the contribution of scientific research and clinical trials where available. (It is of course well known that the great majority of the daily practice of orthodox medicine is itself unsupported by rigorous standards such as positive double-blinded placebo controlled clinical trials). It is worth quoting once more from Rudolf Weiss's text *Herbal Medicine*. Here Weiss presents and comments on Vogel's views regarding clinical studies...

> *Whilst it was necessary to investigate the efficacy of plant drugs with the methods of scientific medicine, we should also not forget the following:*
> *'Demonstrations of medicinal actions should not be based on rigid schemes, but be in accord with the characteristic mode of action of the drug concerned.. Where methods based on exact science are not yet available, medical observation and experience, including the subjective statements of the patient, have to be given equal validity with controlled clinical trials.' The basic stance of rational therapy is untenable because it rests exclusively on the principles of materialistic thought.*
> *'Applied to the problems of medicine and pharmacotherapy this means:*
> *man being a complementary being of body and soul, the subjective statements of the patient concerning drug actions are just as valid as laboratory parameters. Instead of double blind trials, it might be better to adhere to the rule attributed to Abraham*

Lincoln - you can fool all of the people some of the time, and some of the people all of the time, but you cannot fool all of the people all of the time.
Applied to pharmacotherapy, this means that when a drug has been used for a long time, is demanded by patients and prescribed by doctors, its action has to be considered established, even without double blind clinical trials (Weiss, 1988, p.5).

In sharp contrast to the above, Tyler's "explanation" of the widespread popular use of herbal remedies is the placebo effect:

At this point you may ask, "If so many herbal remedies have little or no value or may even be dangerous to a person's health why have they become so very popular in recent years? Why do so many people ,especially those who are unusually health conscious, continue to demand and use them?" The answer lies, at least partly, in the placebo effect (Tyler, HH, p.6).

Millions of people are involved in a daily collective fantasy that the herbs they are taking are making them feel better. For Tyler, placebo is merely a psychological distortion of reality not an intrinsic element of the healing reflex. He believes its value is to discredit false therapeutic claims and poorly designed experiments. For example Tyler says he feels no need to discuss herbs used in homeopathy because "the best that can be said about this now discredited treatment is that it demonstrates the therapeutic value of the placebo effect*" (*Tyler, HH, p.7).

Homeopaths have, of course, for decades been the object of ridicule by those who have no understanding of their subject. Tyler incorrectly defines homeopathy as the use of very small doses of drugs, too small to possibly have any material effect (ie. diluted below Avogadro's Number). Small doses are not the distinguishing feature of homeopathy, which is uniquely characterized by the principle of the similimum (treating like with like). More disturbing however is that Tyler (a pharmacist) apparently ignores one of the basic pharmacokinetic characteristics of drug action - the biphasic dose-response curve. There are many drugs and natural compounds such as most prostaglandins say, whose action in the body varies biphasically with dose (ie there is a bell curve of activity against dose - at a certain point activity increases as dose *decreases*). For Tyler however, "false tenet 6 of paraherbalism is the belief that reducing the dose of a medicine increases its therapeutic activity*" (*Tyler, HC, p.8).

Finally, one might add that the noted German phytopharmacists Bauer and Wagner in their survey of the efficacy of a range of proprietary Echinacea products from Germany actually found that several homeopathic Echinacea preparations were among the clinically active products.

"EXPERT" QUALIFICATIONS?

What then explains the apparent popularity of *The Honest Herbal*? Tyler is presented as an "expert," and this expert reputation appears to be a keystone of his credibility. It is necessary to conclude with a scrutiny of the basis of this claim of expertise. Although now retired, Tyler is usually described as the Lilly Distinguished Professor of Pharmacognosy at Purdue University. Tyler in fact earned his living primarily as a career

academic and administrator; he was Dean of the School of Pharmacy at Purdue, and later was Vice President of academic affairs for the whole university. His reputation in pharmacognosy is not based on any notable contribution to that field such as NAPRALERT - the well-known database of Prof. Norman Farnsworth at Illinois or the NSDA databases of Dr. Jim Duke, but rather his authority appears to rest upon the writings in his apparently extensive publication list.

Out of the more than two hundred and fifty "scientific articles" in Tyler's official bibliography (obtained by the author from Purdue), scrutiny reveals that the bulk of them are in fact general tracts on pharmacy education, miscellaneous biographical stories, and articles on the history of pharmacy. The remainder are a medley of popular magazine articles with titles like "Hazards of Herbal Medicine," and "False Tenets of Paraherbalism," as well as various book reviews. The two popular books covered here and a co-authored textbook on pharmacognosy are included. Tyler's original published scientific research work is sparse, consisting of a few co-authored papers in the 50's and 60's on amanita, Claviceps, psilocybin and ergot alkaloids. None of it is other than routine lab work - verifying constituents of various species and so on.

Tyler, a pharmacist from the 1940's, is not a medical doctor. He had no training in herbal medicine and is lacking in clinical experience either with herbs or as a physician. His original research in natural product chemistry was minimal in volume and consequence. His publications are largely secondary and journalistic. The bulk of his career was as an academic administrator. His "expert" status evaporates under scrutiny.

Tyler scoffs in his books at proponents of "organic" certification, and implies that consumers are stupid for preferring "natural" remedies or products free of animal testing, or pesticides. He repeatedly makes erroneous and unsubstantiated claims about herbs and their safety, and grotesquely misrepresents herbal medicine and its practitioners, yet paradoxically, his books are consistently used as reference texts by physicians, pharmacists and journalists interested in the study of herbs in North America.

Part of the explanation is perhaps that Tyler has in recent years been adopted by the domestic US herb industry and its commentators who, in the absence of a licensed and regulated profession or established science of herbal medicine in that country, need an aura of scientific respectability to promote their own credibility and that of their products. In a climate of regulatory and legal flux about the status of herbs and herbal medicine, the debate on the scientific validity of herbal medicine is being prosecuted by a number of vested interests. From the perspective of today's multi million-dollar OTC supplements market, herbal medicine as such remains a marginal issue, both economically and culturally. Corporate priorities are in the retail market, and the product companies need regulation and legislation that maintain their market share. This is the real context of the current debate about the scientific validity of herbal medicine. A bevy of popular magazines, their journalists and publishers have also discovered a lucrative niche for themselves in servicing the public appetite for information on herbs and natural healing.

The US authorities (FDA, NIH, ATF, CDC etc.) employ lab oriented natural product chemists, and since Tyler at least originated from that quarter he is an ideal figure of respectability for the herb product industry. In a sense this is ironic; Tyler is probably regarded as irredeemably left field by his scientific peers and irredeemably conservative by herbalists. But his continued claim to be a legitimate spokesperson for the contemporary natural product industry would hardly be credible if it rested solely upon *The Honest Herbal* and *Herbs of Choice*. Thus more recently Tyler's image has become spruced up by associating his name with the publication of various texts from German phytotherapy, notably the *German Commission E Monographs* (1998).

The herbal *Monograph* is quite different from a true Herbal. For centuries Herbals explored the "vertewes" of medicinal plants - a direct transmission of the knowledge accumulated and compiled by accomplished and experienced practitioners intimate with the plants whose use they recorded - hence *Gerard's Herbal*, *Culpeper's Herbal* etc. The Monograph is a historically recent artefact. It arose as a political tool in debates about the legal and regulatory status of herbs (as medicines, as dietary supplements, as drugs, as foods etc). The information published in Monographs is agreed by committee and inevitably legitimates the views of the parties (and their lawyers) interested in their publication (whilst usually purporting to be "objective" or "scientific" in the narrowest sense as a means of disclaiming their interest). The now defunct German Commission E, (it ceased to exist in 1994) was part of the German Federal Health Service. Its Monographs define the scope of government permitted use of the herbs in Germany in accordance with legal medical practices in that country.[1] Tyler began to associate himself with the Commission E Monographs in *Herbs of Choice*, and he has written a forward to the English translation of these Monographs. This minor publishing event has been promoted as a new dawn in the scientific validation of herbal medicine. Tyler is a Trustee of the publishers of The Commission E translation by The American Botanical Council (ABC). The ABC promotes the Commission E translation through their journal *HerbalGram*--the book was ironically top of their bestseller list for over a year without it ever having been printed.

Fortunately, there are authors with bona fide qualifications, who are scientifically and medically literate and who speak from the genuine authority of extensive clinical experience with medicinal plants. Obvious inclusions would be practitioners from countries with established professions of medical herbalism and phytotherapy, such as the German MD, Rudolf Fritz Weiss, author of *Herbal Medicine* quoted extensively in this essay, or respected phytotherapists Simon Mills and Kerry Bone, authors of *Principles and Practice of Phytotherapy*.

1 The much promoted Commission E Monographs actually originate from the seventies, are dated, unreferenced, and often refer to commercial preparations available only in Germany . They are conservative, telegraphically short, completely lacking any detail in botany, ethnobotany or pharmacognosy. They have the minor benefit of considering some traditional usage but they mostly reflect the specific situation in Germany - where for example injectable herbal preparations are commonly available.

The only "honest" thing about these texts is their systematic inability to inform the reader correctly about the most basic information about either herbal medicines – the remedies – or their use in the practice of herbal medicine .

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Re-Weissing Weiss:

a review of *Herbal Medicine (Second English Edition Revised and Expanded)*

R F Weiss and V Fintelmann

Jonathan Treasure

Readers familiar with the Beaconsfield edition of R F Weiss's *Herbal Medicine* will likely be more than disappointed by Thieme's second English edition of the book. The original has been comprehensively revised, rewritten, and edited by Dr Volker Fintelmann, a former chairman of The German Commission E, and is now a very different work altogether.

For those unacquainted with Weiss's book, the following brief summary must suffice, at least for the present task of situating the Fintelmann revision.

Rudolf Fritz Weiss (1895-1992) qualified as an MD in 1922 . By 1937 he was the leading proponent of phytotherapy in German postgraduate medical curricula. The first edition of *Lehrbuch der Phytotherapie* was published in 1944. In 1961 Weiss retired from active clinical practice to devote himself full time to the development of phytotherapy. *Lehrbuch* distilled over 20 years of Weiss's clinical experience in its first edition (several years of which he was doctoring as a prisoner in Russian POW camps), and it subsequently matured through six editions over the next twenty years. The first English edition *Herbal Medicine* was rapidly acknowledged as a classic following the publication of a well crafted production by Beaconsfield Publishing in 1988 of Meuss's silky translation of the sixth (1985) German edition of the work. Incredibly, this had been edited by the author in his 90th year, and was thus to all intents and purposes the final statement of his life's work.

Weiss was a libertarian protagonist of herbal medicine *within* the orthodox medical community: he knew he was arguing for a herbal therapeutics that ultimately was neither philosophically nor practically containable within the dominant medical viewpoint whilst operating within that milieu. He therefore addressed the medical community - and set about defining herbal medicine for them, articulating its basic premises, criticizing its weaknesses, and promoting its strengths. In so doing he anticipated many of the major issues that continue to confront western herbal medicine today and was arguably the first real exponent of the now fashionable trend of "integrative medicine". The original book remains a valuable "crossover" tool for introducing herbal medicine to physicians today.

As a philosophical progressive and experienced clinician Weiss was not only an authority *within*

herbal medicine but also an outstanding thinker *about* herbal medicine. In his book, *Herbal Medicine*, he ranged effortlessly over philosophy, materia medica and therapeutics in a way that consistently expresses an understanding of the nature of plants as healing agents, and of phytotherapy as a specific modality of natural medicine whose unique characteristics derive from the nature of medicinal herbs. By any informed historical account, Weiss was a towering figure of herbal medicine in the second half of the twentieth century, comparable to the leading physiomedical and eclectic figures of the preceding era.

Dr Fintelmann on the other hand is obviously conservative and scientistic, holding a dogmatic Commission E stance, with its accompanying limited and narrow "evidence based approach" that ignores and even disparages traditional use and empirical experience. His philosophical position is hard to interpret precisely - his understanding of holistic seems to involve an appeal to recognize both "subjective and objective" aspects of health and disease--theory is clearly not his strong point. He also frequently refers to Goethe, possibly indicating anthroposophical leanings. He displays no particular empathy for medicinal plants themselves and although he professes to be an advocate of phytomedicine, he nowhere reveals the intimate personal clinical knowledge of herbs that is the warp and weft of Weiss's work. He explicitly states that he considers Weiss to be in error on fundamental points, and has eliminated accounts of folkloric and traditional remedies from the text. Weiss's often lengthy clinical accounts of herbs have been cut entirely, or reduced to minimalist lists of the tedious "take this for that - because of this study" genre.

Space does not permit an exhaustive catalog of Fintelmann's violations of Weiss's text, but one or two examples will serve to illustrate.

