For Irish herbalists, the millennium celebrations were nothing short of a wake. The effective banning in Ireland of St. John's wort (Hypericum perforatum) and a number of other botanicals on January 1, 2000, came as a seismic shock to herbal manufacturers, practitioners, retailers, and the Irish public alike. As there are no licensed products available on the Irish market and Irish doctors have no formal training in herbal medicine, the ruling that St. John's wort and other herbal remedies, including Ginkgo biloba, Caulophyllum thalictroides, Harpogophytum procumbens, and Tribulus terrestris, should henceforth be classed as prescription-only amounts to a ban on these herbs in Ireland. It is now illegal for herbal practitioners in Ireland who do have this training to prescribe these herbs. Since October 1999, when the new ruling's implementation was first threatened, a high-profile public campaign raged fast and furiously. Yet the Irish authorities remained obdurate in the face of daily airings of the issue in the Irish media and in the Dail (Parliament), plus a deluge of letters and petitions demanding that St. John's wort should remain as freely available in Ireland as in the rest of Europe. In all of the furor of this very public clash between the Irish Medicines Board (IMB) and the alternative health sector, it has not always been easy to see the forest for the trees and take a dispassionate view of the alleged and actual risks and benefits of St. John's wort. To complicate proceedings further, the dispute about St. John's wort has wider implications, calling into question the future of herbal medicine throughout the European Union (EU). Given the importance of this debate, it is surely time to stand back and make a cool appraisal of the issues involved.

An obvious starting point is to examine the arguments advanced by the IMB to justify its removal of St. John's wort from over-the-counter (OTC) sale. The IMB holds that, because of its use in treating depression, St. John's wort is a medicine not a food. The designation of St. John's wort as a medicine is based on EU Directive 65/65 EEC (European Union Council Directive, 1965), which states that "any substance..., which may be administered..., with a view to correcting or modifying physiological functions... is considered a medicinal product."

The IMB insists that, as a medicinal product, St. John's wort requires a medicines' license. As there are no licensed St. John's wort products in Ireland, the IMB argues that it has no power to enforce warnings on St. John's wort products about possible herb-drug interactions. Let us examine these issues in turn.

There can surely be no doubt any longer of St. John's wort's efficacy in treating depression. Moreover, when taken by patients who are not concomitantly taking prescription medicines, this herb is also remarkably safe. Many studies demonstrating the efficacy of St. John's wort in the treatment of depression have been undertaken, particularly in Germany. A meta-analysis carried out in 1996 evaluated 23 randomized trials (20 of which were double-blind) of St. John's wort in a total of 1757 out-patients with mild-to-moderate depression (Linde et al., 1996). Significant improvement in depressive symptoms was observed in all groups. In 15 double-blind placebo-controlled trials St. John's wort was found to be significantly more effective than placebo. In eight trials comparing St. John's wort to standard antidepressant
Another more recent meta-analysis (Kim et al., 1999) of well-defined clinical trials concluded that St. John's wort was 1.5 times more likely to result in antidepressant response than placebo and, in terms of efficacy, was equivalent to tricyclic antidepressants. It is noteworthy that this meta-analysis showed that there was a higher dropout rate in the tricyclic antidepressant group and that tricyclic antidepressants were twice as likely to cause side-effects. These side effects were measurably more severe than those recorded by the group taking St. John's wort. This meta-analysis concluded that St. John's wort was similar in effectiveness to low-dose tricyclic antidepressants in the short-term treatment of mild-to-moderate depression. The outcome in terms of safety and efficacy of this meta-analysis is borne out by a study published in December 1999 in the *British Medical Journal* (Philipp et al., 1999). The authors of this report concluded that, at an average dose of 350 mg three times daily, St. John's wort extract was more effective than placebo and at least as effective as 100 mg of imipramine daily in the treatment of mild-to-moderate depression. This latest *British Medical Journal* paper also noted that patients tolerated St. John's wort extracts better than they did tricyclic antidepressants and that, in terms of adverse events, the St. John's wort group was comparable to the placebo group.

