January 24, 2012

The Honorable Brenda Landwehr
Chair, Kansas House Health & Human Services Committee
Members of the Kansas House Health & Human Services Committee

Dear Chairperson Landwehr and Members of the Committee:

Thank you for the opportunity to submit testimony regarding House Bill 2330, the "Cannabis Compassion and Care Act". I want to express my support for this bill and encourage the committee to approve the bill as proposed.

I'm Jon Hauxwell, MD, a Family Physician and retired Commissioned Officer, Captain (0-6) in the U. S. Public Health Service. During my career, I focused much of my time in the areas of clinical pharmacology, addictions treatment, mental health consultation, and pain management. I am also a long-time student of ethnobotany, a discipline with significant implications for our present discussion.

I will order this material according to subject matter, and while there are many topics to cover, each item will be addressed more briefly than would be required for a full discussion of the topic. I would be happy to provide more detailed follow-up on any issue upon request.

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Contents

The physiologic basis of cannabis therapeutics

Many human cells are stippled with "receptors" providing cellular access to a variety of internally-produced ("endogenous") molecules, which alter cell functions. Some outside, or "exogenous," molecules can also attach to these receptors, much as a key fits a lock. These structures form the basis for many traditional medicinal interventions, and function naturally to regulate multiple bodily processes.

One particular type of receptor is the "endocannabinoid" variety, of which at least two types are currently known. These receptors, termed CB1 and CB2, are present in a great number of tissues. Our bodies also produce molecules called endocannabinoids to serve as active messengers within the "endocannabinoid system" by attaching to these receptors. *The widespread presence of CB receptors bespeaks a profound and pervasive role in regulation of human physiology.*

Cannabinoid molecules are also found in the cannabis plant; they have appeared in no other plant species, though their receptors are present in all vertebrates and some invertebrates. The endocannabinoid system is very old, and its staying power over millions of years also reveals a major role in animal life processes.

The constituents of cannabis

The two main cannabis species, C. indica and C. sativa, contain more than sixty different cannabinoids. Emerging as significant therapeutic contributors in their own right are other phytochemicals in cannabis: terpenes and terpenoids, which give different cannabis strains characteristic odors; polyphenols; flavenoids; and other chemicals with anti-oxidant properties which act synergistically with each other and with the cannabinoids to impact a variety of disease processes.

While the most psychoactive cannabinoid, delta-9 THC, receives much attention, others contribute strongly to the overall therapeutic effect; cannabidiol (CBD) is an important one of these in cannabis therapy, where it displays both primary effects,

exert a balancing influence on certain of THC's effects. THC alone is a very different drug from whole cannabis, and drugs like synthetic THC (Marinol) can in no sense serve as an experimental or therapeutic surrogate for whole cannabis.

Each strain or variety of cannabis – and there are many – contrasts with the others by virtue of differing proportions and amounts of these chemicals. There is as much genetic variation among cannabis strains as among dog breeds: think Chihuahuas and St. Bernards.

These strains can be cross-bred for specific therapeutic effects. More importantly, strains with established properties can be reproduced asexually, or "cloned," to provide countless offspring genetically identical to the donor plant when grown under similar conditions. Analysis and reliable cloning of important strains can best be achieved when medicinal cannabis is legal and regulated. More on "standardization" later.

The Ensemble Effect – potentiation and synergy

Western medicine traditionally examines the effects of potentially-therapeutic chemicals one at a time, in isolation. This can facilitate determination of specific side-effects, dosage ranges, and mechanisms of action.

The limitation of this approach is that it ignores the well-known phenomenon of "mutual potentiation," the ability of one chemical to alter the effects of another chemical administered at the same time. We rely on this phenomenon routinely when we prescribe formulations containing two or more medicines in the same pill: one plus one equals three. Sometimes one chemical *reduces* problems with another. One pill might contain two diuretics – both lower blood pressure, but the one that preserves potassium levels in the body offsets the potassium-wasting tendency of the other.

Natural processes of trial and error have led cannabis plants to develop a range of survival-enhancing traits that depend on the interaction of multiple chemical constituents. It would take centuries to test every single ingredient in isolation, then in combination with one or many other chemicals, before acknowledging the utility of the combination already vetted by time and natural selection.

However we might focus on separate ingredients, *the variety of chemical profiles found in diverse cannabis strains makes it imperative to test a given strain as a complete entity*; this has allowed a consistent characterization of a particular strain's unique properties as applied to therapy for diverse conditions.

Political and scientific implications for research

Testing individual cannabis constituents in isolation still characterizes much cannabis research.