Weiss's renowned essay, *What Is herbal medicine?,* is a seminal philosophical manifesto of modern western herbalism. This famous doctrine has been completely replaced by Fintelmann's disjointed commentary which lapses at times into complete unintelligibility. Poor translation may be partly to blame for this, however, one thing is clear: Fintelmann explicitly attacks and rejects Weiss's classification of herbal medicines into mild, intermediate and strong type remedies and completely extirpates Weiss's lucid and valuable discussion of the difficulties faced by orthodox physicians and medical education in developing a genuine and effective understanding of medicinal herbs.

Fintelmann's agenda becomes clearer in Chapter 2 *Proof Of The Efficacy Of Herbal Drugs* - which Weiss had only added for the 6th edition. Aware that orthodox medicine would increasingly challenge the efficacy of herbal medicine, Weiss anticipated the problems of applying orthodox medical criteria to phytotherapy by discussing topics such as the limits of clinical trials, the nature of placebo , the importance of empiricism in herbal therapeutics and so on. Fintelmann removes all this and instead launches into a routine promotion of the Commission E as a standard, which simply acquiesces to the criteria of dominant medical model that Weiss had tried to preempt.

Weiss often included accounts of the use of folkloric and traditional remedies, understanding that they are used largely because they work! In his chapter on peptic ulcers for example, Weiss

discusses the use of raw cabbage juice as a simple ulcer remedy, and indeed spends two pages on the topic. Fintelmann however, characteristically says "the treatment of ulcers with cabbage and potato juice does not seem worthwhile from a modern point of view. These folk remedies are more or less outdated" (p.70).

Neither are Weiss's meticulous clinical observations and insights spared the Fintelmann axe. For example, Weiss's twenty page discussion of cardiac glycosides is an outstanding example of modern herbal writing. It has been completely omitted. Fintelmann declares instead "this is already standard knowledge for physicians" (p.149), thereby directly equating plants with pharmaceuticals. The myopic arrogance of this position is highlighted by the recent research interest on the anti-metastatic activity of the cardiac glycosides, especially from *Nerium (oleander*), which makes clinical experience of their different specific glycoside effects, as detailed at length by Weiss, a subject of considerable importance.

The "revising" or "rewriting" of classic or historical texts is generally considered unnecessary and undesirable in academic circles-- a rather uncivilized behavior more at home in politburo propaganda where it serves to overturn the ideological influence of the original work to legitimize some new hegemony. Unfortunately, whether intentional or not this seems to be precisely the process we are confronted with in evaluating these two editions side by side.

Thieme, who are launching their complementary medicine line with this title, are a subsidiary of Hippokrates, who hold the original rights in Germany, and presumably whose profit motives placed exploitation of Weiss's name and book title over respect for his work. The political agenda is clearly that of promotion of a medical-pharmaceutical-scientific model of herbalism designed and packaged for pharmacists and orthodox physicians. This is corroborated by Blumenthal's Foreword to the volume which makes the serially absurd argument firstly that Varro Tyler was deeply influenced by Weiss, and then that the Fintelmann edition is one of the foundational texts of German herbal medicine which we are apparently so fortunate to have available to us in English (along with Commission E of course).

On the subject of English, the poor quality of the translation has already been mentioned. In fact, it is so bad it is funny at times. When a phrase such as "herbal baths" is rendered as "*phytobalneology*" one wonders if the Monty Python team had some involvement in the editorial process. Why a prestigious German international publishing house is content with such inferior translation is another question.

Thieme have managed to add insult to injury by distressingly "improving" the book's appearance, with vulgar graphics and crude typography using garish green (of course!) ink boxes, rules and headings everywhere which uncannily complement the insensitive purging of Weiss's finesse and intelligence from the text. Even the elegant line illustrations of the original have been replaced by poorly reproduced, often out-of-focus, color photographs. Curiously some of the old illustrations have been randomly reproduced at sub postage stamp size in the new "quick reference" section - to what end is unclear since they are all but invisible without

Herbal Hypotheses

I added Herbal Hypotheses to herbological.com in 2005. The name pays tribute to Dr. David Horrobin--scientist and medical physiologist, researcher and world expert in fatty acids and prostaglandins--who died of lymphoma in 2003. Horrobin, always an out-of-the-box thinker, founded the journal Medical Hypotheses in 1975. I included this brief extract from his first editorial on the original homepage of Herbal Hypotheses:

The physical and chemical sciences long ago recognized that observations are not superior to hypotheses in generating scientific progress nor are hypotheses superior to observations. Both are necessary. While the ideal research worker may be one who is equally able to generate hypotheses and to test them experimentally, these sciences also recognized that such paragons are very rare indeed. Most scientists are much better at either one or the other activity. In physico-chemical fields this is fully accepted and the contributions of both theoretical and experimental scientists are recognized. In contrast, in the biomedical sciences there seems to me much ignorance of the way in which scientific advance actually occurs. Physical scientists often dismiss biology and medicine as backward and the biologists quite legitimately react by pointing out that they are usually dealing with much more complex phenomena. But I have a suspicion that there is some truth in what the physical scientists say and that biology and medicine are backward because they have relied almost exclusively on observation. They have failed to recognize adequately that observation is always more effective when disciplined and channeled by hypothesis.

Many journals will occasionally publish a theoretical paper from a scientist with an outstanding reputation but will not consider similar papers from relative unknowns. The rule that is almost universally applied biology and medicine is that ideas can be presented or criticized only by those with a record of experimental work in a field. Even then they must be kept strictly to the discussion sections of papers and their presentation must usually be rigorously curtailed because ignorant and pedantic referees and editors object to 'unjustified speculation' and complain that the discussion 'goes beyond the observed facts'. It is hardly surprising that the best physicists and chemists find medicine and biology primitive and unsophisticated."

I once heard Horrobin lecture on essential fatty acids. His ability to seamlessly transition from the molecular pathways of prostaglandins and leukotrienes through to the most complex clinical issues such as schizophrenia and neurodegenerative diseases made a lasting impression on me. For the time period, (well before modern 'omics') it was rare to see such a fluent mapping of the molecular to the clinical via a vital physiology of the whole organism. Years later, after reading Thurston's 1900 text on The Philosophy of Physiomedicalism I saw how Thurston and Horrobin, though nearly a century apart, shared a common viewpoint of the limitations of the medical science of their time, and of the central importance of theory. Horrobin was a molecular vitalist.

Horrobin never let up. Only months before his death, he wrote about his cancer to the Lancet, including a critique of the methodology of using immortal cell lines to assay "in vitro" therapeutic anticancer agents because of the artificiality of this system compared to the complexities of cancer in the living body.

Traditional Western herbal medicine is facing the challenge of how to preserve its core principles while acknowledging the insights of modern scientific research, without conceding to what Horrobin would probably have described as the most "primitive and unsophisticated" aspects of biomedicine.
The underlying assumption of Herbal Hypotheses (HH) was the serious lack of attention to theory and ideas in Western herbal medicine. HH aimed to set out ideas, speculation and hypotheses about herbal medicine based on Horrobin's recognition that theory is as essential as observation in medical practice, and by extension, in the development of modern herbal medicine.

The first selection I've included is HH1, Warding of Evil in the 21st Century: St John's Wort as a Xenosensory Activator. This is an exercise in reframing the misconceptions in both herbal and mainstream thinking that posit SJW as a highly interactive agent that represents an archetype of all herb-drug interactions. The piece speaks for itself, and illustrates something I have always considered important in discussions that fall under the general rubric of "modern science vs. traditional knowledge"-- an overworked cliché that permeates much of the herb world, from commerce to clinical practice. When invoking "science" in this way, it is important that the "science" part of the equation be based on a thoroughly literate understanding of the actual science involved. In this case, without some prior understanding of orphan nuclear receptors it is not possible to consider the role of SJW as xenosensor--which is clearly what it is! In more general terms, when herbalists critique "science" they rarely appear to be familiar with how far modern science has progressed beyond a coloring book version of "reductionism for dummies."

HH2, Medline and the Mainstream Manufacture of Misinformation is an analysis of how the indexing process of peer review journals in the National Library of Medicine covertly creates a structural bias against herbal medicine. This could be dubbed the "bias of bias" since it is more or less the inverse of "pub-

lication bias" which refers to the well-documented problem of overemphasizing positive results through the systematic failure to publish negative ones. Here we are dealing with the overemphasis on publishing negative information and the omission of positive. This is compounded by the fact that much negative information about botanicals in Medline is simply pure nonsense gleaned from the correspondence columns of various journals written by random physicians. Repetition and self-reference compound errors until the circular process eventually morphs biased misinformation into "data." Though herbalists familiar with scientific literature are well aware of the inevitability of such bias and its downstream effects, they remain exasperated by the complete of lack of acknowledgement of the issues in any discussions of bias in scientific discourse.

I included Treading on the Tiger's Tail, to illustrate a problem inherent in the peer review process, which Horrobin himself identified in the Aims and Scope of Medical Hypotheses:

> *Medical Hypotheses takes a deliberately different approach to peer review. Most contemporary practice tends to discriminate against radical ideas that conflict with current theory and practice. Medical Hypotheses will publish radical ideas, so long as they are coherent and clearly expressed. Furthermore, traditional peer review can oblige authors to distort their true views to satisfy referees, and so diminish authorial responsibility and accountability. In Medical Hypotheses, the authors' responsibility for the integrity, precision and accuracy of their work is paramount.*

I originally submitted this article to the peer-reviewed Journal of Molecular Nutrition after a guest editor solicited an article from me for a special issue on herb-drug interactions. My article was originally to be titled Herb-Drug Interactions in Oncology.

In its draft format, the piece was duly submitted for peer review, and as the author I was also invited to submit possible names for reviewers. I suggested three, each of whom reviewed the article and who made several dozen very useful detailed suggestions between them, all of which I incorporated into an amended version and resubmitted. All three reviewers had incidentally commented that the article was "controversial," but agreed it was important and valid to include articles expressing different points of view. At this point my guest editor was asked by the now presumably concerned Journal Editor to send my article to a second round of reviewers, to be chosen from their own "stable". Two of the reviewers were distinctly negative about the "controversial" nature of the piece, but the third reviewer made the strongest recommendation: to NOT publish at all. I examined the comments of this one reviewer in detail to look for his rationale, and discovered that he had focused specifically on one fairly blunt criticism I had made concerning the position taken by a well-known "oncological naturopath." NONE of the other five reviewers had even commented upon this critique. It suddenly dawned on me that the reviewer was the author I had criticized. Long story short, the article was rejected on the basis of that recommendation without further discussion or debate, and

as I later established, the reviewer was indeed the author I had criticized in my article. This whole exercise graphically illustrates Horrobin's assertions about peer review: radical ideas are discriminated against, and authors are constrained to satisfy their referees and reviewers who can, as in this case, compromise the integrity of the author.. In theory, peer review is an important concept. In practice, it is also another form of bias that preserves the status quo.

Warding off Evil in the 21st Century:

St John's Wort as a Xenosensory Activator?

Jonathan Treasure

According to folklore St. John's wort (SJW) was once known for its special ability to ward off evil spirits and protect against magic spells. For herbalists, such uses are typically regarded as non-trivial (1). Fast-forward to the late 1990s, and SJW in the guise of a standardized phytopharmaceutical with a slew of controlled clinical trials supporting its efficacy, is celebrated as a remedy for "mild to moderate depression". By most accounts the herb appeared to be at least as effective for this condition as pharmaceutical anti-depressants, and standardized SJW supplements became an enormously popular best-seller. If its efficacy for depression compared to pharmaceuticals was debatable, the safety of the herb - particularly in comparison to prescription antidepressants – was uncontroversial. Prior to 1999, SJW was considered benign: natural was safe.

The publication of convincing reports of interactions between St. John's wort and digoxin (2), cyclosporine (3), and indinavir (4) was a decisive turning point. St. John's wort was transformed almost overnight from a benign herbal remedy into public enemy number one, with authorities such as Professor Ernst heading the volte face (5). Although regulatory and official bodies acted swiftly, a longer term consequence was to provide the status quo with a much needed gift horse – SJW's fall from grace was the Achilles heel that the mainstream had desperately needed to counter the hitherto seemingly inexorable rise in public popularity of herbal medicines.

The subsequent five years has seen increased understanding of the pharmacology of SJW and its constituents, and the herb is now known to be associated with a number of clinically significant pharmacokinetic interactions as suggested by the original reports (6). These interactions are mediated by its effects on several key components of drug metabolism, including the P450 mixed oxidase system, various conjugases and transferases, as well as the transporter proteins that modulate drug efflux across intestinal, renal, and biliary epithelia. Taken together these systems comprise what are often referred to as Phases 1, 2 and 3 respectively of the detoxification system. Phylogenetically ancient, this system is present in lower animals and has been conserved during evolution; it has the dual function of metabolizing endogenous compounds (such as steroid hormones) and protecting the organism against the damaging effects of potentially harmful environmental xenobiotics.