The IMB has never contested the efficacy of St. John's wort in treating depression. On the contrary, ironically, St. John's wort's very success in this regard has been cited by the Irish authorities as yet another reason for its designation as a prescription-only medicine. The IMB asserts that depression is a serious condition that should only be treated by registered medical practitioners. A press release issued by the IMB in November 1999 stated: "The IMB consider [sic] that patients with mild to moderate depression should be under medical supervision and that self-diagnosis and self-medication (non-prescription sale) are inappropriate." Apparently the IMB sees no place for the intervention of herbal practitioners or self-treatment in the management of this disease. Whether this position is sustainable is discussed below.

Ever since it first broadcast its intention to designate St. John's wort as prescription only, the IMB has continued to insist that St. John's wort can have a significant monoamine-oxidase inhibitor (MAOI)-type pressor effect giving rise to potentially serious side-effects when combined with tyramine-rich foods such as red wine or cheese. The IMB press release also stated that that St. John's wort "is reported to act as a monamine-oxidase inhibitor (MAOI). Prescription MAOIs must be used with care because there is a risk of a hypertensive crisis when they are taken with over-the-counter sympathomimetics (e.g., cough mixtures), antidepressants or foods containing tyramine (e.g., red wind or cheese). The IMB is concerned that similar interactions may occur with *Hypericum perforatum*. "December 1999, in its written response to the Health Products Alliance (HPA) submission made earlier to the IMB, the IMB stated that "the mechanism of action of St. John's wort is unclear; literature reports suggest that the hypericin fraction of St. John's wort (extracted in methanol) is a very weak inhibitor of MAO and thus the potential for interaction with tyramine-containing foods is minimal. However, the literature also reports the potential for crude St. John's wort to irreversibly inhibit MAO-A and MAO-B. No information is available on the quality and constituents of St. John's wort products currently available on the Irish market and therefore concerns remain regarding the potential for St. John's wort to interact with tyramine-containing foods."

This continued assertion by the Irish authorities that St. John's wort can have a potentially disastrous MAOI interaction with common foods appears to be totally unfounded. Worldwide sales of St. John's wort are currently in excess of several hundred million units per annum, yet a literature search has failed to identify a single recorded case of a MAOI-type of adverse reaction in someone taking St. John's wort. The IMB position on the MAOI activity of St. John's wort was flatly contradicted in a *Lancet* letter from Wheatley (Wheatley, 2000) who described’ this alleged action as a myth. Wheatley stated that "St. John's wort does not act by inhibition of MAO any more than does any other synthetic antidepressant from imipramine (Tofranil; Ciba-Geigy, Horsham, Sussex, United Kingdom) to fluoxetine (Prozac; Eli Lilly, Basingstoke, Hants, United Kingdom) with the exception of those classed as MAO inhibitors." Wheatley's point is underlined by a report "Dietary, Supplements and Natural
Products as Psychotherapeutic Agents" (Fugh-Berman and Cott, 1999) that stated unequivocally "nor have there been any reported cases of MAOI inhibition associated hypertensive crises in humans using St. John's wort." The report cites in justification of this statement the meta-analysis of randomized clinical trials for St. John's wort for depression by Linde et al (1996). As Wheatley himself points out (Wheatley, 2000), further evidence that the supposed MAOI action of St. John's wort is unsubstantiated comes from Cott (1997) working at the U.S. National Institute of Mental Health. Cott found that hypericin lacked significant MAO-A or MAO-B inhibition at concentrations up to 10 µM. Finally, on this point, one of the most recent reviews of the action of St. John's wort by Nathan (1999) observed that St. John's wort "has a unique pharmacology in that it displays the pharmacology of many different classes of antidepressants. The likely mechanism of action is the inhibition of the monoamine reuptake (5-HT, NA and DA) with comparable potencies to known antidepressants." Nathan concluded with the important observation that "the benefit of Hypericum over other antidepressants may result from its favorable clinical side-effects profile."

