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Editorial

Complex and simple

Premarin[®], the natural blend of hundreds of metabolites derived from pregnant mare urine, is one of the only true complex, ethical drugs (possibly the only other being the racemic mixture of two isomers comprising the anticoagulant Warfarin[®]), and also, one of the most commercially successful drugs of all time [1,2]. As a potential promoter of breast cancer in the peri- and post-menopausal women for whom it is prescribed, Premarin[®] is now, as at many other times in its over 50-year-old history, under fire [3,4]. Nevertheless, as a model for looking at complex drugs, it is unequalled.

In fact, contained within the highly complex mix of steroids and steroid-like compounds (its makers cite 10, but other sources place the number in the high 300's) that is Premarin[®], are the well known pure pharmaceutical estrogens, estrone and 17-beta estradiol. These compounds together supply nearly all the market share for HRT that Premarin[®] does not, yet users of Premarin[®], and apparently also their physicians, prefer the complex agent [5].

Why is that? Proponents suggest that the natural product is superior because of its mammalian origin and thus similarity to human estrogens, yet an artificial mixture of synthetic steroids prepared from soybean precursors also exhibits apparently synergistic HRT properties [6]. Here, as in the classic equine combination, the whole was greater than the sum of its parts.

As physicians and researchers, we all tend to favor the pure compound to the “soup.” With a single molecule, it is relatively straightforward to establish precise dosage, and the knowledge of structure lends itself to the mapping of elaborate and elegant “mechanisms.” Unfortunately, with the blend of flavonoids and related polyphenols comprising Pycnogenol[™] (extracted from pine bark or grape seeds), which has recently been shown to promote HL-60 human promyeloid leukemia cell differentiation and apoptosis [7], or similar HL-60 differentiation-stimulating polyphenols from pomegranate [8], polyphenols from propolis against proliferation of MOLT-4 human leukemia cell [9] or human herpes virus [10], or from red wine in inhibiting nitric oxide formation [11], we do not have single agents, but “soups,” messy and complicated to standardize or to fix mechanisms. Undoubtedly because of this messiness, nary a single complex

drug besides Premarin[®] has appeared in the modern physician's dispensary for half a century.

However, even if we do not yet fully understand them, complex agents may have advantages. The first is, even more so than for single agents, that complex agents act with diverse mechanisms, at diverse reaction sites. This leads in general to redundancy, providing alternative pathways for inducing pharmacologically desirable effects.

A second possible advantage of complex agents is for one component to have a facilitating effect on the action of another component. For example, in an herb with known antibiotic properties, the presence of a complementary compound has the effect of disabling the “multiple drug resistance pump” mechanism of bacteria to the toxic effect of the alkaloid berberine [12]. Also, in cancer, a cytokine can enhance tumor absorption of the chemotherapy drug doxyrubicin [13], while anatomically discrete and distinct chemicals in the pomegranate synergistically inhibit prostate cancer invasion [14,15].

The ultimate potential advantage of a complex formula may in fact be synergy itself. Different drugs may work together to produce clear, mathematically verifiable effects greater than the sum of the effects caused by the different components if used separately, possibly through effects on protein expression [16]. Other possible mechanisms relate to different receptors being acted upon simultaneously, or different parts of same receptors stimulated in parallel. Actions may complement each other, or enable penetration or inactivate defenses. In traditional herbal medicines, such multiple components are sometimes purposely combined to provide physiological balance or to otherwise “harmonize” a drug effect [17].

Complex physiological responses occur from pharmacological “simples” [18] while complex drugs may possess pharmacological activity greater effect than simple agents because the former have a greater potential for “unleashing therapeutic chaos” [19]. Simples in herbal medicine refer to individual plants, rarer in traditional prescribing than the mixtures of different plants which comprise the herbal formula [20]. These single agents though, each possess an incredible complexity with paradoxical potential to exert a

unified and “simple” physiological benefit. In the case of life-threatening and intractable disease, we should not let our prejudices against complex agents interfere with our ability to exert life-saving actions. Such complex simples are worthy of our continuing investigatory attention.

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