During the same five year period, the mainstream medical literature generated a minor industry of publishing secondary articles containing

hyperbolic warnings of the dire dangers of herb-drug interactions, often coupled with strident demands for increased regulation and restriction of availability of herbs and dietary supplements. The quantity of this derivative literature may have been growing but the scientific quality of publications is generally low and in some notable instances, such as the notorious 1998 review by Lucinda Miller, overwhelmingly erroneous and ill-informed (7). Essentially by means of the process best described as the *mainstream manufacture of misinformation*[1] potential drug interactions associated with botanicals have been promoted as the most significant safety concern about herbs for consumers and healthcare providers alike. In the face of this, the reaction of many herbalists, rear-footed by their obligation to demonstrate responsible regard for patient safety, has been unnecessarily defensive, which tends by default to concede the terms of debate to the mainstream.

In fact, the mainstream spin on interactions is deeply flawed for several reasons, foremost among which are some basic conceptual issues. Most importantly, the meaning of "interaction" is rarely defined, and the term is used inconsistently to cover a variety of situations which are not strictly interactions at all (8). Logically, a true interaction is properly an "unpredictable" or unexpected result of combining two agents. The result is a non-linear (synergistic or antagonistic) departure from the expected combined effect, and is logically required to be independent of underlying mechanism (although in practice may not necessarily be so) (9).

Many so-called adverse pharmacodynamic herb-drug interactions suggested in the secondary literature are in fact simply additive combinations. If such a herb-drug pair is coadministered unknowingly or inappropriately due to ignorance (or negligence) it is possible that excessive effects may result but this is logically equivalent to an overdose rather than interaction. Administration of kava with benzodiazepines is a good example – an additive sedative effect is not an interaction but a predictable consequence of combining of two CNS depressants. (This is quite apart from the drug-herb combination violating standards of botanical practice which would consider this kind of combination at best redundant, at worst contraindicated.) Other additive "interactions" simply do not exist at all, but are speculatively extrapolated by arguing "in reverse" from in vitro pharmacological observations backwards, without a single supporting clinical or experimental datum on the combination. This is clearly a specious form of logic, but is nonetheless used regularly in the secondary literature: the commonest example is the extrapolation of an

1 "mainstream manufacture of misinformation" characterizes the process whereby inaccurate negative information about herb safety, adverse effects and herb-drug interactions in the mainstream medical literature is propitiated as an artifact of the MEDLINE indexing system, which logically equates miscellaneous editorial correspondence with peer reviewed articles via the database <title> field. The whole exercise ultimately results in the curious phenomenon of the apparent existence of a self-referential body of ostensibly peer-reviewed negative literature on herb safety, which is in reality a smoke and mirrors chimera bearing little connection to clinical or indeed any other reality at all.

interaction with anticoagulant drugs from in vitro platelet aggregometry data of a given herb in the absence of any evidence whatsoever of the effects of the herb-drug combination either in vitro or in vivo.

Pharmacokinetic interactions result in alterations in drug bioavailability and hence modify the magnitude of dose-response relations as opposed to intrinsically synergistic or antagonistic pharmacodynamic effects. Pharmacokinetic interactions are considered by some to be theoretically "predictable" if the specific metabolic pathways of the drug are known, together with likely effects of the herb upon those pathways. This has led to persistent mainstream calls for in vitro screening of herbs of to establish the "risk" of potential (pharmacokinetic) interactions with drugs. Such demands for systematic screening of herbs for potential (pharmacokinetic) interactions, ignore the fact that drug disposition is actually unpredictably mediated by a wide variety of dietary compounds, foods, herbs, beverages and life style products, and is also affected by a wide range of individual variables from genomics (SNPs = single nucleotide polymorphisms) through biological, lifestyle and socioeconomic factors, all of which render meaningful screening virtually impossible. Additionally, the results of in vitro tests are often contradictory and quite at odds with clinical reality, due to the inherent differences between experimental systems and the in vivo complexities of herbal administration; therefore they have limited predictive value (10).

Secondly, the scale of the herb/drug interaction problem is not only overexaggerated but more importantly its underlying causes are conveniently "inverted". This is due to the collective delusion of the medical establishment of the inviolable identification of medicine with pharmacotherapeutics. Medicinal herbs, certainly those that are commonly available to consumers, generally have a wide spectrum of therapeutic effects with broad safety and toxicity margins with considerable latitude in effective dose range. The opposite is generally the case for drugs. Although the interactions issue is typically presented in mainstream medical literature as being a problem of herbs interfering with drug efficacy, it is perfectly obvious that the primary problem is caused by narrow therapeutic index drugs, their associated toxicities and their side-effects. It is clearly more sensible and necessary that pharmaceuticals should be the initial subject of more rigorous screening and tighter regulatory controls. Officially, testing and screening procedures for new drugs are claimed to be improving, but the recent fiasco over COX-2 inhibitors would suggest otherwise. Prescription pharmaceuticals continue to be a leading cause of death in the USA (11), and enormous safety problems are by non-prescription OTC medications such aspirin and acetaminophen (12).

Perhaps these are obvious points, and probably more than familiar to many herbalists and practitioners of natural medicine but to date they have not been clearly articulated in a way that pointedly enables the mainstream case against herbs generated from herb-drug interactions to be effectively challenged. Given the defining role of SJW as centerpiece of the interactions narrative, a review of the recent scientific data on the mechanisms underlying the pharmacokinetic interactions of SJW from a conceptually pro-herbal medicine perspective is

a mandatory strategic element of any riposte to the mainstream position.

Recent research suggesting that hyperforin, an active phloroglucinol constituent compound of SJW, acts as a uniquely high affinity ligand for the orphan nuclear receptor PXR (pregnane X receptor) is highly significant (13, 14). Activation of the PXR leads to upregulation of a battery of genes controlling multiple aspects of xenobiotic metabolism, including Phase 1 (CYP 1A1, 1A2, 2B6, 2C9, 3A4) mixed oxidases, Phase 2 conjugases (UDP-glucuronosyl-transferases, glutathione-S-transferases, sulfonyltransferases) and Phase 3 drug transporters (MDR1/P-glycoprotein, MDR2, organic ion transporter peptide (OATPs) (15-17). The implication is that the PXR and related nuclear receptors such as CAR (constitutive androstene receptor) and AHR (aryl hydrocarbon receptor) effectively act as high-level co-ordinators of a xenobiotic detoxification system (18, 19). This system was described by Pascussi and colleagues as a "tangle of networks of nuclear and steroid receptors, where receptors share partners, ligands, DNA response elements and target genes and where the different pathways exhibit cross-talk at several levels" (20). In fact this network constitutes a sophisticated "pharmacosurveillance" system, capable of detecting and responding to an enormous number of potential xenobiotic insults. In this sense the nuclear receptors can be described as "xenosensors", capable of downstream regulation of the detox-ification pathways.

Different nuclear xenosensor/receptors exhibit varying degrees of "fine tuning" (ie substrate specificity). For example, the nuclear aryl hydrocarbon receptor complex (AHR) is tightly linked to metabolism of polycyclic aromatic hydrocarbons via several narrow-band low-throughput CYP450 enzymes including 1A1, 1A2 and 1B1, enzymes which primarily metabolize environmental carcinogens (21, 22). Before its polymorphous nature was properly understood, the PXR was described as "promiscuous", due to the wide range of compounds that appeared to serve as its ligands. This lack of specificity means that a wide range of lipophilic compounds can bind to the receptor independently of any unique structure-function characteristic. CYP3A4 which is upregulated by PXR activation, is itself well known as a broad band high throughput drug metabolizing enzyme (in contrast to 1A1 and 1A2 for example) and is heavily concentrated in human intestinal wall and hepatic microsomes.

Hyperforin is to date the most potent known ligand for PXR, and this confers upon SJW the ability to act as a unique xenosensory activator. The downstream effect of PXR activation includes induction of CYP450 3A4. Therefore SJW triggers a concerted xenosensory upregulation of the most generic and broad spectrum aspects of all phases of the xenobiotic detoxification system, intended to eliminate the maximum number of potentially toxic environmental insults. Put another way, SJW will obviously "interfere with more than 50% of pharmaceuticals", by ensuring their elimination from the body is promoted.

The hypothesis that SJW is a xensosensory activator generates novel therapeutic applications for the herb that are testable. Detoxification has not been synonymous with "puking and purging" for some time. Recently, heroic herbal medicines have taken a second

place to accessory nutrients in contemporary therapeutic interventions targeting the molecular level of hepatic detoxification. These important approaches were originally developed by the Functional Medicine Group (23). Diagnostic tests used probe drug evaluation of Phase 1 and Phase 2 hepatic pathways to generate assay-driven nutritional supplement protocols to balance and facilitate detoxification. Essentially, this approach focuses only on the "effector" side of the system. The emerging understanding of nuclear receptors as xenosensors of the pharmacosurveillance network enables botanicals that are ligands of these receptors to be conceived of as exerting an overarching sensory side "gain control" that genetically upregulates functionality of all three phases of detoxification. Therapeutically this approach could be used, for example, both in case of acute toxic exposures to environmental xenobiotics, or chronically in functional imbalances such as estrogen dominance, to facilitate clearance of endogenous steroid hormones. Novel targeted actions in integrative settings are possible, such as combining SJW with prescription aromatase inhibitors in adjuvant treatment of post-menopausal endocrine positive breast cancer patients to decrease exposure to peripheral estrogen. Induction of detoxification enzymes is also an important aspect of cancer chemoprevention, not only through carcinogen metabolism, but also through induction of cytoprotective antioxidant mechanisms; reactive oxygen species and xenobiotics are cellular level stressors both capable of triggering adaptive responses via genes encoding detoxifying exzymes (24). Compounds that induce Phase I enzymes have been termed mono-functional inducers, those inducing Phase I and II enzymes have been termed bifunctional inducers (25). In this terminology, PXR ligands would be described as multifunctional inducers.

To date there are very few natural compounds besides hyperforin that have been shown to have potent PXR ligand activity. CYP3A4 may also be induced, activated or inhibited without PXR involvement, and a number of natural compounds display induction of this enzyme and other PXR controlled proteins without mediation of the nuclear receptor. A luciferase methodology has recently been developed that enables PXR activation to be measured in vitro, and positive results were found for kava extracts using this method (26). Recent data also suggests that forskolin from Coleus forskolii (which can already be considered as a "meta-regulatory compound" due to its cyclic-AMP modulatory effects) and the sesquiterpene lactone artemisinin from Artemisia annua, both act as PXR ligands (27, 28). The non-botanical alpha tocopherol (Vitamin E) also may operate in this way (29). It should be added that the PXR receptor itself is subject to polymorphisms, although the clinical significance of such genomic variations remains be established. However, they will likely alter xenosensory sensitivity to specific subsets of xenobiotic com-pounds (30).

For most herbalists, the conceptual leap from warding off evil to the detoxification of pharmaceuticals is unlikely to overstrain the imagination. For those uncomfortable with the 'shamanistic' implication that pharmaceuticals could possibly be malefic, perhaps designating St. John's wort as a "pharmacovigilante" may be scientifically, if not politically, more correct.

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HERBAL HYPOTHESES TWO

Medline & The Mainstream Manufacture of Misinformation

Jonathan Treasure

The legacy of political suppression of herbal medicine in America in the early 20th Century casts a long shadow - in the early 21st Century the practice of herbal medicine in the United States still remains effectively illegal. In 1910, the Rockefeller-financed Flexner Report on Medical Education that forced the closure of all botanical medical schools (Haller 1994), was a result of the fledgling alliance between the new pharmaceutical companies and the then recently formed AMA. The same alliance has become the dominant feature of the contemporary medical landscape (Smith 2003; Smith 2005), and the current intensification of anti-herb propaganda in response to widespread resurgence of public interest in herbal medicines suggests that history does indeed repeat itself.

A persistent strategy of the mainstream is to hold herbs and herbal medicine accountable to the tribunal of medical "science". Unchecked, this process has potentially disconcerting implications for herbalists; ultimately it implies that mainstream medical science is the authoritative arbiter, not only of the efficacy of herbal medicine, but for the form and availability of herbal medicines, and possibly of the legitimacy and validity of clinical herbal practice itself. As herbalists we have yet to elaborate much more than sporadic, partial or emotional critiques of the epistemic credentials, clinical relevance and socio-political values that characterize mainstream medical science, and as a consequence we are not especially well-equipped with the theoretical tools to battle its encroaching influence, both overt and covert, over our own territory.