The confidence in the safety of St. John's wort expressed by Nathan and other researchers is spectacularly at odds with a catalogue of alleged side-effects attributed to this remedy by the IMB in its circulated response to the HPA submission regarding St. John's wort (IMB, 1999). According to the IMB, the U.S. Food and Drug Administration (FDA) lists thirty-four adverse events reported in connection with St. John's wort including, among other serious Adverse Drug Reports (ADRs), two deaths. The IMB writes about these that one was "due to liver failure, the other cause of death is unknown". The reference for these adverse events is bizarrely a Web site article entitled "St. John's wort Literature Review" by C. Cracchiolo (1999). This citation might be laughable were the allegation not so serious. Is the IMB not aware that random self-posted data on the Inter-terrier is notoriously unreliable and often grossly inaccurate? Such assertions hardly encourage confidence in the Irish regulatory authority. It seems extraordinary that, if there be such cases, none of the many recent reviews and letters published in premier medical journals should have alluded to them or that the U.S. authorities would not have taken action against St. John's wort on the basis of such serious adverse reactions. The U.S. National Institute of Mental Health and National Center for Complementary and Alternative Medicine of the National Institutes of Health have jointly designed and funded a $4.3-million clinical trial to determine the efficacy of St. John's wort for depression" (Fugh-Berman and Cott, 1999). It is unlikely that such a project could receive this kind of major backing were the ADRs mentioned in the Web site to have any credence. Extraordinary to relate, the reliability of the FDA in recording herbal ADRs has recently been called into question by the U.S. General Accounting Office (GAO), which questioned the basis of FDA measures to regulate the sale and supply of the herb Ephedra sinica (Blumenthal, 1999). The GAO found the FDA regulatory proposals regarding ephedra to be based on unreliable and unsubstantiated Adverse Event Reports. Interestingly, the GAO also pointed out that when the FDA conducted its analysis of ephedra, the agency overlooked the many doses of ephedra products (estimated at 2 billion serving units/doses a year) that have been consumed by Americans (apparently safely) over the years. Such a history of many years of use is a required component of any health-risk analysis.

The IMB itself admits to having just one validated ADR report in connection with St. John's wort (IMB, 1999). While insufficient consumer usage in Ireland may account for this lack of recorded adverse events, the widespread use of this herb in Germany and in the United Kingdom has also failed to show any interactions with foods or OTC medicines resulting from taking St. John's wort (see below for a discussion about possible herb-drug interactions with prescription-only medicines). The online ADR information Printout provided by the United Kingdom Medicines Control Agency (MCA) (UK MCA, 1999) records, for the period between July 1963 and December 1999, just twenty-nine total ADPS connected with St. John's wort, giving rise to a total of fifty-four adverse reactions. Side-effects reported (Fugh-Berman and Cott, 1999) for St. John's wort were generally mild; gastrointestinal symptoms and fatigue have been reported (Linde et al., 1996). A relatively rare side-effect appears to be photosensitization especially in fair-skinned people (see below).

In his commentary on St. John's wort (Ernst, 1999), Ernst asked why so few ADRs have been published "particularly in Germany where Hypericum extracts outsell fluoxetine by a factor of four." He answered his own question, writing: "In Germany, extracts of St. John's
wort are commonly prescribed by physicians who are more experienced in the use of herbal medicine products than their colleagues in the U.K. or U.S.A. Perhaps these physicians prescribe it for patients who take no other medications. A more probable explanation is underreporting. There is, of course, another possibility curiously not mentioned by Ernst. This is that the incidence of St. John's wort ADPs is indeed rather low.

In assessing the potential for direct adverse reactions from taking St. John's wort, other concerns also need consideration. The first is the question of the herb's phototoxicity, mentioned above. The second is the alleged association between the regular intake of St. John's wort and the development of cataracts. Two additional recent papers associating other side effects with St. John's wort are also considered below.

There is no question that St. John's wort is phototoxic when taken in vast quantities. Cattle, sheep, and horses grazing on St. John's wort can eat a kilo or more of the fresh herb in a day. Once, these animals are exposed to sunlight, they are likely to develop characteristic blistering because of the large quantities of St. John's wort consumed. It seems that one of the active constituents of St. John's wort, hypericin, is particularly likely to sensitize light-sensitive individuals (e.g., fair-skinned people) to the sun (Fugh-Berman and Cott, 1999). Photosensitivity has been demonstrated in a controlled clinical trial involving hypericin and exposure to metered doses of ultraviolet (UV) A and UVB radiation (Brochmoller et al., 1997). This effect has also been seen in humans taking high doses of synthetic hypericin (Anderson et al., 1992).