There are more than 29,000 published studies on cannabis and/or its components. Many of these employ single cannabinoids, however. They come from many countries, while cannabis research in the US is hobbled by non-medical concerns, e.g. political and legal constraints.

The institution of cannabis prohibition in 1937 and subsequent years was *not* based on scientific studies disproving its usefulness or indicting its safety. Rather, the first Drug Czar, Harry Anslinger, was quite candid in his opposition to cannabis: in a bald appeal to racism, he characterized it as the drug of choice for black musicians and Hispanic laborers. This drug, he charged, enabled "those people" to seduce and degrade white women.

Today the unscientific and outdated Schedule I designation for cannabis frustrates many researchers who seek to conduct the additional research both cannabis proponents and denialists encourage. This designation maintains that a drug both lacks acceptance as medically effective, and possesses a significant risk of toxicity and abuse. In the case of cannabis, physicians in 16 states acknowledge cannabis' therapeutic efficacy and safety and can recommend it under state law. The Federal government still provides free cannabis cigarettes (for each patient, 300 cigarettes every 30 days!) to a small group of patients for medical treatment, as recommended by their physicians. If cannabis has "no accepted" therapeutic use, and if it's so prone to abuse, how can this practice be justified, much less reconciled with a Schedule I status? Its abuse potential cannot compare with that of many current Schedule II and III drugs, such as opiates and stimulants; even methamphetamine is legal to prescribe!

In 2003, the government obtained a patent on medical use of cannabinoids, citing among other things their usefulness in "the treatment and prophylaxis of a wide variety of oxidation-associated diseases, such as ischemic, age-related, inflammatory, and autoimmune disease." Does this sound like a Schedule I drug?

The DEA conducted two years of administrative hearings before Administrative Law Judge Francis L. Young, featuring testimony of patients, physicians, and researchers, with voluminous scientific and medical data on cannabis therapy. At the hearing's conclusion, Judge Young urged reclassification of cannabis, stating: "The evidence in this record clearly shows that marijuana has been accepted as capable of relieving the distress of great numbers of very ill people, and doing so with safety under medical supervision. It would be unreasonable, arbitrary and capricious for the DEA to continue to stand between those sufferers and the benefits of this substance in light of the evidence in this record." The DEA's own judge refuted the rationale for instituting cannabis' Schedule I status.

The FDA, plagued by political interference and industry entanglements, has been unable to address cannabis constructively. But even when the FDA approves a whole cannabis study, the project is likely to be quashed by the DEA, as it recently did to a study of whole cannabis, strain-specific therapy for PTSD in military veterans. The DEA maintained that allowing researchers to cultivate a specific strain for study, a strain differing in substantial degree from the single "official" strain grown at the government-contracted "pot farm" in Mississippi, would create an unacceptable "security risk."

Limiting whole-plant research to a single outdated strain is as sensible as limiting dogsled research to Chihuahuas, while excluding Huskies from consideration.

NIDA, the National Institutes on Drug Abuse, has sponsored some cannabis research, but they have been quite candid about their goals and methodologies. Their "mission," as they see it, focuses entirely on liabilities associated with drugs. They are by their own admission uninterested in studies aimed at exploring any therapeutic potential of cannabis, and selectively seek studies seeking evidence for adverse effects. It's biased and blatantly unscientific, but this attitude has dominated the government's approach to cannabis.

However, some decent studies do achieve approval, with FDA-vetted methodologies. Such studies have verified the efficacy and safety of inhaled cannabis in treatment of chronic pain, spasticity associated with MS, AIDS-related wasting, among others.

Double-blind controlled studies are valuable, but they do not constitute our sole resource for learning about cannabis' potentials and liabilities.

For the past 50 years or so, a vast uncontrolled experiment has been conducted on the American people – indeed, people world-wide. Though this generates a lot of "noise,"it is possible to extract a valid "signal" from this background.

When "anecdotes," or experiential observations, are both widespread and consistent, they assume a level of evidentiary value beyond wishful thinking and the placebo effect. It was just such a compendium of unsystematic observational data that led to the characterization of AIDS, and the discovery of HIV.

Though much reviled, anecdotes can provide useful information to individuals seeking therapy, and guide future research. That's just what happened when we examined a certain sweet potato used for contraception by pre-Columbian Amerindians, and discovered the basis for contraceptive hormones. Who would've even looked at a sweet potato, were it not for the anecdotes?

Strain selection, dosage, and routes of administration

Many cannabis strains have been selectively bred to develop a composition of active components which have proved effective when applied to specific diseases or disorders. Each strain varies little from plant to plant when propagated through cloning. Since thousands of people have already been allowed to use these strains medicinally, their general properties are well known, allowing patients to match strain with disorder.