Central to a discussion of how mainstream medical science impacts herbal medicine is the issue of what kind of data should be taken as meaningful evidence in support of the claims and credibility of herbal medicine. In modern biomedicine the measure of 'scientificity', i.e., scientific authoritativeness or credibility, has progressively come to rest upon a hierarchical taxonomy of methodologically defined evidence, within which controlled clinical trial data is the 'gold standard'. Therefore any analysis must at some point deal critically with the appropriateness of applying of this hierarchical system to herbal praxis, now commonly known as 'evidence-based herbal medicine'.

A robust critique of evidence-based herbal medicine is clearly a priority, but there is an

even more pressing problem, which although it appears superficially to be connected with issues of evidence, explanation, and scientific credibility is in fact a pseudo-scientific epiphenomenon that I call the "mainstream manufacture of misinformation" about herbal medicine. This will be analyzed below with particular reference to the unique role of MEDLINE in the process, using examples from the topic of herb-drug interactions; but initially we have to clarify some terms and definitions about science itself.

GOOD SCIENCE, BAD SCIENCE AND NON-SCIENCE.

It has been remarked that scientists typically have no more understanding of the philosophy of science than fish do about fluid mechanics. Whilst some sciences such as quantum physics have a more developed connection with their philosophical ramifications, others, including hybrid disciplines such as medicine are peculiarly deficient in this respect. In any event, philosophy does not seem to be a pressing cause for concern for working physicians who appear to view metaphysics with the disinterest typically reserved for clinical specializations unrelated to their own. A survey of epistemological beliefs of 237 resident physicians found that more than two-thirds did not know what epistemology was; less than 25% could give an appropriate definition of science, and none could state the philosophical presumptions of science (Peña, Paco, and Peralta 2002). Here we need to ask two initial questions: how do we properly distinguish between "science" and "non-science"? and how do we distinguish between "good" vs. "bad" science?

Following the publication of Thomas Kuhn's seminal Structure of Scientific Revolutions (Kuhn 1962) the philosophy of science became progressively dominated by historical relativism. With hindsight, the notion that the questions asked by science may be significantly affected by values, assumptions and sociopolitical factors extrinsic to the process of scientific inquiry is hardly controversial. Indeed, it is arguable that much of the content of the claims of science are also intrinsically determined by such "non-scientific" factors. An interesting consequence of this is an exacerbation of the difficulty of determining philosophically exactly how science can be differentiated from non-science.(Dupré 1993)

Consequently, philosophers and historians of science have recently tended to abandon big-picture questions like "what is science?" in favor of micro-examination of the actual practice of particular sciences, down to specific laboratory experiments and technologies as well as their socio-historical setting. As a result, philosophy of science today has followed the post-modern tendency and migrated to some form of pluralism, in which the now discredited vision of one 'unified science' progressively attaining true (ultimately mathematical) knowledge of the natural world via 'the scientific method' has been replaced by the idea of a number of different coexisting sciences with complementary (or possibly even contradictory) methodologies, each the product of its peculiar field of enquiry and associated historical determinants.

Such pluralistic views range from the anarchic extreme of Feyerabend who argued that all methodologies however incongruent can be held equally valid (Feyerabend 1975), through

to those that maintain the apparent disunity of sciences is simply a necessary reflection of the "dappled world"(Cartwright 1999). This view varies in detail from an agnostic position typified by Evelyn Fox Keller (Keller 2002), who describes a democracy of scientific methodologies based on relative "explanatory satisfaction" for their practitioners, through to the more extreme view that the diversity is an expression of an underlying real disunity in the nature of nature itself (Dupré 1993).

What is most important for our purposes here is the notion that 'science' is actually a collection of distinct sciences and there co-exists a corresponding pluralism of more or less different but equally valid explanatory systems. Although this has fascinating implications for a potential redefinition of herbal science, it has obviously complicated the original question of demarcating science from non-science.

However, when it comes to the mainstream manufacture of misinformation we are concerned with an entirely different kind of non-science. This is a false, purely sociological form of non-science that is easily identifiable, best characterized as "scientism". Scientism describes the use of the term "scientific" applied in honorific reference to the sociological or institutional trappings of science in order to accord a pseudo-authoritative status to the opinions of individuals simply because they have a doctoral degree in a subject generally regarded as a science. When white-coated actors (or paid physicians) make hyperbolic testimonials about drugs in TV commercials for pharmaceutical companies the process is ludicrously obvious, and may cause embarrassment even for some medical commentators (Moynihan et al. 2000).

However, scientism has more insidious and subtle manifestations. Scientism was originally defined by Habermas as follows:

"…science's belief in itself: that is the conviction that we can no longer understand science as ONE form of possible knowledge, but rather must identify knowledge with science."
(Habermas 1971)

Today, scientism is generally considered a term of abuse, and is usually understood in an ideological sense in reference to arguments that appear authoritative by claiming to be scientific "independent of any general consensus about what makes scientific claims any more deserving of credit than beliefs from any other source" (Dupré 1993).

This brief excursion into definitions of science enables a taxonomic classification of the problem at hand; what we have termed the 'mainstream manufacture of misinformation' of herbal medicine can now be identified as a form of scientism, (which is by definition non-science). Our specific hypothesis is that it derives substance from intrinsic or structural features of MEDLINE.

MEDLINE

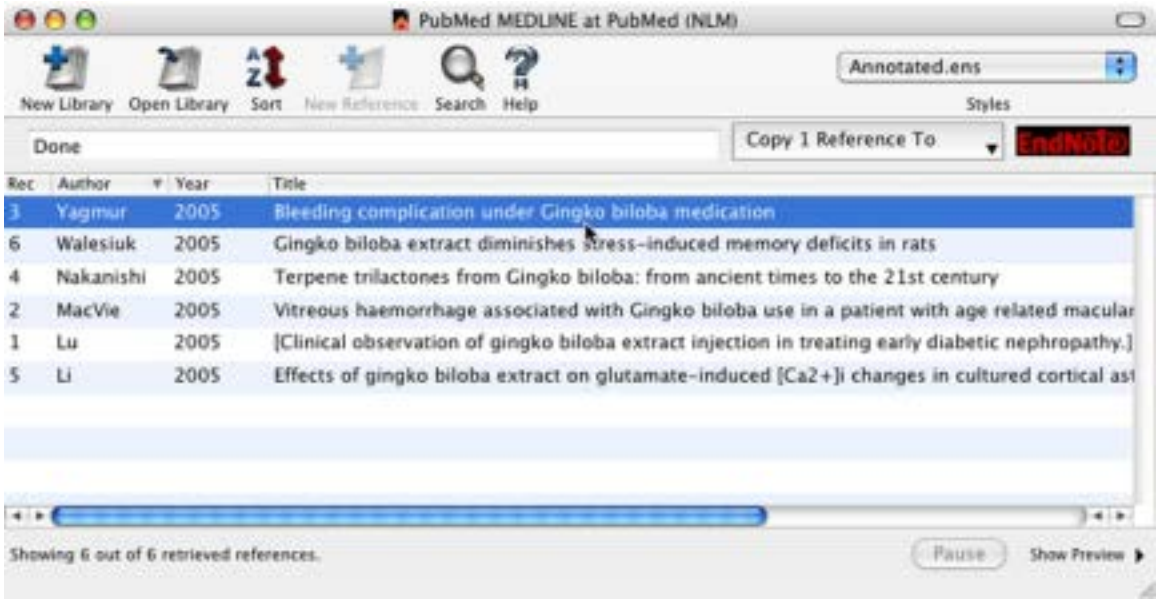
Publication of peer-reviewed papers in learned journals is sociologically accepted as a defining aspect of scientific activity. A corpus of academic literature defines the knowledge base of a given science, acts as a forum and vehicle for the communication and development of ideas, testing of hypotheses and recording research findings for its professional practitioners. In

biomedicine, the National Library of Medicine operates a well-known electronic database called MEDLINE consisting of over 4,800 learned journals containing over 12 million citations relating to medicine and life sciences which are searchable via the world wide web at no charge. The indexing system of MEDLINE incorporates a regularly updated thesaurus of MESH (Medical Subject Headings) terms which are attached to each record or article in the indexed journals. In addition to its MESH tags, every article (record) is identified by a number of standard database field descriptors which are also searchable such as <title>, <abstract>, <author>, <journal>, <date of publication> etc. Although the system is somewhat more sophisticated than outlined here, this basic description is sufficient for our analysis.

BAD SCIENCE (BS)

It is hard to imagine a paper being accepted for publication by a learned journal if the title and text of the paper systematically incorporate a major spelling mistake of the principal subject, for example a paper on the NSAID drug ibuprofen spelled throughout as "bifupropen". But when it comes to mainstream medical articles about herbs anything goes, including major spelling errors. For example, a search of MEDLINE for papers published on <ginkgo> interactions misses some potentially important reports because they are entered under the misspelled name gingko (sic) hence do not appear in a search for <ginkgo> in the title.

Inaccurate spelling of herb names is not uncommon in medical literature as all herbalists can attest, but more frequently there is a complete failure to use proper scientific nomenclature for botanicals. This is not a trivial issue, because without a validated description of a herb by its binomial name (and preferably the naming Authority) the identity of the herb cannot be established. A botanically educated reading of these reports can however, by means of a little sleuthing, reveal the not uncommon error of mistaken identity.



Screenshot of MEDLINE interactions search for <gingko> (sic) results showing title spelling errors not retrieved by a <ginkgo> search.

THE GINSENG - PHENELZINE "INTERACTION"

The technical literature persistently claims there is an adverse herb-drug interaction between the monoamine oxidase inhibitor phenelzine and Asian ginseng (Panax ginseng C.A. Meyer). This is documented by conventional medical authorities such as Stockley's (Stockley 2002), and is repeated in several botanical monographs e.g. World Health Organization (WHO 1999).

The original report of this alleged interaction was a brief mention in a 1985 editorial by the then editors of the Journal of Clinical Psychopharmacology, Shader and Greenblatt. In this speculative commentary they devoted a couple of lines to the case of 64 year-old woman who took (an undisclosed dose for an undisclosed time) of a combination dietary supplement product apparently called "Natrol High" while concurrently taking phenelzine 60 mg qd. She experienced symptoms of "insomnia, headache, and tremulousness."

The authors did not include any medical details or history, and crucially did not identify the ingredients of the Natrol product, other than the fact that it contained "ginseng". They attributed her symptoms to the adverse effects of ginseng and phenelzine in combination (Shader and Greenblatt 1985).

In sleuthing mode, this writer was able to rapidly establish that the product "Natrol High" contained no Panax ginseng whatsoever. This discovery required a simple e-mail inquiry to the manufacturer who sent back in ten minutes the (now discontinued) product label with its ingredients list which revealed that it actually contained Siberian ginseng (Eleutherococcus senticosus (Rupr. & Maxim.) Maxim.).

In other words this is a typical case of mistaken herbal identity. These authors simply assumed incorrectly from the diminutive common name "ginseng" that the material was Panax ginseng.

High Nutrition Product Label reveals "Siberian" ginseng not Panax ginseng contents (reproduced by acknowledgement to Natrol ® Inc.)

Verification of the herb's identity, either at the time of the observed adverse event, or at least before publication of the report, would hardly have been onerous but it clearly never occurred to Shader and Greenblatt. Similar confusion of these two herbal medicines has been established by Chen as being involved in several of the infamous so called "ginseng abuse syndrome" reports (Chen 1981). Mills and Bone have also pointed out that this error is frequent in mainstream literature (Mills and Bone 2005). One of the basic scientific aspects of an apple is that it is not a pear. Except in MEDLINE reports about herbs that are replete with elementary errors of nomenclature and plant identification.

The fundamental point is, of course, that the Shader editorial is not really a report at all; it lacks the most rudimentary elements of scientific precision and rigor, and ultimately is nonsense because it misidentifies the herb involved. As is typical for drug-herb interactions claims, the authors fail to consider the known adverse effects of the drug alone, which in this case are entirely consistent with the observed symptoms, particularly at the high (60 mg qd) dose involved. In one of the few critical appraisals of the literature that has reviewed validity of interactions reporting, this report was classified as "unreliable" (Fugh-Berman and Ernst 2001). A clear example of bad science, it nonetheless has the fatal implication that any published report about botanicals that does not verify the identify of a herb is prima facie inadmissible as evidence of anything (other than ignorance). Perhaps the original authors might claim in mitigation that they only intended this as a speculative editorial comment, but herein lies the genius of the MEDLINE mechanism…

MEDLINE AND THE CHINESE WHISPERS CASCADE EFFECT (MORE BS)

Crucially, different derivative <article types> such as editorial opinions and readers letters, typified by the ginseng-phenelzine example, that are not 'peer reviewed' primary data are classified in MEDLINE with the same MESH attributes that are attached to bona fide primary papers. Furthermore, although primary papers such as clinical trials are usually clearly described by their titles, the opposite is often the case with op-ed and correspondence items. Apparently, journal editors often assign inappropriate titles to these items, which ultimately become searchable via the <title> field of MEDLINE. For example, the same journal that carried Shader's speculative editorial later published a letter from Jones a couple of years later that also claimed to describe an interaction between ginseng and phenelzine under the title "Interaction of ginseng with phenelzine" (Jones and Runikis 1987). This letter had almost as little detail as the original Shader editorial and failed to ID the herb once again, but by simply virtue of the title 'proof' of the interaction has become established. The <title> field of MEDLINE always shows whatever the title may be.