Photosensitization is generally mild and transient disappearing within a few days of drug discontinuation. Although this effect is usually associated with the extracted constituent, hypericin, or with higher-than-recommended doses of St. John's wort, the reaction can occasionally occur at lower doses (Fierenzuoli and Luigi, 1999). However, these events appear to be uncommon (Golsch, et al., 1997; Vandenbogaerde et al., 1988) and it has been estimated that the minimal dose of St. John's wort extract necessary to cause a phototoxic reaction is more than 30 times the normal therapeutic dose (Geise, 1980).

In 1999 alarm regarding the association of St. John's wort with the development of cataracts was spread by misinformed press reports that warned that people taking St. John's wort on a regular basis could put themselves at risk if they were exposed to bright light (Johnston, 1999). These reports arose as a result of work carried out by Roberts et al. (1999). The researchers mixed a solution of hypericin (one of just one of at least forty constituents in the whole plant St. John's wort (Marcowitz et al., 1999) at a level equivalent to taking several thousand times the recommended dose of the whole herb together with proteins isolated from calves' eye lenses and exposed the mixture to light. The researchers found that damage was caused to some of the proteins in the solution mixture (cataracts are formed when damaged proteins precipitate out of solution in the eye giving it a characteristic cloudy appearance). The authors thus concluded that exposure to bright light could cause damage to the eye if St. John's wort were taken on a regular basis. However, the extrapolation of such an outcome as a result of taking the whole herb based on work done on an isolated active constituent is seriously misleading. No eye problems have been reported in any of the many trials involving St. John's wort. The somewhat eccentric and highly alarmist warning by Roberts reported in New Scientist (Johnston, 1999) that "those taking St. John's wort should wear hats and wraparound sunglasses" should be seen for what it is worth in this context.

A recent experimental paper (Ondrizek, et al., 1999) reported impaired human sperm mobility in sperm directly incubated in St. John's wort. Sperm motility was inhibited at high concentrations (0.6 mg/mL) of St. John's wort that would seem to represent a concentration thousands of times higher than the therapeutic dose (Woelk, et al., 1994). Another paper (Nierenberg et al., 1999) details two case reports of mania associated with St. John's wort. However, the paper itself acknowledges its major flaw that because both cases involved patients with a history of manic depressive disorder "these patients may simply have cycled through depression to mania a part of their underlying illness."

So much for possible ADPs resulting from St. John's wort by itself .... In recent months, attention has focused on potential interactions of St. John's wort with potent prescription-
only medicines, such as cyclosporin, warfarin, digoxin, and theophylline. Recent reports also indicate that if St. John's wort is taken with some orthodox antidepressants (e.g., selective serotonin reuptake inhibitors [SSRIs] such as Prozac) patients may experience side-effects that are characteristic of elevated serotonin levels in the brain.

It is evident that St. John's wort can induce the cytochrome P450 enzyme system that is responsible for metabolizing a number of conventional medicines. Recent research indicates that St. John's wort is a potent inducer of the subenzyme CYP3A4 resulting in an approximate doubling of CYP3A4 activity (Roby et al., 1999). The CYP3A4 is possibly the most important of the cytochrome P450 family of enzymes involved in the metabolism of many common drugs (Glue and Clement, 1999). Thus, the potential for herb-drug interactions involving the CYP3A4 metabolic pathway needs to be considered for individuals who are taking St. John's wort. Concomitant use of St. John's wort with CYP3A4 eliminated medicines may bring about an accelerated clearance of these compounds, which may result in reduced efficacy of a particular medication. Alternatively, the sudden withdrawal of St. John's wort may cause a rise in the levels of a particular drug that had been stabilized while St. John's wort was being taken on a daily basis.

Such herb-drug interactions have been observed as recent publications in the *Lancet* attest. One such study alerts doctors to the fact that AIDS treatment may be rendered ineffective because a significant reduction in indinavir concentrations were noted in patients concomitantly taking St. John's wort (Piscitelli et al., 2000). Another recent *Lancet* letter reports the acute rejection in two transplant patients because of the metabolic interaction of St. John's wort and cyclosporin (Ruschitzka et al., 2000). A letter from the Swedish Medicines Product Agency (MPA) in the same journal reports that, since 1998, the MPA has received seven case reports of a reduced anticoagulant effect of warfarin (Qin-Ying et al., 2000). The Agency states that although none of the patients developed thromboembolic complications, the decrease in International Normalized Ratio (INR) was thought to be clinically significant. The INR returned to target values either after the warfarin dose was increased or S. John's wort was withdrawn.