The dosage appropriate for a given patient can be determined safely and reliably with minimal oversight. This process is known as "titration," and involves starting with a small dose, then gradually increasing it until relief occurs, or side-effects become significant. When a given strain "fails" the test of efficacy, it is simple to conduct this safe bioassay on another strain. Optimal dosages will vary with the plant strain, the disorder, and the individual patient's characteristics, and can best be determined by the patient's own response to the medication.

Obviously this approach would be dangerous if applied to, say, many of the opiates, muscle-relaxants, stimulants, and other psychoactive drugs – not to omit the myriads of non-psychoactive drugs such as heart or kidney pills. The difference is that these other drugs can be very dangerous if inadvertently overdosed; many are lethal.

Cannabis, on the other hand, has *no known lethal dose*! If a personal bioassay results in a putative "overdose," the patient merely turns on some music and waits an hour or so, after which any disagreeable effects will have dissipated.

While some practitioners insist on maintaining power over their patients, many of us support a true therapeutic alliance, in which the *patient* is allowed to exercise power over some aspects of decision-making and the implementation of therapy. In the case of cannabis, this approach can be both safe and functional.

The optimal route of administration also varies. For those with intermittent, rapid-onset problems such as headaches or nausea, inhalation might be preferable, either via smoking, or vaporization.

For those with chronic persistent symptoms, such as pain, inflammation, spasticity, etc., sustaining a stable therapeutic serum level is easier to achieve with the "sustained release" effect offered by the oral ingestion route – supplemented, when necessary, by occasional "rescue" doses via inhalation.

The three routes (inhalation of smoke or vapor, or oral ingestion) can manifest different advantages and drawbacks. Selection should be tailored to the individual, as is appropriate for many current medicines. Factors influencing route selection

can often be determined in advance, but the marked acute safety profile of cannabis makes it safe to delegate much of that ultimate determination to the patient herself!

See attached handout for specific guidelines on dosage and administration.

Therapeutic applications

Due to cannabis receptors' widespread presence in many different body tissues, it is not surprising that when any given tissue is the focus of disease, cannabis might well prove to be active in restoring normal function. "Homeostasis," the adjustment of physiologic processes to maintain a functional balance, appears to be one of endocannabinoids' major roles in human health.

Therefore the spectrum of disorders which have proved responsive to cannabis therapy is wide. I'll list just some of the conditions for which research and/or experiential or observational data indicate significant benefits of cannabis therapy.

Autoimmune diseases, such as MS, Rheumatoid arthritis, Lupus.
Muscle spasticity, including dystonias.
Sleep apnea.
Fibromyalgia.
Irritable bowel.
Urinary frequency and pain, as seen in interstitial cystitis.
Certain types of refractory seizure disorder (CBD-dominant strains; THC-dominant strains could aggravate some seizure types – a good reason to bring this into the realm of medicine where such dichotomies can be detected, and strain selection tailored to the individual.)
Post-traumatic Stress Disorder (PTSD) (prevents aberrant memory-retrieval)
Symptoms of psychosis, or side-effects of antipsychotic medicines (CBD-dominant strains only).

Some clinical applications deserve additional exploration.

Cannabis' neuroprotective effects are very promising. While there is no evidence That prophylactic use of cannabis will mitigate acute brain and spinal cord injuries when they do subsequently occur, acute treatment can prevent the toxic accumulation of glutamate which characterizes the body's reaction to brain trauma, acute spinal cord compression or transection, or stroke. This potential is a matter of some excitement among those who provide treatment or rehab for nervous system injuries.

Of the various sorts of chronic pain we confront, one of the most difficult is "neuropathic" pain, pain generated from within nerves themselves. It's common among diabetics and amputees, for example. Neuropathic pain is notoriously resistant to treatment; opiates don't work very well, and the various "adjuncts" like seizure drugs and anti-depressants quite frequently cause very disagreeable, and sometimes dangerous, side-effects. FDA-approved studies in California and elsewhere demonstrate cannabis' safety and effectiveness for neuropathic pain, in absolute terms, or particularly by comparison with many current drugs.

Cannabis has also been shown to enhance opiates' pain-relieving effects.
Since opiates have numerous severe side-effects, it would benefit many chronic pain patients to be able to sustain good analgesia with lower doses of opiates. In some cases, cannabis can allow discontinuation of opiates, a win-win scenario – good pain relief, fewer dangerous effects.

Cancer is another set of diseases some of which have been shown responsive to cannabis or its constituents. We even have good data to explain the mechanisms involved in producing these effects – some of which do not seem to rely on cannabis receptors per se, but utilize other systems.