Now the "method used" in almost all the secondary literature (i.e. review articles) on herb-drug interactions is … to perform a literature search. Although it is theoretically possible to include a Boolean operator such as <NOT CORRESPONDENCE> in such search algorithms, this is apparently not a common practice. Thus the searches that are used as 'evidence' for interactions routinely retrieve

assorted MEDLINE records by title which contain unverified and erroneous data, but that are treated by the database as equivalent to peer reviewed data. Authors of such secondary and derivative papers rarely appear to evaluate the full texts of the citations they gather, (more bad science) and, in turn, their reviews become quoted as principal sources in subsequent generations of reviews.

This process is like the classical game of Chinese whispers, in which repetition progressively adds distortion, but here also involves a cascade amplification effect. To observant readers, the conspicuous repetition of egregious errors from previous papers is a "give-away" fingerprint symptom of the process. For example, one of the most infamous anti-herb reviews on the subject of herb-drug interactions was by pharmacist Lucinda Miller, published in the Archives of Internal Medicine (Miller 1998). This article was so riddled with errors of commission and omission that it has become a legendary example of its genre. Among Miller's many mistakes was the incorrect assertion that … "echinacea is hepatotoxic if used for more than 8 weeks, due to the presence of toxic pyrrolizidine alkaloid ingredients". This speculation was a curious hybrid combination of the well-known Commission E myth on duration of administration of echinacea, together with ignorance about the chemistry and pharmacology of certain trace alkaloids present in certain Echinacea spp. (which are not at all hepatotoxic). Despite publication of ruthless criticisms of Miller's review article, and total lack of evidence for her claims about echinacea, they have been endlessly perpetuated by subsequent generations of secondary reviews… for a recent example… " if echinacea is taken for more than 8 weeks hepatoxicity may result"(Kumar, Allen, and Bell 2005).

Miller also provides disconcerting confirmation that reviewing authors may look only at the <title> of MEDLINE records before jumping to conclusions when she asserts that "Kava when used with alprazolam has resulted in coma"(Miller 1998). This erroneous claim is based upon an imaginatively titled letter "Coma from the health food store – an interaction between kava and alprazolam"(Almeida and Grimsley 1996), which upon detailed evaluation certainly did not involve coma, and probably did not involve a kava interaction. According to the systematics of scientific publishing, a 'primary' paper is an original report or study. 'Secondary' literature reviews the primary literature, and the 'tertiary' literature is made up of formal meta-analyses of the available/eligible primary studies (such as in the Cochrane database). Primary observations shown to be significant by tertiary analyses are deemed to be validated 'real' effects. Here however, we see that the system actually works in reverse, with successive generations of secondary reviews amplifying the errors of previous derivative articles that were in turn based on erroneous primary data or speculation.

For example, performing a MEDLINE search using the MESH term <herb-drug interactions> for the year 2000 will retrieve about 35 records. Of these, one was a solid case report (St. John's Wort and cyclosporine), none were clinical trials. Repeating the same search for the year 2005 generates a total of 164 records. Of these, once again there was one single case report (myrrh and warfarin), and one was a clinical trial. Interestingly, this trial found, contrary to mainstream myth, several herbs commonly

alleged to interact adversely with warfarin in fact did not alter coagulation or clotting parameters (Jiang et al. 2005). However, the main point is that actual number of bona fide primary papers on interactions has remained consistent and very low over the five year period, whilst the derivative literature has proliferated by an order of magnitude. The vast majority (98%) of the remaining 2005 records retrieved are assorted secondary reviews, correspondence items, and editorial opinion pieces.

Their overall effect however is the illusory appearance of a substantial body of negative literature about purported interactions of herbs with pharmaceutical drugs that appears authoritative but which lacks any meaningful foundation in clinical, scientific or any other reality. Overstated and speculative mis-information and scare stories are subsequently peddled to consumers via dumbed-down news wires, press releases and attention-deficit driven headlines by a sensation-hungry mass media (Moynihan et al. 2000). Popular perception is inevitably influenced by the process, and ultimately herbal practitioners have to spend valuable time reassuring fearful patients concerned about largely non-existent dangers, while consumers become neurotically suspicious of even the most benign herbal remedies. By contrast, and almost unbelievably, no attention is given to the alarmingly high mortality associated with even the most commonly available OTC drugs such as aspirin (Pirmohamed et al. 2004) and acetaminophen (Watson et al. 2004), let alone to the fact that pharmaceuticals are by objective accounts a leading cause of death in the US. (Lazarou, Pomeranz, and Corey 1998)

INDEXING BIAS (PILED HIGHER AND DEEPER).

The mainstream manufacture of misinformation is in large part possible because of the inherent property of MEDLINE to act as a "scientistic" device, lending pseudoscientific authority to information that may in fact have not a shred of genuine credibility. This is distinct from the important questions about bias in the process of selecting which journals are indexed in MEDLINE in the first place, which cannot be entered into in depth here. Suffice it to say that the process of selecting the journals for indexing is carried out in secret by a non-accountable committee. There is a significant under-representation of journals relating to areas such as nutritional, environmental and alternative medicine, quite apart from the huge absence of literature from non-English speaking countries. The ostensible reasons for rejection of journals for indexing is that they are "not scientific" enough in content (Hickey 2005). This of course, is purely a "scientistic" defence, since Time magazine, Newsweek, never mind the Kansas Historical Quarterly and similar trivia are all indexed in MEDLINE. Although there is an increasing concern and debate about bias in the selection of journals for indexing, it is unlikely that the process will change dramatically in the near future.

LIBERATING KNOWLEDGE

On the positive side, MEDLINE and its inherent biases could become increasingly irrelevant in the future. The movement for "open access" of scientific publications is rapidly gathering momentum and support; this sidesteps the entire question of MEDLINE structural bias

and indexing. Simultaneously, new forces are emerging in the 'bioinformatics' marketplace for scholarly literature, most strikingly in the form of privately owned search engines such as Google, Yahoo, and MSN search. Arguably, despite their corporate ownership, these can be seen as a contribution to the process that Mae-wan Ho has called Liberating Knowledge, which she describes as a "one of the most urgent tasks facing humanity". (Ho 2006)

The original analysis of scientism was developed by Habermas and others partially to account for the cynical and deliberate exploitation of science by governments to justify policy and manipulate public opinion (the use of science by Nazi fascism being the classic example). In an ironic socio-historical twist, the present Bush administration is arrogantly anti-science rather than sophisticatedly scientistic, to the absurd point of advocating creationist ideologies such as "intelligent design" or simply denying rather than distorting science e.g. on global warming. Meanwhile, contrary to Mae-wan Ho's view which identifies corporate ownership of intellectual rights as a critical issue, progressive corporations developing free search engines appear (to date) to be above concerns of professional territorialism, mainstream bias and conservatism and free of pharmaceutical corporation influence.

Google Scholar already provides access not only to the PubMed collection, but to many thousands of medical conference papers, poster reports, slide presentations and journal articles including alternative medicine resources, and this constitutes a significant threat to the hegemony of MEDLINE. The BMJ recorded that during one month (November 2005) 446,000 visits to its web site articles came from Google and Google Scholar, and only 14,522 from PubMed in the same period (Giustini 2006). Even herbological.com, the author's own modest web site and second home to Herbal Hypotheses receives over 1000 hits per month directly from Google searches. Meanwhile, other Google plans include Google Print, an open access support project, along with the more controversial Library Digitisation scheme. While the data retrieval and ranking systems of Google Scholar need refinement, they are nonetheless free from MESH taxonomic constraints and includes innovative features such as "cited in". A laudable BMJ editorial has already called for a dedicated medical portal to Google (Giustini 2006). Free public access to on- line medical literature including herbal and alternative medicine will increasingly develop from this trend; this could eventually transform the current landscape of mainstream misinformation about herbal medicine.

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HERBAL HYPOTHESIS THREE

Treading on the Tiger's Tail: Interactions Between Herbs and Anticancer Drugs

Jonathan Treasure

> ***"I have no data yet. It is a capital mistake to theorize before one has data. Insensibly one begins to twist facts to suit theories instead of theories to suit facts."***
>
> *- Sherlock Holmes (A Scandal in Bohemia)*

For many cancer patients today, it is a commonplace that their oncologists will actively discourage the use of botanicals or dietary supplements such as antioxidants during conventional treatment. The prevailing justification for this position is that concomitant use of such agents with chemotherapy (or radiation) involves the likelihood of incurring potential adverse herb-drug interactions whereby the efficacy of the treatment may be reduced, to the extent of causing therapeutic failure.

For the thinking cancer patient who starts to research the mainstream literature as part of the now obligate post-diagnosis rite of becoming self-informed about their condition, it is disconcerting to discover that lack of efficacy and adverse effects are actually intrinsic features of anticancer chemotherapy itself. Any standard oncology text such as De Vita or Abeloff contains the facts: with the exception of some hematological and germ cell cancers "cure" is a rarity. Chemotherapy and radiation are associated with life-threatening toxicities. The efficacy of available systemic cytotoxic treatments for advanced disease is distressingly low while their cost-effectiveness and impact on quality of life is abysmal. (1) A substantial case can be made for the failure of the "war on cancer" and the optimistic spin on the very moderate success of current cancer treatments. (2) Contrary to the assertions or beliefs of many oncologists, "evidence-based" support for a substantial proportion of established oncological interventions is in reality often lacking. (3) Meanwhile new drugs often gain "fast track approval" by regulators on the basis of questionably small incremental increases in survival times based on a single trial, which is usually sponsored by the drug manufacturer.

However it has to be conceded that much of the information available to oncologists in the professional literature about the nature of non-conventional therapies, their possible relevance to cancer and the extent of their use by cancer patients, let alone issues such as potential interactions between herbs and anticancer drugs is both confused and confusing. At the same time

useful contributions from non-conventional medical sources on the topic are largely lacking, whilst at a consumer level, the internet and popular media abound with unscrupulously promoted products and therapies making unsubstantiated claims targeting cancer patients. The following review, a partial clear-cutting of the context and concepts involved in this controversial field, is intended to facilitate an improved understanding of the subject for oncologists, conventional and non conventional healthcare professionals and patients alike.

Herb-drug interactions (HDI) by definition constitute an "integrative" topic. A better term might be "transdisciplinary" since multiple knowledge disciplines are involved in understanding HDI - these include but are not limited to: a grasp of clinical botanical medicine and (not the same thing) of herbal medicines and (also not the same thing) natural product chemistry and pharmacology; research methodologies used to investigate drug metabolism in vitro and in vivo; pharmacology especially current developments in pharmacogenetics and pharmacogenomics; understanding of the multiple issues involved in evaluating and extrapolating from experimental and theoretical data to clinical settings; and ideally a non-partisan and "integrally informed" understanding of the clinical settings or contexts in which potential interactions between therapeutic modalities of biomedicine and botanical medicine as well as the interaction between their respective tools - pharmaceutical drugs and herbal medicines - may arise. Given that expertise in more than one or two these areas is unusual, most providers, especially busy oncologists, are faced with the need for collaborative transdisciplinary contexts, in which specialized expertise can be fruitfully exchanged and a common understanding created between all practitioners and providers.