In the same *Lancet* letter, the Swedish MPA also suggests a potential interaction between St. John's wort and oral contraceptives based on reports received from manufacturers of St. John's wort products. The MPA details eight cases of intermenstrual bleeding in women taking the contraceptive pill as well as one of changed menstrual bleeding in women taking St. John's wort and the contraceptive pill at the same time. The MPA comments that this "suggests an induction of CYP3A4, which is involved in the metabolism of steroids."

However, these few reports, together with the three mentioned by Ernst in his *Lancet* commentary (Ernst, 1999), should be evaluated against the fact that St. John's wort has an extraordinary widespread use in Europe and the United States. Sales of St. John's wort in the United States in 1998 were estimated at $200 million (Nierenberg et al., 1999) while sales in Europe in the following year amounted to a staggering $6 billion (Glue and Clement, 1999). As Ernst commented, (Ernst, 1999) "women use hypericum products more than men" so that it follows that it is likely that a very considerable number of women are taking oral contraceptives and St. John's wort at the same time. Ernst does not detail the dosages taken by the women in the cases he cites and neither he nor the MPA mention that breakthrough bleeding (spotting) is a well-documented occurrence in women taking low-dosage (third-generation) oral contraceptives. Although the MPA says that "there was recovery after St. John's wort was stopped in three patients for whom the outcome was known," this, of course still leaves six of the patients mentioned unaccounted for. While it is important that the possibility of the interaction of oral steroids and St. John's wort should be further elucidated, it is noteworthy that because the possibility of interaction between St. John's wort and oral contraceptives was first suggested in 1998 (Rev and Walter, 1998), there has been no significant rise in the number of similar reports. Can these few cases perceived against the worldwide sales of St. John's wort and the known side-effects of oral contraceptives be said to be statistically significant?

The Swedish MPA also commented that "it seems likely that St. John's wort is an inducer of a broad range of drug-metabolizing enzymes. ' In support of this, other studies have been published indicating interactions between St. John's wort and digoxin (Johne et al., 1999) as well as theophylline (Nebel et al., 1999). Work published on the interaction between St. John's wort and digoxin (Johne et al., 1999) indicates that this herb-drug interaction is not
mediated in this case by induction of cytochrome P450 but rather by induction of the drug transporter P-glycoprotein that is active in the intestinal absorption, distribution, and renal excretion of digoxin. Several flavonoids, such as those found in St. John's wort, have been shown to be substrates or modulators of P-glycoprotein (Conseil et al., 1998). Hardly surprisingly, therefore, St. John's wort is not alone in this effect. It has recently come to light that grapefruit juice similarly induces P-glycoprotein activity in cell culture (Soldner et al., 1999). (For more about the action of grapefruit and other foods see below).

In his commentary in the *Lancet* Ernst (1999) reports five cases of serotonin excess apparently caused by taking SSRIs with St. John's wort. He lists the resulting side effects as including "changes in mental status, tremor, gastrointestinal upset, headache, myalgia and restlessness" all of which he says are indicative of the "serotonin syndrome" (Martin, 1996). The five cases in which patients taking prescription antidepressants added St. John's wort to their regimes with adverse consequences as logged by Ernst are recorded in a paper by Lantz et al. (1999). What is striking about all these five cases is that they all appear to come from the same New York hospital. Given the huge number of people using St. John's wort in the United States, it seems justifiable to wonder why these five cases all occurred in a cluster. Can there have been other factors involved? Nevertheless, because there is at least one other recorded case of a similar interaction (Gordon, 1998) it is certainly advisable for patients who are taking conventional antidepressants not to mix them with St. John's wort unless so advised by a health professional. As Wheatley points out however (Wheatley, 2000) "most drugs listed in the pharmacopoeia carry drug-interaction warnings, which are very necessary to avoid dangerous combinations but do not constitute an embargo against any one drug used singly or in combinations with others with which there are no such interactions. So, the clinician must balance the benefits of the pharmacological interventions against possible harm that they may cause .... In untreated resistant depression there is a high probability of fatal outcome and it is accepted practice to use combinations of different antidepressants, though there is a risk of interactions between them." In reviewing the wider regulatory and educational issues thrown up by St. John's wort and its potential interactions with prescribed medicines, it seems appropriate to take into account the similar effect of certain dietary factors. Several common foods and drinks are also now known to influence the family of cytochrome P450 enzyme systems. As already noted, grapefruit acts on the drug transporter P-glycoprotein and it is also well documented that grapefruit is a potent inhibitor of cytochrome P450 (Bailey et al., 1998). Conversely, cruciferous vegetables, such as broccoli, cabbage, and Brussels sprouts, are P450 inducers(Vistisen et al., 1991). Similarly, charcoal-grilled beef (Kall, 1995), red wine (Chan et al., 1998),ethanol (Djordjevic et al., 1998), and cigarette smoke (Guengerich et al., 1994) have also been demonstrated to induce the cytochrome P450 system and thus have the potential to alter the rate at which many drugs are metabolized. Cytochrome P450 enzyme activity may be influenced by age, gender, and even race. Diets high in protein and low in carbohydrates may increase this enzyme activity while psoralens (found in parsnip, parsley, and celery) as well as diets low in protein and high in carbohydrates have the potential to inhibit this effect. Fasting, too, can induce a subgroup of this enzyme (CYP1A2), increasing elimination via this route (Glue and Clement, 1999).