Cannabis is clearly useful in preventing or reducing nausea associated with cancer therapy, improving mood, stimulating appetite, and reducing "wasting." (These properties are present in complementing AIDS therapy as well.)

This is a case in which other anti-nauseants exist, but are sometimes ineffective or intolerable. Any nausea treatment which requires a vomiting person to swallow a pill and retain it long enough to be absorbed, or to insert a slow-acting suppository, must be suspect, compared to inhaling a drug which is very rapidly absorbed, and very quickly takes effect.

It should be noted that oral Marinol, or synthetic THC, sometimes prescribed for nausea, cannot even begin to reproduce the effects of whole cannabis. It cannot serve as a surrogate for whole cannabis in any sense, for nausea or any other indication. The missing cannabinoid context of Marinol totally alters its efficacy compared to whole cannabis. Many people who have used both can only chuckle at the naivete of those who pretend that Marinol serves as the equivalent of whole cannabis. Even its side-effects tend to be worse than those of cannabis.

Many current cancer treatments – chemotherapy and radiation – harm non-cancerous tissues too. This can be seen as hair loss, or bloody diarrhea or voimiting. Cannabis can *selectively* hasten "accelerated apoptosis" of cancer cells without doing harm to "normal" tissues. Apoptosis is the cell death programmed into all cells; cancer cells seem to have "turned off" the apoptotic genes, and refuse to commit

suicide like they should. Cannabis can reprogram the cancer cells, inducing them to simply kill themselves.

Cannabis can also shut down the formation of the new blood vessels that cancerous lesions stimulate to nourish themselves. There have been some other "anti-angioneogenesis" medications, such as Avastin, but in practice these have turned out to have limited effectiveness in prolonging quality life, and can produce serious or even life-threatening side-effects. Cannabis interrupts the formation of new vessels in tumors, but not in normal tissues, or during wound healing, when new vessel growth is needed. Its use as a cancer-treatment adjunct is likely, and in certain tumors it might become a primary therapy component.

Cannabis is unlikely to interact adversely with current treatment modalities, might well enhance their benefits, and has a better safety profile than most of the toxic drugs it could supplement or replace. It is reprehensible that cancer patients and their providers should be deprived of this option, based on what we *already know* about its activity
in certain cancers.

Denialists are fond of conceding systematically-proven benefits of cannabis for certain disorders, but then trying to dismiss them by citing side-effects. This is purely disingenuous, a case in point being the proven ability of cannabis to relieve spasticity in patients with Multiple Sclerosis. Yes, spasticity responds, but cannabis can cause problems with gait.

Many drugs can be effective for their intended purpose, yet cause side-effects. Proper drug management involves follow-up after institution of a new agent, precisely to determine whether it works, and whether there are side-effects. The patient should be granted a voice – if the relief from discomfort is substantial, and the side-effect relatively non-threatening, it's reasonable to continue therapy despite the presence of a side-effect.

Relief from the pain and dysfunction of spasticity might make it well worth a patient's taking extra care when walking; canes and walkers might be cumbersome, but they don't hurt nearly as much as spasms!

We are still discovering things about cannabis. What we *already know* provides a strong rationale for making this option available to patients and their providers immediately. We are still learning things about aspirin too, some good and some bad, but many people have benefited from using aspirin despite some deficits in our knowledge about it. Interestingly, aspirin, *used as directed*, kills around 5000 Americans every year due to a known side-effect of the drug itself - kidney damage. Many more succumb to fatal intestinal bleeding or strokes. Compared to aspirin or Tylenol, cannabis is far safer; many prescription drugs with marginal effectiveness are also far more hazardous to patients than cannabis.

Due to the rapidly-increasing number of diseases shown amenable to cannabis therapy*, regulators should not limit physicians' ability to prescribe cannabis to some short list of "approved" maladies*. "Off-label" prescribing of many drugs, including

those with severe liabilities, is a common practice. I was prescribing methotrexate successfully for rheumatoid arthritis long before it was formally shown effective, and then approved, for this condition. I based those decisions on what we already knew about both the drug and the disease. This latitude is nowhere more appropriate than when prescribing cannabis.

Furthermore, cannabis should not be restricted to use as a "last resort." If cannabis offers reasonable expectation of safety and efficacy for a given patient, it's absurd that we should be compelled to ignore it until first marching through an obligatory series of predictably toxic or ineffective drugs.

Adverse effects

Like any medication capable of altering human physiology, cannabis has the potential in some patients to cause adverse effects.