THE INTERACTIONS LITERATURE: LACK OF EVIDENCE & LOGIC

A distinguishing feature of the evidence for an interaction (as well as drug adverse effects), whether drug with herb, nutrient or another drug, is that the standard 'Evidence-Based Medicine' hierarchy of levels evidence tends to be inverted, with individual case reports and anecdotes actually providing prima facie indication of the existence of an interaction in clinical practice. Stockley's standard drug interactions textbook contains an encyclopedic compilation of such reports (4) and it was Ruschitzka's well documented report in The Lancet in 2000 (5) of a case of acute graft rejection in a heart transplant patient taking cyclosporine and St. John's Wort concurrently that signalled the real clinical importance of interactions between that herb and narrow therapeutic index drugs, that had already been demonstrated experimentally with indinavir and digoxin. (6, 7) The premium value placed on the importance of accurate case reports for establishing both the existence and clinical significance of interactions has been likened to catching the criminal "red handed at the scene of the crime". (8) This in turn places a great emphasis on the requirement for accurate comprehensive and consistent reporting "from the scene of the crime" in order that the "perpetrator" is properly identified according to the rules of evidence required in court. Unfortunately, it is widely acknowledged that the standard of interactions case reporting in the mainstream literature is variable,

inconsistent, and generally below that required for a successful prosecution. In a well-known review by Fugh-Berman in 2001, the majority of HDI case reports reviewed were evaluated as "improbable" whilst a good number were completely "unevaluable" on the basis of the inadequate data provided. (9) Unfortunately the poor quality of case reports alleging herb-drug in interactions or adverse effects persists, despite documented examples of "mistaken identity" of herbs (for example the so called ginseng-phenelzine interaction) as well as errors due to lack of elementary knowledge about botanical and nutritional therapeutics. (10)

A logical corollary of the empirical-anecdotal evidence requirement for demonstrating the existence of an interaction is that an interaction between two agents may logically be independent of currently known mechanisms of action, (conversely, agents acting via similar mechanisms may not result in an interaction at all). Failure to understand this basic point is at the heart of one of the most pervasive problem in the interactions literature – the proliferation of "theoretical interactions", the logically most specious form of which is what might be called "the reverse-extrapolation adverse interactions fallacy." The general form of the fallacy is (where A is a clinical or physiological parameter):

- Herb X affects A
- Drug Y affects A
- Therefore combining Herb X with Drug Y implies an (adverse) herb-drug interaction involving A.

Usually, the fallacy is further compounded and confounded with concealed issues about routes of administration, animal species vs. human data, dosage levels in vitro vs. in vivo and so on…for example

- Herb X injected into streptozocin-induced diabetic rats at dose 100n lowers blood glucose
- Drug Y, in human Type 2 diabetics is used to assist glycemic control
- Therefore oral Herb X in humans causes an adverse interaction when combined with Drug Y.

There are literally hundreds of these unconfirmed "fantasy interactions" listed in databases usually compiled in abbreviated format by pharmacists for physicians and available on electronic hand-held devices or in print and web based resources. Typical examples of reverse extrapolation adverse interactions like the one above include any herb with mild glucose normalizing properties adversely interacting with hypoglycemic drugs or any calming herbs interacting negatively with hypnotics and sedative drugs and so on. Sometimes the extrapolations are even more tenuous, made on the basis of quite incorrect understanding of the pharmacology of isolated single herbal constituents. The classic example of this genre being any "coumarin containing herb" interacting adversely with warfarin anticoagulation. Invariably there are no case reports demonstrating these "theoretical interactions", and often in vivo evidence exists that actually disproves the hypothetical extrapolations. However, the telegraphic format in which the databases present these alleged interactions is devoid of informed discussion both of the evidence and of the possible implications of the interacting combination for clinical practice. Some of these combinations may simply be "contraindicated" for any practitioner

versed in the elementary principles and practice of botanical therapeutics. In other words, a hypothetical adverse interaction for a herb-naïve pharmacist or physician could be viewed by a herb-literate professional as a violation of established principles of botanical prescribing. For example the combination of the anxiolytic drug alprazolam with the herb kava (Piper methysticum) would never be prescribed by a professional experiences in herbal therapeutics. Detailed analysis of reports of several of the cases of alleged hepatotoxic reactions due to kava consumption have been shown in fact to be due to kava-alprazolam combinations resulting from conventional physician recommendation in Germany. (11).

Where a herb-drug pair that is "potentially" a theoretically interactive combination that cannot be completely characterized due to lack of experimental and clinical data (which is the case with the great majority of possible combinations) it is both logically admissible and from an "integratively informed" clinical perspective quite appropriate to reformulate the above hypothetical example as follows:

> *Use of herb X may theoretically eliminate, postpone or enable reduced dose requirement of Drug Y to control parameter A, which may be beneficial in terms of lowered costs, increased compliance, reduced side effects and increased quality of life. Clinical trial evidence is lacking, however practitioners familiar with botanical prescribing might consider an empirical trial of co-administration of Herb X with drug Y while monitoring the results (lab values, symptoms etc) on A.*

MYTHS, MEDIA & BIAS

Some of the most egregious examples of claims regarding "theoretical adverse herb-drug interactions" are simply unsubstantiated speculations about the extent and significance of HDI in general. Unfortunately the oncological HDI literature is replete with examples, such as the following from the introduction to a review article entitled "Herbal Remedies in The United States, potential Adverse Interactions With Anticancer Agents"(12). Author Dr Alex Sparreboom, of the National Cancer Institute writes:

> *"More than 100,000 deaths per year in the United States can be attributed to drug interactions, placing drug interactions between the fourth and sixth leading cause of death, and it has been suggested that the greater part of these may be linked to the use of herbs."*

Firstly, the well known estimated statistic of drug associated morbidity referred to by Sparreboom relates to non-error related prescription drug adverse events, not drug interactions. (13) The author's subsequent claim that herb-drug interactions underlie these morbidity statistics is pure invention. That a statement containing this magnitude of error and misinformation can pass the process of peer review hardly reassures readers about the validity of the succeeding content of the article. Similarly, a review article entitled "Herb-drug interactions in Oncology" - focus on mechanisms of induction" (14) the authors make the following statement in the abstract:

"It is however estimated that CAM-anticancer drug interactions are responsible for substantially more unexpected toxicities of chemotherapeutic agents and possible undertreatments seen in cancer patients"

This again is pure invention, and entirely unsupported by anything in the author's paper or its accompanying references, or indeed by any other data anywhere at all. Later in the same paper the authors offer the following extraordinary non-sequitur as if it were a self-evident fact:

"Induction of CYP or drug transporters will, in the case of active parent drugs, often lead to therapeutic failure because of lower plasma levels of the chemotherapeutic drug. As therapeutic failure in the treatment of cancer is common, very often this effect may not be recognized as the consequence of an interaction with CAM."(ibid. p745-6)

Despite lacking both logical merit and factual support these speculations appear in indexed journals, which are subsequently quoted and re-quoted, as authoritative. Given the lack of evidence for these claims, bias against herbs and non-conventional therapies has to be considered as a possible explanation for these statements, along with journalistic tactics such as sensationalism and "buzz word" enticements to attract reader attention (scientific articles are rated by "impact factors"). Whether intentional or not, the overwhelming impression created is that herb-oncological drug interactions are a major cause of treatment failure and consequent morbidity. The cumulative effect of this, speculative, self-referential repetitive negative literature receives additional authority simply by virtue of its MEDLINE indexing, which leads to what has been called The 'Mainstream Manufacture of Misinformation' regarding herbal medicine .(10)

Consumer media coverage of HDI tends to exaggerate and amplify the problems found in the professional literature, a fact compounded by the unfortunate but increasingly common practice for researchers to present preliminary findings at press conference as a means of publicizing and promoting their research and the institutions that supported it. Among the proponents of such media manipulation is Memorial Sloane Kettering Cancer Center, whose Dr Larry Norton was famously quoted on the front page of The New York Times, on October 26, 1997, as saying that…

"large doses of Vitamin C could blunt the efficacy of chemotherapy for breast cancer"

apparently based on his unpublished research. In fact, when the research was published nearly two years later it turned out to be an experimental study with mouse cancer cells looking at only Vitamin C transport - and had nothing to do with the effects of Vitamin C with chemotherapy for breast cancer. On September 15th 1999, a press conference was held by the authors of the paper when it was finally published, in which they were quoted as saying …

"large amounts of Vitamin C could interfere with the effects of chemotherapy or even radiation therapy."

This claim was rapidly extended from Vitamin C to antioxidants in general, as it was widely disseminated via the American Cancer Society,

the internet, the mass media and other press to become an enduring myth. Today this is a persistent belief shared by most oncologists and many patients, despite its origin in an inappropriate comment to a national newspaper based on unpublished research that was not even relevant to the claim. None of these derivative sources review or discuss the relevant literature, which although controversial, on balance currently supports rather than opposes therapeutic co-administration of antioxidants with most chemotherapy. (15-19)

Antioxidants aside, the principal concern identified by the majority of speculative discussions about HDI in the oncological setting is that of the possible effects of herbs on drug bioavailability. In terms of classical pharmacology, this of course means pharmacokinetic (PK) interactions ie those relating to drug absorption, distribution, metabolism and excretion (ADME).

PHARMACOKINETIC INTERACTIONS & THE SJW MODEL

Despite the importance of all aspects of ADME, in practice, most HDI literature emphasizes the metabolism aspect, focussing on Phase 1 (the hepatic-intestinal CYP450 mixed oxidase system), Phase 2 (conjugation reactions such as glucuronidation by UGTs) and Phase 3 or drug efflux transporters such as P-gp (P-glycoprotein). Most classical anticancer drugs are substrates of these systems, undergoing transport and either bioactivation or metabolic degradation via these pathways; in some cases these drugs are themselves also co-inducers or co-inhibitors as well as substrates of different enzymes and transporters. The ubiquitous overemphasis on herbal influences upon upstream determinants of drug bioavailability is in large part an extrapolation from the example of St. John's Wort (SJW), the implicit assumption being that SJW models the effects of other less well studied herbs on these systems. However there are a number of problems with this assumption.

Firstly, SJW is effectively unique amongst herbs in that it exerts co-ordinate effects on phases 1, 2 and 3 of drug metabolism due to the ability of the active phloroglucinol constituent hyperforin to act as high affinity ligand for the PXR nuclear receptor. Using cell-based luciferase reporter methodology a small number of other herb-related natural compounds have recently been shown to act as PXR ligands in vitro - including artemisinin and guggulsterone. (20, 21) However, although it has been claimed that PXR binding is theoretically predictive of PK interactions (22), in fact neither guggul nor artemisinin are noted for such interactions; on the contrary artemisinin co-administered with carbamazepine for example increases the drug AUC. (23) It thus appears that SJW is unique in its capacity to co-ordinately activate multiple xenosensory mechanisms that have been conserved throughout evolution to regulate xenobiotic exposure. To date no other herb has been shown capable of exerting the magnitude of effect exhibited by SJW on these mechanisms. However, it is essential to contextualize these effects within the larger picture of other influences on drug ADME.

It is well known that drug- metabolizing enzymes are subject to both inhibition and induction by a wide variety of foods, beverages dietary and related agents such as tobacco smoke, as well as lifestyle activities, including

exercise etc. For example red wine decreases cyclosporine bioavailability more than SJW. (24) Although the subject of dietary influences on drug ADME is little studied, there is substantial evidence that many dietary substances including cruciferous vegetables, citrus juices, ethanol, charbroiled meat, cigarette smoke etc all can modulate drug metabolism and transport. It is impossible to tell patients to refrain from nutrition during treatment with medication, (although ludicrously, warfarinized patients have been told to stop eating green vegetables!) It is also nonsensical to suggest that supplements should carry warning labels for potential HDIs whereas food, often containing higher doses of the relevant compounds, is "exempted" from such proposed labelling. For example fish oil supplements have been shown by in vitro to inhibit CYP2C19, CYP2D6 and CYP3A4 at dose levels which would be exceeded 100 -3000 fold by typical annual human fish consumption. (25)

There are further variations in drug metabolizing enzyme activity according to genetic and physiological factors such as age, sex and disease status - especially renal and hepatic impairment. Interestingly, neoplastic tissues may differentially express CYP450 enzymes compared to normal tissue, potentially providing a specific target for clinical responses to chemotherapy, CYP1B1 overexpression in hormone mediated cancers being the best studied example. (26)

Cancer chemotherapy invariably involves drug polypharmacy, not only of antineoplastic agent combinations but often involves comedication with disease-related or pain-related drugs. Since a large number of prescription medications are inducers and/or inhibitors of Phase 1, 2 and 3 systems, as well as possible co-substrates with chemotherapy drugs for the same enzymes, interaction effects are often extremely hard to establish or predict. This in turn places an over-reliance on in vitro data and animal experiments to attempt to discover pharmacokinetic HDI parameters. Unfortunately, extrapolations from experimental data are fraught with difficulty. (27) In a thoughtful review of the topic by Butterweck et. al. the authors argued that rather than using problematic in vitro methods such as high throughput fluorescent screening technologies in large scale trawling attempts to screen for any possible herb effects on CYP450. They suggest a more appropriate strategy would be to approach the subject of potential interactions from the perspective a comprehensive characterization of the PK parameters of narrow therapeutic index synthetic drugs. The obvious logic being that it is essentially the narrow therapeutic index drugs which are responsible for the clinical significance of interaction problems, rather than herbs. (25) Herbs tend to have wide therapeutic margins due to the simple fact that the CYP system co-evolved to work with plants and compounds of natural origin, and botanical compounds are synthesized in eukaryotic cells.

