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LETTER TO THE EDITORS

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Cannabis is more than simply Δ^9-tetrahydrocannabinol

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In response to your recent publication comparing subjective effects of Δ^9-tetrahydrocannabinol and herbal cannabis (Wachtel et al. 2002), a number of comments are necessary. The first concerns the suitability of the chosen "marijuana" to assay the issues at hand. NIDA cannabis has been previously characterized in a number of studies (Chait and Pierri 1989; Russo et al. 2002), as a crude low-grade product (2–4% THC) containing leaves, stems and seeds, often 3 or more years old after processing, with a stale odor lacking in terpenoids. This contrasts with the more customary clinical cannabis employed by patients in Europe and North America, composed solely of unseeded flowering tops with a potency of up to 20% THC. Cannabis-based medicine extracts (CBME) (Whittle et al. 2001), employed in clinical trials in the UK (Notcutt 2002; Robson et al. 2002), are extracted from flowering tops with abundant glandular trichomes, and retain full terpenoid and flavonoid components.

In the study at issue (Wachtel et al. 2002), we are informed that marijuana contained 2.11% THC, 0.30% cannabinol (CBN), and 0.05% (CBD). The concentration of the latter two cannabinoids is virtually inconsequential. Thus, we are not surprised that no differences were seen between NIDA marijuana with essentially only one cannabinoid, and pure, synthetic THC. In comparison, clinical grade cannabis and CBME customarily contain high quantities of CBD, frequently equaling the percentage of THC (Whittle et al. 2001).

Carlini et al. (1974) determined that cannabis extracts produced effects "two or four times greater than that expected from their THC content, based on animal and human studies". Similarly, Fairbairn and Pickens (1981) detected the presence of unidentified "powerful synergists" in cannabis extracts, causing 330% greater activity in mice than THC alone.

The clinical contribution of other CBD and other cannabinoids, terpenoids and flavonoids to clinical cannabis effects has been espoused as an "entourage effect" (Mechoulam and Ben-Shabat 1999), and is reviewed in detail by McPartland and Russo (2001). Briefly summarized, CBD has anti-anxiety effects (Zuardi et al. 1982), anti-psychotic benefits (Zuardi et al. 1995), modulates metabolism of THC by blocking its conversion to the more psychoactive 11-hydroxy-THC (Bornheim and Grillo 1998), prevents glutamate excitotoxicity, serves as a powerful anti-oxidant (Hampson et al. 2000), and has notable anti-inflammatory and immunomodulatory effects (Malfait et al. 2000).

Terpenoid cannabis components probably also contribute significantly to clinical effects of cannabis and boil at comparable temperatures to THC (McPartland and Russo 2001). Cannabis essential oil demonstrates serotonin receptor binding (Russo et al. 2000). Its terpenoids include myrcene, a potent analgesic (Rao et al. 1990) and anti-inflammatory (Lorenzetti et al. 1991), beta-caryophyllene, another anti-inflammatory (Basile et al. 1988) and gastric cytoprotective (Tambe et al. 1996), limonene, a potent inhalation antidepressant and immune stimulator (Komori et al. 1995) and anti-carcinogenic (Crowell 1999), and alpha-pinene, an anti-inflammatory (Gil et al. 1989) and bronchodilator (Falk et al. 1990).

Are these terpenoid effects significant? A dried sample of drug-strain cannabis buds was measured as displaying an essential oil yield of 0.8% (Ross and ElSohly 1996), or a putative 8 mg per 1000 mg cigarette. Buchbauer et al. (1993) demonstrated that 20–50 mg of essential oil in the ambient air in mouse cages produced measurable changes in behavior, serum levels, and bound to cortical cells. Similarly, Komori et al. (1995) employed a gel of citrus fragrance with limonene to produce a significant antidepressant benefit in humans, obviating the need for continued standard medication in some patients, and also improving CD4/8 immunologic ratios. These data would

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strongly support a demonstrable clinical role for cannabis terpenoids.

Flavonoid components of cannabis, especially likely to be of benefit in oral or sublingual administration, include apigenin, a unique agent that has strong anti-anxiety effects without sedation (Salgueiro et al. 1997).

Finally, although anecdotal, this author (E.B.R.) has had the opportunity to interview an estimated 200 patients who have employed Marinol and clinical cannabis, whether smoked or ingested. In no instance were the effects of the former considered of equal efficacy to cannabis, but rather more productive of dysphoric and sedative adverse effects (Calhoun et al. 1998).

In essence, clinical cannabis demonstrates herbal synergy and is more than a simply a vehicle for THC administration.

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