"Intoxication." - Particularly in "naïve" patients who have no prior experience with it, cannabis can produce a disconcerting euphoria, as they learn to accommodate changes in concentration and perception. Tolerance to this effect develops very rapidly; that is, the euphoria produced by a given dose fades quickly with repetition. Fortunately, tolerance to the therapeutic effects does not seem to occur much. Therefore, with a little patience or a dosage adjustment, one can expect the psychoactive effect to recede while the therapeutic effects continue.
Any capacity for uncomfortable psychoactivity can also be reduced or eliminated by switching to a CBD-dominant strain, or changing the route of administration.

Those whose only experience with intoxication comes from having used alcohol should not assume that cannabis' effects are at all similar. Drunken people tend to lose inhibition, become aggressive or rowdy, and underestimate their degree of impairment. Cannabis users can be harder to spot based on behaviors. They often become less aggressive and more cautious.

"Impaired driving." – Cannabis can impair driving, especially in naïve users. Rather than speeding in and out of lanes, they tend to drive more slowly, which can annoy other drivers. They might overlook the exit they planned to use, and have to circle back. They can have more difficulty reacting to sudden, unexpected events like the car ahead making an unsignaled lane change or stop.

We do not condone impaired driving due to any cause. The law makes impaired driving illegal, period. The potential for impaired concentration and coordination plagues many current medications. Pharmacists daily go through dozens of sticker-labels warning users not to drive, or to drive with caution, while using the med. Many over-the-counter meds can impair driving too, such as sleep aids and allergy pills. The liabilities we acknowledge with those legal drugs should not be used selectively to oppose medicinal cannabis.

"Addiction." – A small percentage of long-term, heavy cannabis users, around 9%, will develop a pattern of use and behavior consistent with an addiction syndrome, properly defined. (My working definition is "the obsessive-compulsive repetition of a behavior despite adverse consequences." This accommodates non-chemical addictions too.)

The physiologic dependence in such cases is relatively mild, and withdrawal symptoms involve such things as insomnia, irritability, perhaps hampered concentration. Contrast this with the withdrawal syndromes from SSRI's (e.g. Prozac), opiates, barbiturates, hypnotics, benzodiazepines (Valium) – all of which are legal drugs, and some of which can produce fatal withdrawals. Of course, withdrawal from that popular OTC drug, alcohol, has killed thousands of drinkers.

The addictive potential of cannabis, while real, is hard to compare with that of many legal drugs. Alcohol addicts often die as the direct result of alcohol's metabolism within the body – DT's, cirrhosis, esophageal hemorrhage, stroke, heart attack. Tobacco addicts die from the direct effects of tobacco components – cancer in multiple organs, high blood pressure, strokes and heart attacks, limb amputations. While opiates do not damage specific organs in the same way, they can cause fatal respiratory depression, sometimes when used as directed by a prescriber.

Addiction to these legal drugs, and others, occurs rapidly, develops a severe intensity, and is very hard to overcome.

Most cannabis users suffer little or no direct toxic damage from their drug of choice. Adverse social consequences are the primary problem among those who might qualify as "addicted." Chief among these would be legal consequences, which have no relevance to physiologic problems.

We must note that counselors in the chemical dependence treatment industry – for such it is – see a heavily-skewed sample of cannabis users. Of these, many would not be candidates for treatment based entirely on their symptomatology. Once they've been arrested for possession or sharing among friends, a court might offer them "treatment" as a "compassionate" alternative to jail. Most will accept this offer on pragmatic grounds. No fee-for-services treatment facility is likely to discharge such a court-ordered "client" immediately after screening, even if addiction criteria aren't met; jail or not, they're a captive audience. And any client with legitimate protestations against being diagnosed as an addict will be dismissed as "in denial."

Addiction and success numbers generated in treatment facilities should be regarded with informed skepticism.

"Lungs and airways." – It is true that "cannabis smoke contains (potential) carcinogens." Burning virtually any biomass generates carcinogens. However, robust, large-scale studies indicate that smoked cannabis alone does not cause lung cancer. In fact, it might protect against head-and-neck cancers.

This is not the case when users also smoke or chew tobacco. Chemicals in tobacco smoke include "pro-carcinogens" like nicotine, which is not itself carcinogenic. Nicotine can cause flat cells lining the airways to "round up," creating gaps between cells through which carcinogenic tars and particles can reach the underlying tissues to set up a focus of cancerous growth. Cannabis doesn't prevent this, and could even contribute to the total carcinogen load experienced by tobacco smokers. Cannabis or not, people should not use tobacco!

Chronic Obstructive Pulmonary Disease, (COPD) is a natural concern when people inhale hot gases and particles. One of these, emphysema, does not seem to be related to cannabis smoke. The other, chronic bronchitis, is associated with chronic heavy cannabis smoking.

For anyone whose treatment requires frequent dosing to sustain therapeutic effect – a phenomenon we see with many other meds – I would make several recommendations.