The fact is that actual case reports of SJW interactions in the literature are steadily decreasing. (28) This could be due to increased awareness of potential interaction problems associated with the herb, however Meyer recently analyzed six well known interactions including SJW-cyclosporine and SJW-digoxin across a number of "tertiary sources" of documentation and found only three out of six "reference sources" even included all the interactions. (29) Nonetheless trials continue to be performed on PK drug interactions and SJW, which not only

is unnecessary as argued by Butterweck but the quality of most of these trials remains limited. (25), According to a review of 22 trials of SJW interactions by Mills et al, only 15 trials assayed the herb used for content, and dosing regimes and duration of herb exposure widely varied without rationale. Further methodological limitations were noted in the studies including blinding and randomization issues. (30) Many of these studies failed to comply with the standard FDA guidelines for pharmacokinetic study design. (31)

With regard to anticancer drugs, it is often the case that the precise details of drug metabolism are unknown, especially for many of the older cytotoxics, for which detailed PK data was not required for drug licensing. In the case of newer drugs, ongoing research reveals a complexity of metabolic transformations that often confounds any simplistic attempt to extrapolate herb-drug interactions from incomplete in vitro or in vivo experimental data, whether or not there is some theoretical possibility of potential HDIs.

For example the estrogen receptor modulator tamoxifen is often cited as being subject to potential herb-drug interactions. Recent studies have begun to reveal the detailed complexities of tamoxifen metabolism. Tamoxifen is known to undergo bioactivation by 4-hydroxylation, mediated primarily by CYP2D6 to a 4-OH-metabolite that is 100 fold more active as an estrogen antagonist than the parent drug. However, another metabolite – endoxifen - was recently discovered, also a product of 4 hydroxylation by 2D6. Endoxifen is actually 1000x more active than the parent drug, or 10x more active than the previously known bioactivated derivative. It further transpires that endoxifen plasma levels are 4x greater than those of 4-OH tamoxifen. In other words, previous studies were not looking at the most active metabolite. Tamoxifen also undergoes N-demethylation, but in vitro studies show that demethylation can be effected by no less than ten different CYPs, including 2B6, 2D6, 2C19, and 2C9. In addition, CYP1B1 may be a primary mediator of tamoxifen resistance because it can inactivate both the parent drug and the 4-OH derivatives by trans-cis isomerization; and as mentioned above, CYP1B1 is overexpressed in certain endocrine dependent malignancy including some breast cancers. For a recent review of tamoxifen biotransformation, see Rochat. (32) Most importantly, clinical evidence has now accumulated that variations in CYP2D6 genotypes may be the major contributor to response variability in women using tamoxifen for breast cancer. (33, 34) Pharmacogenomics - the study of how genotypic variation affects drug disposition and effects - is now acknowledged as a highly significant contributory factor in cancer drug response variability. (35, 36)

PHARMACOGENOMICS & INDIVIDUAL VARIABILITY OF RESPONSE TO ANTICANCER DRUGS

The core challenge of cytotoxic anticancer chemotherapy is the high interindividual and intraindividual variability of response to the drugs, not only in terms of efficacy (tumor cell kill) but also in terms of general drug toxicities such as neutropenia which can be dose-limiting and life threatening, as well as various agent-specific toxicities such as cardiotoxicity, nephrotoxicity and lung fibrosis. In reality, a major determinant of variability in drug response has been known since the 1950s, when

it became apparent from observational studies by Vogel and others that there is an inherited basis underlying the individual differences in drug and xenobiotic effects. Although various concepts of "individuality" have long been axiomatic in natural medicine, it is only the recent emergence of pharmacogenomics (and other "-omics" disciplines such as metabolomics and proteomics) that has enabled modern biomedicine to finally incorporate the concept of patient "biochemical individuality" on a scientific basis. Although a relatively new field, pharmacogenomics has attracted considerable interest and research endeavour due to the prospective benefits of prediction or profiling of individual responses and hence appropriate doses to narrow therapeutic index drugs in order to ameliorate toxicity and increase efficacy. Determination of cytotoxic cancer drug dosage today is still governed by the body surface (BSA) system, which not only fails to address the genomic determinants of variability, but is actually is devoid of any rational theoretical foundation whatsoever. (37).

Pharmacogenomic determinants of drug response result from the existence of single base exchanges (Single nucleotide polymorphisms, or SNPs) in genes encoding proteins related to various different aspects of drug disposition and action, which generate significant phenotypic differences in drug responses. All the major families of human CYP450s exhibit polymorphisms leading to differences in enzyme functional activity. This can lead to different drug metabolizing phenotypes ranging from "poor > intermediate > extensive > ultra-rapid metabolizers" for a given substrate, depending on the allelic distribution of SNPs. The resultant differences in pharmacokinetic parameters for many drugs are clinically significant, especially with substrates of CYP2D6 and CYP2C9 where ten-fold variations in clearance have been recorded in healthy volunteers with different genotypes. (38) Individual polymorphisms of genes encoding Phase 2 and 3 proteins are also now well established as significant causes of drug response variability, and a genotype-phenotype analysis of entire drug pathways is now accepted as a necessary condition for complete characterization of drug responses.

For many drugs, considerable data has accumulated implicating not only SNPs of genes that affect the upstream mechanisms of drug transport and metabolism, but also those affecting drug target sites, such as DNA repair, metabolism and transformation systems, as well as downstream mechanisms of drug actions, which for anticancer drugs includes the intrinsic and extrinsic apoptosis pathways, as well as chemokines related to signalling cascades, such as IL-10, Il-6 and TNF-alpha. Each of these stages (upstream, drug target & downstream) therefore has potential to contribute to individual differences in drug efficacy, toxicity and resistance. (39) See diagram 1 below.

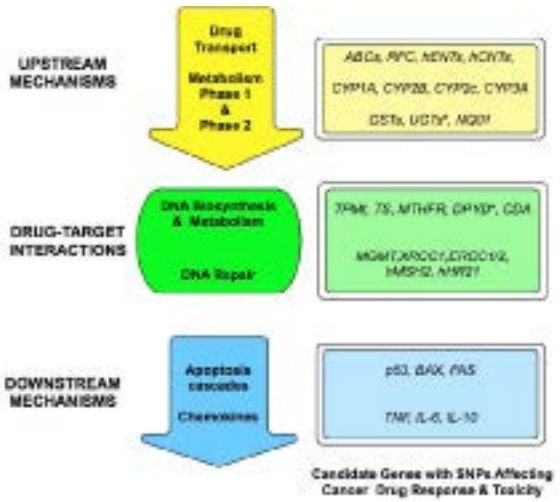

Diagram 1: Candidate genes with SNPs contributing to upstream, drug target and downstream mechanisms of cancer drug response and toxicity variability. Based on Efferth, 2007 See appendix for abbreviations.

IRINOTECAN & ST JOHN'S WORT: DECONSTRUCTION OF AN INTERACTION

As already emphasized, there are no clinical case reports of pharmacokinetic interactions caused by herbs being taken with chemotherapy drugs published in the literature to date. Without such reports the clinical significance of a hypothetical interaction is unknown, even if there is apparently supportive data for an interaction from experimental or trial data. This can be illustrated by a detailed analysis of the combination of St. John's Wort (SJW) and the anticancer drug irinotecan, often cited in review articles as an example of a genuine "evidence based" chemotherapy drug-herb interaction. (12, 14)

Irinotecan (CPT-11) is a semisynthetic analogue of the alkaloid camptothecin (CPT), which naturally occurs in the botanicals Camptotheca acuminata (Nyssaceae) and Mappia foetida (Icacinaceae). CPT is a topoisomerase-1 inhibiting agent that has activity against a variety of solid tumors. Irinotecan is a water soluble pro-drug, that is cleaved enzymatically by tissue and hepatic carboxylesterases to form the active metabolite SN-38 Irinotecan is FDA approved for the treatment of colorectal cancer,

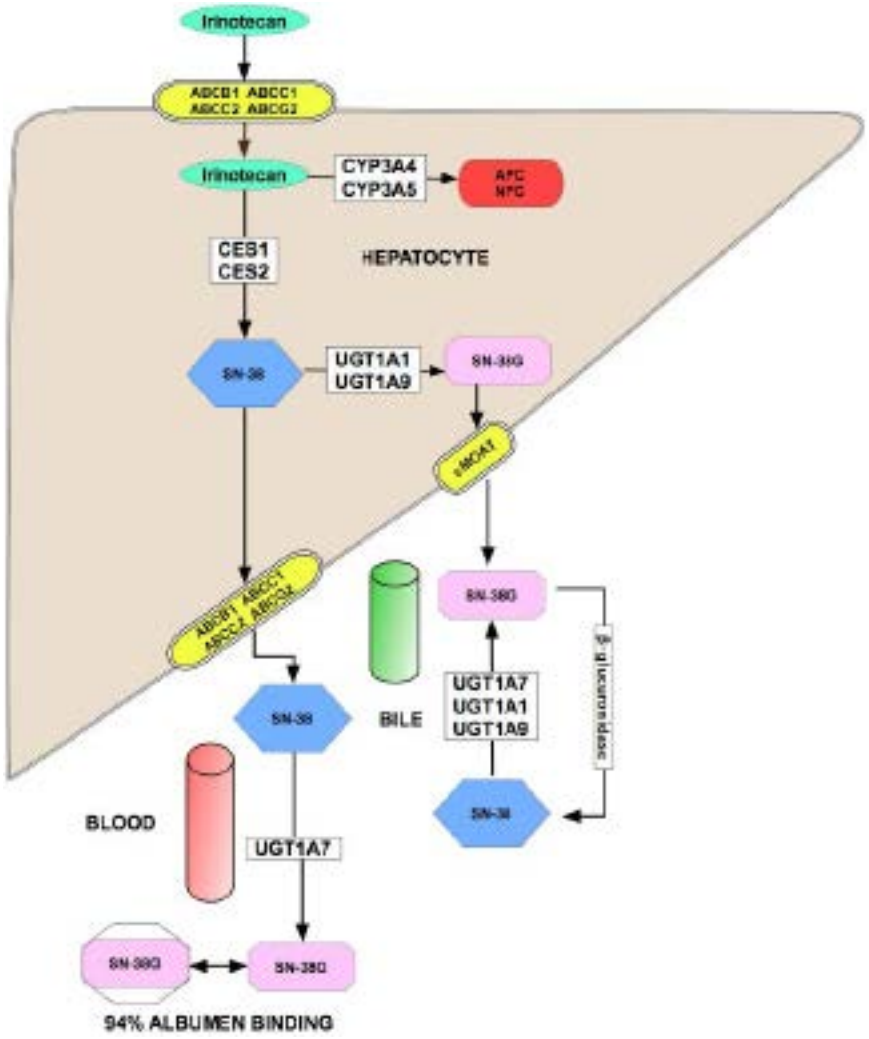

Diagram 2: The metabolism of irinotecan

the third most common malignancy in the United States, but is associated with severe dose limiting toxicities, namely grade 4 neutropenias and diarrhea. These can lead to dehydration, infection, hospitalization, additional medication requirements and death.

The metabolism of irinotecan is complex, and is summarized in diagram 2 below. The critical determinant of available drug levels is the balance between the activated form of irinotecan prodrug (SN38) and its inactive glucuronide conjugate (SN-38G), which is produced via uridine diphosphate glucuronosyl transferases (UGTs), especially UGT1A1. Most UGTs are subject to polymorphisms that can significantly modify their functional activity. A common polymorphism of the enzyme that inactivates SN38 is UGT1A1*28.

