Preface To The Fourth Edition

To emphasize distinctions between the whole substance of the therapeutic plant part and extracts that represent various fractions of this whole, the title of this edition has been modified. The altered name, *Herbal Contraindications and Drug Interactions*, utilizes the term "**herbal**" in its ramifications of incorporating all components of the medical part including its fiber in their entirety (herb, or "herbal drug" in European parlance) along with the chemically-complex extractives of the herb (botanicals, or "herbal drug preparations" in Europe). The implication of using a more expansive term acknowledges the fact that the majority of studies use herbal extracts or concentrated fractions of herbs, rather than the herbs themselves. These extracts include, for example, juices, teas, tinctures, volatile oils, and other liquid or solid forms that are physically and/or chemically processed derivatives from fresh or dried herbs. The importance of recognizing and understanding the differences in these distinctive preparations from the same herb is described in my last book, *Complex Herbs - Complete Medicines* (2004).

Another significant alteration made to the title of this fourth edition is the addition of a subtitle: ***plus Herbal Adjuncts with Medicines***. Those interactions or herbal-drug combinations which are potentially advantageous have been identified separately in the text of this new edition. This third category, designated **Complementary Adjuncts** and included under 98 of the 321 herbs in the text, describes potentially beneficial combinations with drugs listed in bold type, along with the name of the condition benefitted by the combination underlined in bold.

These complementary combinations have demonstrated enhanced outcomes in comparison with the use of the drug alone for the underlined conditions; those for six herbs exclusively address substance abuse. These complementary adjuncts, along with others suggested by less compelling *in vitro* research, have been compiled in Appendix E.

The first section, *Potentially Beneficial Combinations of Herbals with Drugs*, functions basically as a table of contents for complementary adjuncts in the main text and is followed by specific sections on potential herbal use in association with substance abuse, anti-inflammatory medications, chemotherapy and chemoprevention, radiotherapy and phototherapy, and anti-infectious agents. This compiled research on herbal-drug combinations demonstrating advantages beyond those derived from conventional therapies alone is provided to promote further investigation, discussion, and hopefully eventual incorporation of complementary herbals into integrated clinical practices.

The information on specific adjunctive combinations can be readily accessed through the Index listings where the indicated conditions have bold underlines and the enhanced drugs have subheadings identifying the underlined indicated conditions. In these listings, when the under-

lined condition subheading under the drug or a drug subheading under an underlined condition is preceded by an "AE", this indicates that the condition being alleviated is an adverse effect of the drug. In some of these cases, the herbal simply helps palliate the condition symptomatically. In other cases where the pharmacological activity of the herbal complements the drug, the adverse effect may be reduced in association with decreasing the drug dosage while simultaneously achieving greater therapeutic effect than the drug alone delivers in its toxic dose.

With the growing demand for information about herbal remedies by both the general public and health care community, accurate assessments of herbal properties, beneficial uses, and safety concerns are required. Statistical analysis is necessary to assess outcome data and determine whether differences are significant, though this by itself does not validate an application. Results reported here as "significant" are deemed so based on a statistical P value of < 0.05, at most. However, statistical significance in changes to biological markers may not correspond to a clinically significant effect when it comes to assessing therapeutic outcomes.

In the complex world of herbal medicine where the products themselves and approaches to their application can be widely variable, expectations about actions and interactions that may ordinarily seem evident can require careful discernment. Potential risks from contraindications or adverse interactions may be uncertain in regard to the actual degree of risk, based on conflicting evidence. For this reason, in such cases the inclusion of contradictory data in a separate paragraph prefixed with the all-capitalized word, "HOWEVER," has been used as a means of emphasizing the equivocal nature of the extant evidence for some controversial contraindications or interactions.

Preliminary laboratory data about herbs or their constituents is often presented as if these were established clinical facts, whether in regards to pharmacological data to support use or toxicological data to dissuade from using. Such speculation based on pre-clinical research misrepresents its limited validity when it is construed as directly applicable to humans, while it remains merely suggestive. Scientific claims for herbal medicine must necessarily be based on human studies, though modern understanding should incorporate the light of insights from compiled traditional knowledge of empirical applications in humans. To further help understand human responses to herbal remedies, pre-clinical data can support or challenge human empirical observations, but laboratory data alone is inadequate for making conclusions on clinical effects.