1) Consider making the oral route the primary mode of management, only supplementing with inhaled treatments;
2) Use a vaporizer for inhalation;
3) If one must smoke, use a pipe instead of a cigarette, to avoid fumes from burning paper.

A recent study indicated that people who smoke a "joint" or pipe of cannabis as often as once a day for as long as seven years suffer no loss of lung function, and even enjoy a small improvement in function over baseline. However, many medicinal users require higher doses than that, so this study isn't the final word on pulmonary effects of smoked cannabis.

"Cardiovascular effects." – Cannabis tends to lower blood pressure. For most people, this is a neutral or beneficial effect. A patient who normally runs a low-end blood pressure, or has already been using blood-pressure-lowering medicines, could experience light-headedness with cannabis.

Some blood-pressure medications trigger the heart to beat faster to "compensate" for what the body still believes is "wrong," normal blood pressure! This is known as "compensatory tachycardia." In someone with pre-existing coronary artery disease,

a rapid heartbeat might be undesirable. When medicinal cannabis is brought into the medical system, such persons can be screened and identified, and advised not to use cannabis.

"Impaired immunity."
Some studies indicate that modest decreases in the numbers of certain immune cells can occur when they are exposed to cannabis constituents in the lab. Possibly because of the modulating effects of the whole chemical package in actual human usage, no clinically-significant immune compromise appears problematic in real life. Indeed, many prestigious medical facilities which specialize in AIDS treatment routinely utilize cannabis in states where it's legal to do so. The benefits are unequivocal. Although these patients have extremely fragile immune systems, cannabis use has been associated with increased survival rates in this population.

"Psychosis." Studies addressing any potential for cannabis to provoke psychotic illness are inconsistent and sometimes contradictory. However, it does appear that certain predisposed individuals can experience the emergence of psychotic symptoms at least in part as a result of using cannabis. The younger the age of onset of use, the heavier the use, and the longer the use, the greater the risk.

The real-world magnitude of this phenomenon appears to be low, however. The vast majority of cannabis users do *not* develop psychotic syndromes. Moreover, while cannabis use has markedly increased in the past 50 years, the incidence of psychotic illness has remained flat.

Contrast this with the pattern we saw relating tobacco to lung cancer. By the end of WWII, half the American adult population was addicted to tobacco, mostly smoked. After a physiologically-plausible lag time, the incidence of lung cancer (previously a rare disease) began to increase, and its rate of increase precisely paralleled that of tobacco use. This is known as the "dose-response" curve, and it established beyond question the causal role of tobacco in lung cancer. Despite adequate elapsed time since the take-off of cannabis use, no such pattern exists to link it to psychosis.

Other substances can trigger psychosis, include commonly-used anti-inflammatory steroids like prednisone. They remain on the market because such events are relatively rare, and the benefits are clear.

"Effects in adolescent users."
During childhood and adolescence, the endocannabinoid system plays a major role in the migration of nerve cells to their ultimate functional resting places in the

developing brain. Altering this time-limited process in progress, via the administration of outside cannabinoids, certainly has the potential to interfere with it in ways that could affect the formation and consolidation of personality. I strongly advise against cannabis use in children, therapeutically or otherwise. There are a few limited exceptions; some children have experienced dramatic improvements in refractory seizure disorders or ADHD when cannabis was substituted for, or added to, their medical regimen under doctor's supervision.

It's worth noting at this point that in states which have implemented medicinal cannabis laws, youth initiation of cannabis use has remained stable or slightly decreased, while nationally it has increased. Medicinal cannabis laws do not increase youth access, and reducing its image as a "forbidden fruit" might have something to do with this. Also, cartel pushers generally don't ask for ID! Our current approaches to reducing youth use of cannabis, however, are clearly not working well, and cannabis is as readily available in non-medicinal-cannabis states as in those with medicinal cannabis provisions.

Socio-political arguments

Medicinal "excuse" marijuana
Cannabis denialists are fond of repeating a cutesy catch-phrase, "medical excuse marijuana." They would have us believe that the tens of thousands of responsible Americans - who have discovered that cannabis provides them with remarkable therapeutic improvements current drugs just can't offer - are just fakers, or at least deluded.

This is a cruel and cynical deception.

Many currently-legal drugs are diverted for non-medical uses, and cannabis is no exception. Many of these other drugs can and do kill the people who abuse them; prescription drug diversion accounts for thousands of deaths every year, and it's getting worse. Cannabis doesn't do that.

Doctors must be vigilant, and sometimes we get scammed. But we as a society have made a commitment: the con men don't get to call the shots. Abusers can't deprive legitimate patients of relief.