No one, of course, is suggesting that the sale of grapefruit, cabbage, or broccoli should be restricted. Instead, pharmaceutical companies are now issuing warnings about grapefruit juice on the product information leaflets of drugs that are known to interact with this fruit. However, in view of the fact that herbs such as St. John's wort are regarded as medicines, it is clear that the appropriate regulation of herbal remedies in the EU is overdue. Detailed proposals to this end have been submitted to the European Commission by the European Herbal Practitioners Association (McIntyre, 1999). As pointed out in a recent letter published in the *Lancet* (Jobst et al., 2000), suitable legislation for herbal remedies would enable St. John's wort and other herbal products to be labeled with precautions so they can adequate that continue to be sold safely OTC. (Herbal practitioners, of course, like doctors, can continue to use their judgment when prescribing in individual cases.) The fact that St. John's wort remains unlicensed for depression in both the United Kingdom and in Ireland is a reflection of the inflexibility of current EU medicine's law (EU Directive 65/65 EEC). The regulatory hurdles of safety, quality, and efficacy required for licensing are inappropriate for herbal products and are ill suited to evaluate the biochemical and chemical complexities presented by plant medicines. For example, the mode of action of St. John's wort in the
treatment of mood disorders and depression is still not completely understood. This is presumably why, despite a number of license applications in the United Kingdom, none has been successful because, as Lord Hunt, Parliamentary Under Secretary of State, explained in a recent debate about St. John's wort in the House of Lords (Hansard, 2000), "the data provided have failed to satisfy current regulatory requirements for efficacy." Moreover, given that many herbal medicines have been in use for hundreds or even sometimes thousands of years, their patenting is fraught with difficulty. A study on the status of herbal remedies in the EU conducted on behalf of the European Commission (Association Européenne des Specialités Pharmaceutiques Grand, 1999) highlights this legislative difficulty, pointing out that, with respect to herbal products, Member States face problems in applying EU medicine's law. A solution to this problem appears to be in sight because, at the 48th meeting of the European Pharmaceutical Committee in Brussels, Belgium, on September 27, 1999, all fifteen Member States agreed to work together to try and draft new EU legislation to license "traditional medicines." Such legislation would enable herbal remedies to be sold and prescribed safely by carrying appropriate safety data. It is obviously important for pharmaceutical companies to provide patients and/or customers with appropriate information about potential food or herb-drug interactions while doctors, herbalists, and other health care professionals should be educated about these same issues.