To be understood correctly, information about each herb must be viewed in its proper context. Not all reports based on the isolated experience of a health care practitioner using one preparation or fragmentary research by laboratory scientists using another will necessarily permit valid comparisons at face value. Clinical observations, laboratory outcome data, and suggestive implications are most relevant in a limited set of circumstances. A comprehensive perspective needs to be accurately focused on the preparation, the patient, and the situation. For a specific

remedy to be safely and effectively applied, clinical experience adapts knowledge of botanical pharmacology and human research data to specific circumstances that differ as individual patients are encountered. When clinical and laboratory studies with a particular preparation confirm each other and agree with observations in practice, a consistent therapeutic outcome becomes reliably established.

The content of an herbal preparation and the size, timing, frequency, and duration of its dosing determine the relative benefit and risk that is associated with that particular product. These factors can and will differ depending on the condition being addressed and other pertinent factors involved in each clinical case in the field. The art of health care requires adaptation of knowledge to the reality of each patient, not the rote application of pre-formulated designs based on generalized assumptions and conclusions.

It is important to at least identify the general form if of preparations used in studies to the extent that characterizations of these products are available in published research. Some major commercial preparations are specifically identified by their generic designation, rather than the advertised proprietary names. Unfortunately, clinical investigations have often failed to identify the characterizing features of the agent studied or its relative dosage in terms of the amount of herb from which it was derived (mistakenly referred to as the "equivalent" amount of herb). This renders some research of limited or no value. An informed perspective of associating outcome with preparation form and dosage is urgently needed.

The challenge for a book like this is to avoid projecting as absolute those determinations that are largely, or in part, relative to the circumstances. Pre-judgements based on limited data and/or experience may not be representative of the unique case at hand. Sources that simply provide black-and-white 'sound bite' assessments misrepresent the need to carefully analyze the totality of each case.

In addition, scientific knowledge is most complete when information is up-to-date. Without ongoing re-assessment, the reliability of former assessments can become compromised. For this reason the intent of Eclectic Medical Publications is to continue to provide free updates available online through its website (**http://www.eclecticherb.com/emp**) for this edition, as was done with the third edition. Over 1600 new reference citations were incorporated into the additions for the third edition. These online updates and additions form an integral aspect of the value this book provides in addressing issues on the basis of comprehensive compiled research, as the database grows and the correlations become more demonstrable or nuanced.

The editions of this book have been based on prior published claims from available research regarding contraindications and drug interactions, along with pertinent accompanying evidence to support or challenge these assertions. Some rearrangements of content have been made in order to better emphasize the relative strength of evidence on which these designations are based.

For **Contraindications**, two divisions has been made. Category I. includes contraindications established empirically in humans based on reported cases or research, and/or by practitioner consensus on the weight of pre-clinical evidence. Category II. involves restrictions based on isolated animal or *in vitro* evidence; these are speculative only and may be deemed more as precautions.

For **Drug Interactions** with herbals based on evidence from reports of human use, the new arrangement emphasizes a distinction between Category Ia., those based on findings from research with patients or healthy volunteers, and Category Ib., those observed only through case reports or case series. Usually data provided from case reports is inadequate to make a certain determination as to cause and effect, often due in part to insufficient documentation establishing the positive identity, form, and dose of the botanical used. In some cases, animal and *in vitro* evidence is incorporated to provide either contradictory or supportive evidence to help assess the likelihood of interaction reports involving herbals and drugs in humans or to provide insight into potential mechanisms.

As mentioned above, pre-clinical laboratory studies *in vivo* with animals in Category II. and/or with *in vitro* cell or tissue cultures in Category III. are insufficient to extrapolate to humans as stand-alone evidence of drug interactions with herbals. The reasons for this are many, as described in the Introduction. For one, animals and their intestinal bacterial flora differ from humans in their abilities to digest, absorb, and/or metabolize the many different types of components found in any complex botanical preparation. Similar but distinct problems exists with *in vitro* laboratory studies utilizing cell organelles, cell cultures, tissues, or isolated organs. The systemic exposure of living tissues to complex solutions extracted from plants following intestinal absorption does not involve the same chemical content and proportions as is used in laboratory conditions where cells and tissues are exposed directly to the complete extract. Case reports or human case series are potentially of more actual value in substantiating a clinical effect than extrapolating herbal laboratory data to a human setting. In the absence of controlled clinical studies or case reports, considering pre-clinical evidence on herbal preparations simply provides a basis of informed speculation suggestive of possible outcomes of which to be aware.