For many patients, cannabis isn't an "excuse," it's a life-saver.

Trojan Horse – medicinal cannabis as stepping-stone to comprehensive legalization.
This is said to be proponents' "real" agenda.

I've conversed with many proponents of medicinal use, and I have yet to hear anyone suggest that medicinal use is unimportant, and that we merely want to exploit it to advance full legalization.

Our interest lies in the patients whose suffering cannot currently be alleviated by available modalities, and who should have the option, under medical guidance, to determine whether cannabis will work better. Often it does, and to a remarkable degree.

Many people do regard the so-called "War on Drugs" as a destructive and expensive failure, whether or not they're involved in medicinal issues. But repealing prohibition is a very different proposition, and should not distract from our current discussion.

Many psychoactive drugs are legally available by prescription, including Oxy-Contin, Valium, amphetamines, and barbiturates. In none of these cases has medical legalization led to recreational legalization.

Patient safety requires "standardization" of the medicine.
Most FDA-approved medicines contain exactly the same amount of active ingredient in each dosage unit. This is critical to their safe use, since many of these meds don't work if taken in insufficient doses, and can cause serious or lethal effects if doses are too large or inconsistent.

This is not the case with cannabis. While there can be some uncertainty about the exact composition of a new strain, the aforementioned titration process eliminates liabilities related to ambiguity. A systematic trial-and-error approach is feasible, effective, and safe.

The best analogy might be our approach to a bowl of artificial sweetener with unknown potency. Since there's no risk that a cup of coffee that's "too sweet" will hurt anybody, one can add a little, sample the taste, and add a little more until getting it just right!

"We don't need cannabis, because the drugs we have work well enough already."
This is among the most egregious examples of willful ignorance among these arguments.

As any doctor can attest, there are many patients whose needs cannot be fully met with available medicines. Some would be effective, but produce adverse effects which make their use intolerable. Some simply don't work very well, though they're well-tolerated.

Even today, with all the primary and adjunctive options available, we encounter cancer patients who say "Doc, our family talked it over, and I don't want to continue these treatments. I realize what that means. Maybe the treatments postpone my

death a little, but we both know where it's headed. I'd rather die than "live" like this."

Or consider a patient with diabetes, kidney insufficiency, high blood pressure – and severe arthritic pain. This is a pretty common scenario.

How will we treat her pain? Because of her kidneys and blood pressure, we can't use NSAIDs like Motrin or Alleve, or Tylenol. Opiates are likely to aggravate her constipation or her chronic itching, or her nausea, all common among patients with kidney damage; they also risk respiratory depression, and of course are very dependence-prone. Other pain-relievers like Tramadol just don't work very well for many people. Cannabis could relieve itching, wouldn't affect constipation, and could help both painful joint inflammation as well as the refractory neuropathic pain common in diabetes.

For a specific example of the current drugs assumed to obviate any need for cannabis, consider a drug called belibumab.

Belibumab was recently introduced as the "first drug of any kind to be approved for lupus in more than 50 years." Side-effects include nausea, diarrhea, and fever, and less frequently, serious infusion and anaphylactic reactions, depression with suicidal ideation, and complications of pregnancy (women of child-bearing age must use contraception during and for four months after treatment, potentially a problem for members of certain religions).

It has not been tested for adverse interactions with other drugs, except for steroids, which isn't unusual for FDA-approved drugs. Known drug-drug interactions kill many Americans, due to oversights on the part of prescribers or dispensers. But some such interactions can only be avoided if known in advance.

The drug must be given over one hour every two weeks for three doses, then every four weeks, using antihistamine premedication to reduce infusion reactions and hypersensitivity. It costs about $35,000 per year.

And what's the payoff for this hazardous, expensive new wonder drug? 52 weeks into treatment, *less than half of those treated with the drug had improved*, 43% versus 34% who used placebo. After 76 weeks, there was *no difference at all* between the two groups.

Systemic Lupus Erythematosis is a chronic disease that can be fatal. Some SLE patients have already found that disease activity and associated sympoms can be reduced with cannabis, with minimal or tolerable side-effects.

"Bypassing" the FDA

"If we allow people access to medicines that haven't been FDA-approved, any old bogus treatment can be promoted, and our pharmaceutical regulatory system would collapse, taking with it the safety of our drug supply."

The FDA has been compromised by politically-driven agendas, internal or imposed by congressional and other entities with access to and influence over the agency. Its entanglement with the industry it's supposed to regulate is no secret.

Consider the cases involving new "COX-2 inhibitors" marketed for arthritis pain.