Finally, in conclusion of this review, we re turn to the question of whether depression is a condition that should only be treated by registered medical practitioners. The IMB, which holds this opinion, wrote that, "it is our view and that of our experts that depression is a medical condition .... There is concern that individuals with clinical depression may fail to recognize the severity of their condition[s] and may self-diagnose and self-treat. Such treatment with St. John's wort may lead to masking of the symptoms of a more serious underlying depressive disorder" (IMB, 1999). It seems pertinent to point out here that it would appear that doctors themselves often disagree in their diagnosis of clinical depression. A study carried out by the Royal College of General Practitioners et al. (1986) showed considerable differences between group practices in their propensity to diagnose mental illness. This research showed that individual practitioners were likely to vary in their diagnosis of depression by a factor of ten. Nor, of course, is it true to say that depression is always treated by doctors because many patients are treated by psychotherapists and counselors who are not doctors. As Wheatley, himself a psychiatrist, pointed out (Wheatley, 2000),* "the Hamilton Depression Rating Scale is the accepted international measure of the severity of depressive symptoms and it is usual to classify this as an illness when the score is seventeen or over. Furthermore, a score of six or less indicates normality." Treatment of depression as an illness should always be supervised by a health care professional. "But what," asked Wheatley, "of those patients with depressive mood and a score between these two limits for whom antidepressant drugs would not normally be prescribed? Assuredly if their doctor[s] cannot help them, they will seek treatment elsewhere. To make it difficult for them so to do, would appear illogical in view of the unrestricted sale....... of potent drugs as aspirin or NSAIDs [non-steroidal anti-inflammatory drugs] for aches and pains and antihistamines for allergies and sleep problems. Informed self-help is commendable and supportive of the doctor-patient relationship when this is required." (*Personal communication, D. Wheatley, 2000.) The alarm raised in Ireland and a plethora of letters and articles in medical journals about the safety and efficacy of St. John's wort is currently causing several other countries to issue new guidelines regarding the sale and use of St. John's wort. In March 2000, the UK MCA acting on advice from the Committee on Safety of Medicines issued a list of medicines (United Kingdom, Department of Health, 2000) that may interact with St. John's wort, cautioning that their concomitant use should be avoided. The specific drugs named are warfarin and digoxin, both mainly used for heart conditions and blood clots; anticonvulsants (carbamazepine, phenobarbitone, phenytoin), used to treat epilepsy; theophylline, used for asthma; SSRIs (citalopram, fluoxetine, fluvoxamine, paroxe-tine, sertraline), used for depression; triptans (sumatriptan, naratriptan, rizatriptan, zolmitriptan), used to treat migraine; cyclosporin, administered following transplantation; indinavir, nelfinavir, ritonivir, saquinavir, efavirenz, and nevirapine, used to combat HIV infection; and oral contraceptives. The Deputy Chief Medical Officer, Dr. Pat Troop, was however at pains to point out that "St. John's wort when taken alone and with many drugs causes no harm" (United Kingdom Department of Health, 2000). This balanced and proportionate approach by the UK MCA contrasts with the very different action taken by the Irish IMB regarding the same issue. The Swedish MPA has recently asked companies that
are manufacturing and selling St. John's wort products to include cautions on their products, instructing that St. John's wort products should not be used concomitantly with any medicinal products. According to a report in the *Irish Times* (February 16, 2000) the FDA is working with herb manufacturers to ensure that labeling of St. John's wort products is revised in the United States, highlighting the potential for herb-drug interactions.

In all this, it is important to keep a sense of proportion. St. John's wort has had thousands of years of safe use on a worldwide scale because it has been a traditional remedy of considerable importance in cultures as diverse as Ireland and China. It is ironic that, in part, the threat to its continued use actually arises from its recent proven success in the treatment of depression. An additional factor is its potential interaction with several potent prescription-only medicines, many of which, like warfarin, cyclosporin, and digoxin, require frequent blood tests for safe usage so that it should be easy enough to warn patients who are taking them that the concomitant taking of herbal medicines is to be avoided. The use by the public of St. John's wort to self-medicate for low-mood disorders is part of an evident sea-change as patients increasingly take control of their own health and demand equal partnerships with their medical advisors when it comes to treatment. The "prescription-only attitude" by the Irish authorities with regard to the treatment of depression should be contrasted with the more relaxed attitude of the Swedish MPA which accepts that "slight mood lowering has been deemed an appropriate indication for self medication." (QingYing, et al., 2000). Because the flavonoids in St. John's wort are believed to be responsible for activating the cytochrome P450 system (Breinholt, et al., 1999; Obermeier, et al., 1995) and these are widely found in our diet, a knee-jerk banning of St. John's wort or other herbs that may be found to have a similar action is a clear overreaction. What is needed is for politicians, legislators, and the medical establishment to recognize the legitimacy of extraordinary worldwide public demand for herbal medicine and to provide specific legislation for these medicines, ensuring that cautions about herb-drug interactions are appropriately declared at the point of prescription or sale.

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