In patients receiving the drug there is an established association between homozygosity of the UGT1A1*28 allele and severity of neutropenia (40, 41). The accumulated data on the effect of the 1A1*28 polymorphism on drug levels and consequent toxicity was sufficiently convincing for the FDA to license a genomic test back in 2005 to identify homozygous who are at risk of life- threatening neutropenias. At the same time the drug labelling was changed to recommend dose reduction of irinotecan for known 1A1*28 homozygotes. (42) Emerging research also suggests that polymorphisms of the influx and efflux transporters for which SN-38/SN-38G are substrates may also actively determine differences in drug disposition. (43, 44) Although the current consensus is that pharmacogenomic differences may not explain all the individual variation seen in physiological responses to irinotecan, it makes a sufficiently critical contribution that genetic testing of all patients prior to initiating irinotecan therapy has been suggested as required standard of care. (45, 46)

The supposed "theoretical adverse interaction" here is an extrapolation based on the idea that since SJW can induce UGT enzymes via PXR activation it will hypothetically cause an increase in glucuronidation of the active SN38 to inactive SN38G, causing a drop in therapeutic efficacy due to lowered active drug availability. The evidence for this is attributed to a small unblinded study involving five cancer patients given an irinotecan infusion after18 days pre treatment with SJW at 900 mg daily dose. (47) On subsequent administration of irinotecan, a mean decrease in area under curve (AUC) for the active drug SN-38 was found after SJW pretreatment. However no difference was found in the rate of glucuronidation of SN-38 following SJW administration. SJW was also associated with a significant decrease in neutropenia toxicity compared to irinotecan alone.(47) The SN-38/SN-38G ratios remained unchanged following SJW administration, which suggests a negligible effect of the herb on glucuronidation enzymes, and an unchanged half life of SN-38 in the presence and absence of SJW, further suggests that herb effects on efflux pumps were not involved. The only irinotecan metabolites produced via CYP3A4 (ANC and NPC) actually decreased rather than increased which would be expected if SJW had exerted typical inductive effects. (47) Another unrelated study recently has confirmed that SJW pretreatment also leads to decreased not increased glucuronidation of SN-38. (48)

There are major problems in drawing any conclusions from this data. Firstly, the study was small (n=5), and the sample patients each had different cancers. Secondly, irinotecan infusion is administered with dexamethasone, a known modulator of drug metabolizing enzymes and transporters. Thirdly, and most important, the variation of SN-38 AUC (14%-70%) after SJW treatment was well within the normal limits of variation that exists between different genotypes of UGT1A1*28. But the authors not only failed to genotype the subjects, but did not even discuss the possibility of pharmacogenomic variations in interpreting their results.

Given the complexities of irinotecan biotransformation and the known role of pharmacogenomic factors, this underpowered study clearly offers no support for the existence of a "classical SJW mediated induction" interaction – if anything it disproves such the typical SJW interaction. Yet despite dubious data and methodological flaws this trial is repeatedly cited without discussion as evidence for such an interaction. Interestingly, one of the co-authors of the study is also the author of a HDI-anticancer drugs review paper, which asserts the existence of the SJW-irinotecan interaction. The author is therefore obliged to disregard the detailed findings of his own study by saying in his review "regardless…(of this study of mine [ed.])…the modulation of CYP3A4 and P-glycoprotein activity observed with St. John's Wort is particularly worrying, bearing in mind its crucial role in the elimination of many important cancer drugs". (12) In other words the well known inductive effects of SJW are being generically invoked by the author to argue for an interaction whose existence is in fact contradicted by his own study. One is reminded again of Sherlock Holmes' caution: "Insensibly one begins to twist facts to suit theories instead of theories to suit facts."

The most appropriate management guideline to give to prospective candidates for irinotecan therapy would be to recommend genomic testing for UGT1A1*28 polymorphism. In other words, the priority and focus needs to be on the dangers of the drug, and individual patient centered profiling of possible toxicities, not speculations about SJW (or any other herb). At the time of writing, genomic testing of patients prior to use of irinotecan still appears in practice to be the exception rather than the rule. Finally, from an "integrally informed" perspective, it is entirely appropriate to consider using appropriate botanicals to ameliorate the toxicities of irinotecan, although this strategy requires botanically literate prescribing by experienced or specialized professionals.

In this context a recent editorial by oncologist Ethan Basch discussing a paper on "Controversies surrounding CAM in Cancer" given at an EORTC (European Organization for Research and Treatment of Cancer) conference in 2006 is relevant:

> "*Most oncologists are also aware of important potential interactions, such as St John's wort and P450, and the theoretical interference of high-dose antioxidants with some chemotherapeutics or radiotherapy. It is increasingly recognized that maintaining knowledge beyond this level is not feasible for oncologists, and requires specific expertise. … This multidisciplinary model can also educate oncologists about when referrals are appropriate; for example, to alleviate symptoms or improve quality of life. The*

needs of patients will be best served in such a collaborative context, in which knowledge expectations (and limitations) of both roles—medical oncologist and CAM consultant—are clearly delineated and accepted." (49)

BENEFICIAL HERB - DRUG COMBINATIONS IN ONCOLOGY

A key role for Basch's "CAM consultants" (ie, for our purposes professional providers with knowledge and experience of botanical prescribing) is the strategic employment of beneficial herb-drug combinations. This possibility is disregarded by most HDI literature which persistently emphasizes adverse rather than beneficial interactions to the extent that the term HDI has largely perjorative associations, and is a euphemism for adverse event.

There is arguably a valid question as to whether the intentional and beneficial combination of herb (or nutrient) with drug constitutes an "interaction" as opposed to an "integrally informed" treatment strategy. This tends to be more so for pharmacodynamics where the quantitative nature of pharmacokinetic parameters are usually absent; most drugs can be analyzed in terms of dose-response relationships, however clinical end-points are rarely linear or simple. To oversimplify, an interaction in sensu stricto must either be a supra-additive (2+2=5) or subadditive (2+2=3) result of a combination that might normally be expected to be simply additive as in (2+2=4). Conventional pharmacology has devoted little attention to issues of defining, analyzing and quantifying pharmacodynamic interactions, and very often terms such as "synergistic" are used without any explanation or definition of what "synergy" actually involves, although admittedly non-conventional modalities are probably less rigorous in their misuse of this terminology. (50)A pertinent example is the fact that drug combinations have long been employed in anticancer chemotherapy, although data on whether their effect is additive or supradditive is generally unavailable. For present purposes, a beneficial HDI may be regarded operationally as synonymous with the deliberate strategic combination of herb(s) with drug(s) whose therapeutic intent is to increase treatment efficacy or reduce its toxicity compared to treatment with the drug alone.

For example, returning to the SJW-irinotecan example above, a recent rodent study found that oral SJW pretreatment before irinotecan infusion significantly reduced intestinal (diarrhea) drug toxicity which was associated with reduction of inflammatory cytokine levels. The authors suggested SJW might be further investigated for its potential to reduce the dose limiting intestinal toxicity of the drug. (51) This conclusion was subsequently criticized on the grounds that it ignored the "well known CYP450 and P-gp induction effects of SJW" and emphasized that SJW should not be co-administered with irinotecan due to the fact that the drug is "extensively metabolized by CYP450 3A4." (52) This criticism misses a most significant point for the herb literate practitioner: anti-inflammatory herbs may help reduce chemotherapy induced intestinal side effects such as mucositis and diarrhea. Of course, SJW may not be the herb of choice for this indication, but in reality given the extensive publicity and understanding of the interaction potential of SJW with narrow therapeutic index anticancer drugs, most

physicians, oncologists, educated patients, and all herb-literate non-conventional providers would avoid co-administration of SJW with these agents as a matter of routine.

During chemotherapy, a strategy of using mucosal protective and anti-inflammatory botanicals (those lacking the PK induction effects of SJW) to ameliorate the common toxicity of drug induced intestinal mucositis is clearly appropriate and desirable. Such agents might include licorice and aloe gel which both have good data for this indication, whilst any of many other botanicals could be utilized to systemically downregulate inflammation at a transcriptional level via inhibition of nuclear factor Kappa-B.

Generally, there are several distinct areas where botanicals can be used effectively in conjunction with conventional oncological treatments:

- prophylaxis, antidoting and recovery from general dose limiting toxicities such as myelosuppression.

- prophylaxis, antidoting or recovery from agent specific or organ specific toxicities, such as platinum related nephrotoxicity, bleomycin induced lung fibrosis, or Adriamycin induced cardiotoxicity.

- chemosensitization: increasing the efficacy of chemotherapy by countering multiple signalling pathways involved in drug resistance.

- additive, complementary (and potentially synergistic) combination antitumor activity with chemotherapeutic agents, whether classical cytotoxic or targeted – eg antiangiogenic agents.

- chemoprevention: following treatment, ie encouragement of host resistance to prevent recurrence.

The evidence base for these different "interactions" involves extrapolations from experimental studies using in vitro or animal modelling systems, together with the anecdotal experience of practitioners skilled in traditional botanical prescribing who work in oncological settings. For a comprehensive review of the relevant data in the above areas see for example (53, 54). The dearth of clinical trial evidence here is not only due to ethical issues relating to use of unproven botanical and natural compounds in clinical trials on cancer patients, but also because of lack of interest (research funding) from pharmaceutical corporations in natural products that are unpatentable and unlikely to lead to profitable drug development. There are also significant and much discussed methodological problems of study design involving natural medicine approaches. Herbs are not drugs, their influence is more subtle and physiological than pharmacological, involving time-dependent shifts in multiple metabolic and signalling pathways that are distinctly different from the actions of most pharmaceuticals. This is of course part of their strength, not a weakness. "Molecular multitasking" is characteristic of natural compounds, whether herbs or dietary ingredients; for example, curcumin, derived from the spice turmeric, influences over a hundred known molecular targets in the biological pathways of cancer tumorigenesis, proliferation and metastasis. (55) In fact genomic studies of herbal medicines

and natural compounds are actually suggesting novel multi-target and drug-synergy approaches that are being examined as possible advances upon the limits of current pharmacotherapeutic paradigms. (56-59)

CONCLUSION

The allegations that botanicals are a major cause of harmful interactions with oncological drugs and a significant cause of the ubiquitous therapeutic failure of these agents is not only controversial, but also without foundation, either in terms of clinical case reports or valid experimental and trial evidence. The claimed interactions are almost invariably theoretical, or in conflict with the minimal available data, and contain errors of both omission and commission to the extent that serious questions of bias, vested interest, and defence of professional territory and authority must be considered as plausible motivation.

Significant individual variations in the efficacy and toxicity of conventional chemotherapy are demonstrably associated with genomic, proteomic and metabolomic variables that far exceed likely influences of herb ingestion, especially if botanicals are prescribed for cancer patients by professionals trained in herbal medicine and experienced in the oncological setting. Ultimately a myriad of influences from the genetic to cultural concepts of health, and healing may also be sources of "interaction" with drugs, effectively constituting an "interactions universe", which can be represented in terms of a hierarchy of levels. (see Diagram 3 below)

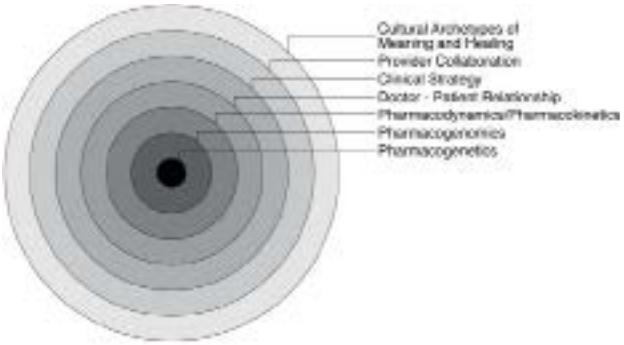

Diagram 3: The Interactions "Universe", reproduced with permission from Mosby: Stargrove, Treasure and McKee (52)

A poignant aspect of negative attitudes towards herbal medicine is that botanicals contain valuable lessons and insights that hold the potential to transform present paradigms of conventional pharmacotherapeutics in a positive way. From contemporary drug development, which is inching away from the classical traditional "silver bullet" concept towards multi-target strategies "molecular multitasking" that is an inherent aspect of much natural compound activity, through to transdisciplinary therapeutic approaches incorporating botanicals that hold promise for improving therapeutic outcomes for cancer patients, the promise of medicinal plants significantly outweighs their perils.

APPENDIX : ABBREVIATIONS USED

ABC (ATP binding cassette transporters)
ADME (Absorption, Distribution, Metabolism, Excretion
CAM (Complementary and Alternative Medicine)
CPT (camptothecin)
CPT-11 (Irinotecan, Camptosar)
CYP450 (Cytochrome P450)

DPYD (dihydropyrimidine dehydrogenase)
ERCC (excision repair cross-complementation gene)
GSTs (Glutathione S-transferases)
HDI (Herb-Drug Interactions)
IL (interleukin)
hMSH (human MutS homologue gene)
hHR (human homologous recombination gene) MGMT (methylguanine-DNA methyltransferase)
NQ01 (NADH quinone oxidase)
PK (Pharmacokinetic)
PXR (Pregnane X Receptor)
RFC (Reduced folate carrier) SNP (Single Nucleotide Polymorphism)
SN38 (7-ethyl-10-hydroxy CPT= activated CPT-11)
SJW (St. John's Wort; Hypericum perforatum)
TPMT (thiopurine S-methyltransferase)
TNF (tumor necrosis factor)
TS (thymidylate synthase)
MTHFR (methylene tetrahydrofolate reductase)
XRCC1 (x-ray cross complementation gene)
UGT (uridine diphosphate glucuronosyl

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