They were supposedly less likely to cause GI bleeding than the older NSAID's. As it turned out, they still raised the bleeding risks. But much worse, the manufacturers had hidden, with at least the acquiescence if not complicity of the FDA, strong evidence of cardiovascular risks. After the meds came to market, the truth began to emerge. As many as 60,000 Americans died from taking these pain pills before they were recalled and discontinued.

As cited in *The Medical Letter*, an independent reviewer of therapeutic modalities with no government or industry ties, sometimes the FDA has approved a new drug solely on the basis of a single, unpublished study conducted by the manufacturer. If the drug appears on that basis to be relatively safe, it need not demonstrate any advance or advantage over existing drugs for the same condition; and in cases like that of belibumab, actual beneficial results can be trivial or non-existent.

This is our gold standard?

Walk down the aisle of a drug or health-food store, and you will see dozens of drugs – one can't call them anything else – that have not been approved by the FDA. Using transparently deceptive language to avoid being charged with making "therapeutic claims," these drugs are marketed without any requirement whatsoever that they first demonstrate effectiveness, safety, or even that they actually contain the active ingredient in the amount stated on the label, and no others.

As previously noted, the FDA has effectively been derelict in its duty regarding cannabis. Certainly it is not the FDA's responsibility to act as advocate for a modality just because many researchers and patients make therapeutic claims on its behalf. But often when cannabis-related studies are proposed to the FDA, absurd delays followed by silly dismissals have frustrated attempts to provide precisely the research everyone says they'd welcome. Add the highly political and unabashedly anti-cannabis stance of the DEA and NIDA, and the FDA is compromised even when it would otherwise support cannabis research.

The current legal and political climate places cannabis in a unique category of medications. The FDA-approval model, useful as it has been in the past, simply doesn't work when applied in this situation. If we "wait for the science" to validate what countless patients and researchers have already discovered, we condemn

thousands of responsible people to endure the unendurable even longer than they already have, when current treatments don't work.

SUMMARY

The endocannabinoid system's nearly-ubiquitous distribution throughout human tissues bespeaks a profound and pervasive role in regulating health and resisting disease. It provides a sound physiologic basis for cannabis-based therapeutics.

Cannabis strains vary in composition, which permits us to tailor therapy for a given individual's illness, using a strain known to be most promising for that indication.
The "ensemble" effect has enormous implications for how we approach therapy.
Individual isolated chemicals extracted from cannabis, or synthesized, cannot in any sense serve as a surrogate for whole cannabis, nor can they inform us of whole cannabis' potential in a given condition. *Marinol is not cannabis*, not even close.

Because cannabis is free of dangerous acute effects, even in "overdosage," it is feasible, effective, and safe to let a patient titrate the dosages and select routes of administration based upon their actual therapeutic response or tolerability of any side-effects. "Standardization" is irrelevant; strains of consistent composition can be propagated asexually, and the net qualities of many are already well-known based on real-world experience.

Though meaningful cannabis research has been difficult to conduct in our country due to political and legal impediments, it is not non-existent, and much research has been done in other countries. We should not ignore the surge in cannabis use over the last 50 years, as reflected in the experience of real patients and the observation
of qualified healthcare providers. When an "anecdote" is widespread, persistent, and consistent, we ignore it at our peril; it is exactly such randomly-acquired experiential and observational data that led to the characterization of AIDS, and the discovery of HIV. Such data is robust enough right now to guide research and therapeutic applications.

A wide variety of disorders, reflecting the pervasive influence of the endocannabinoid system, have been shown in the lab and in practical experience to be responsive to whole cannabis and some of its components. Only the patient, under medical follow-up, can decide whether the medication is working, and whether any side-effects warrant stopping or changing the medicine. This is, or should be, the approach we follow with most pharmacotherapies.

Like many if not most drugs, cannabis can contribute to adverse side-effects, some medically significant and some only mildly annoying. Cannabis has no lethal dosage. When medical supervision is involved, patients can be screened for pre-existing contraindications to cannabis therapy, and followed to determine whether any adverse effects are developing. The known and suspected adverse effects of cannabis use are dwarfed by the actual destructive consequences of many currently-legal drugs; such consequences include death as the direct pharmacologic result of using those drugs, including prescription, over-the-counter, and the purely "recreational" drugs – alcohol and tobacco.

Various cautionary socio-political speculations have been proposed by cannabis denialists. Many of these are inspired and driven by political and even financial agendas, such as the notion that all cannabis patients are either faking or deluded ("medical *excuse* marijuana"), or that absent formal FDA approval, we simply cannot know whether cannabis should continue to be used by patients who've discovered its life-enhancing properties, but without defining them as criminals. Reliable evidence is plentiful and available to those who inquire objectively.