More specific information on human studies involving drug interactions is being provided in this edition so that the relative size of clinical studies and the type, strength, and dosage of the herbal preparation can be appreciated. Though there is seldom complete correlation between commercial products, considering the type of preparation, its phytochemical content, and/or the dosage involved in a documented herbal interaction with a drug should prove beneficial in assessing its likelihood of occurring with similar products, though probably not with dissimilar preparations of the same herb.

Studies on isolated components from herbals have been included in all categories of contraindications, interactions, and complementary adjuncts, especially if the isolate is an acknowl-

edged major active component of that herb and its common extracts. This applies most especially if the isolate is an active marker to which preparations of that herb are typically standardized. This is not to infer that the herbal activity is identical to the isolate but that it is likely to make an important contribution to its overall effect.

Growth of knowledge in pharmacokinetic herbal-drug interactions has been particularly significant, especially as influenced by the Phase I cytochrome P450 (CYP) system of genetically controlled metabolic enzymes termed isozymes. Three more major isozymes (CYPs 2C9, 2C19, 2D6) have been added to Appendix B.7.2 of this edition. Herbals and components that induce or inhibit these or the other major isozymes included in this and in the third edition (CYPs 1A2, 2E1, 3A4) are specifically characterized to identify when the evidence is from laboratory *in vitro* or *in vivo* research or from human studies. These distinctions are especially important when weighing the impact of herbals on drug pharmacokinetics. In addition, particular herbal preparations shown by extant human studies to have no significant influence on a particular isozyme are listed separately. This listing emphasizes that evidence of low pharmacokinetic interaction risk exists for humans when combining these specific botanical preparations with drug substrates of that isozyme.

Nonetheless, influence on Phase II conjugating enzymes (Appendix B.7.3) and Phase III transporter proteins (Appendix B.1) must also be taken into account as influencing bioavailability. In this text the term "bioavailability" is used to describe an estimate from oral exposure, based on the area-under-the-curve (AUC) for plasma concentration over time. Though the total time that the drug concentration is monitored may vary from a few hours to a few days depending upon the study, this general term (bioavailable) is applied to conveniently indicate the total amount of the varying serum levels circulating for a period after taking a drug, especially when it has been significantly altered by use of an herbal preparation.

Expansion in scientific knowledge about medicinal plants, their products, applications, and limitations has been increasingly rapid over the last several decades. This information explosion also involves consideration of many herbals that typically draw little attention in most publications on herbal interactions with drugs, though the herbs themselves have been used empirically for ages. The intent with this text is to be broadly inclusive of herbs whose preparations have traditionally been utilized in Europe and especially America, as well as those that have been introduced into modern use in the West from other cultures and traditions like Indian Ayurveda or Chinese herbal medicine. To this end 81 more herbs have been added to the 240 in the main body of text (not including the appendices) of the third edition.

To promote consistent identification and improve recognition in the marketplace, the use of standard common names for commercial herbs is being advocated. In cooperation with this policy several primary common names utilized in the first three editions have been replaced with

those designated in 2nd edition of *Herbs of Commerce* as the preferred American nomenclature (e.g., changing pennyroyal to American pennyroyal, wild cherry to black cherry, German chamomile to chamomile, lavender to English lavender, goldenrod to European goldenrod, gurmar to gymnema, periwinkle to lesser periwinkle, and couch grass to triticum).

The changes are intended to facilitate use of this text by employing the common names listed on most product labels. Likewise, several names for algae listed in appendix B have been changed to reflect more current and accurate usage. Also, in keeping with the need to reduce confusion and distinguish between preparations, species of the same genus have been listed separately when appropriate (e.g., *Echinacea* spp.) and different plant parts of the same species are given separate subheadings under the herb name when the active components or their proportions in these parts and their preparations differ significantly (e.g., *Echinacea purpurea* whole/aerial plant and roots). Finally, though they are fungi rather than plants, five mushrooms and/or their mycelia are listed here as herbals, since these agents are often discussed in the context of herbal medicines.

Hopefully, the new format and content of this edition and its updates will substantially enhance integration of pertinent developing information to help make the use of both herbals and pharmaceuticals safer and more effective.

Francis Brinker, N.D.
Tucson, AZ