Hypothesized evolutionary purpose of endocannabinoid system

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Abstract. Hypothesis: Endocannabinoids (ECs) are a general purpose "error status" notification system for animal body parts. Specifically, reduced concentrations constitute a chemical signal, generated in a democratic fashion by a large number of cells, that "something is likely to be dangerously wrong with this body part." This signal is then received by receptors (e.g. CB1 and CB2) mainly in neurons and/or immune system cells, stimulating them to try to take corrective action. That action may or may not be beneficial – and when it isn't that can be regarded as a health problem caused by malfunction or inappropriate action of your endocannabinoid system – but hopefully in net when all such events for some species are considered, it is. The same concept ("safe mode") is now near-universally used in, and has been beneficial for, many semi-autonomous spaceprobes. This gives a unified theoretical explanation (which makes numerous predictions) of the vast majority of ≈1000 otherwise random-looking isolated facts.

I artificially divided the confrontation with evidence into two levels: "simple" and "deeper look." At the simple level, the Hypothesis agreed with 100% of my experimental evidence, providing confidence>99.999999% versus the null hypothesis. Looking deeper, when we confront the Hypothesis with a wide spectrum of ≈100 items of experimental evidence it agrees with 90%, the *exceptions* being: (a) it only agrees with about 75% of bone evidence – and only with a specific sub-hypothesis about how it works in bone – and (b) it collapses, with prediction accuracy of about 50% or less, for evidence related to mammalian reproduction. Therefore I think the Hypothesis does not truly explain *everything*, just *most* things. Although no evidence item is very convincing by itself, the total produces at least eight "nines" worth of confidence. Perhaps a&b are because, e.g, mammalian reproduction evolved much later than the endocannabinoid system (at that time, neither vertebrates, nor animals with internal bones – both include all mammals – had yet appeared) and "overrode it"; and to try to see the latter in its "pure form" we would need to investigate encocannabinoid↔reproduction effects in earlier nonmammal animals (an almost unstudied topic). Also complicating (b) is the fact that *human* pregnancy and birth is very atypical among *mammals*.

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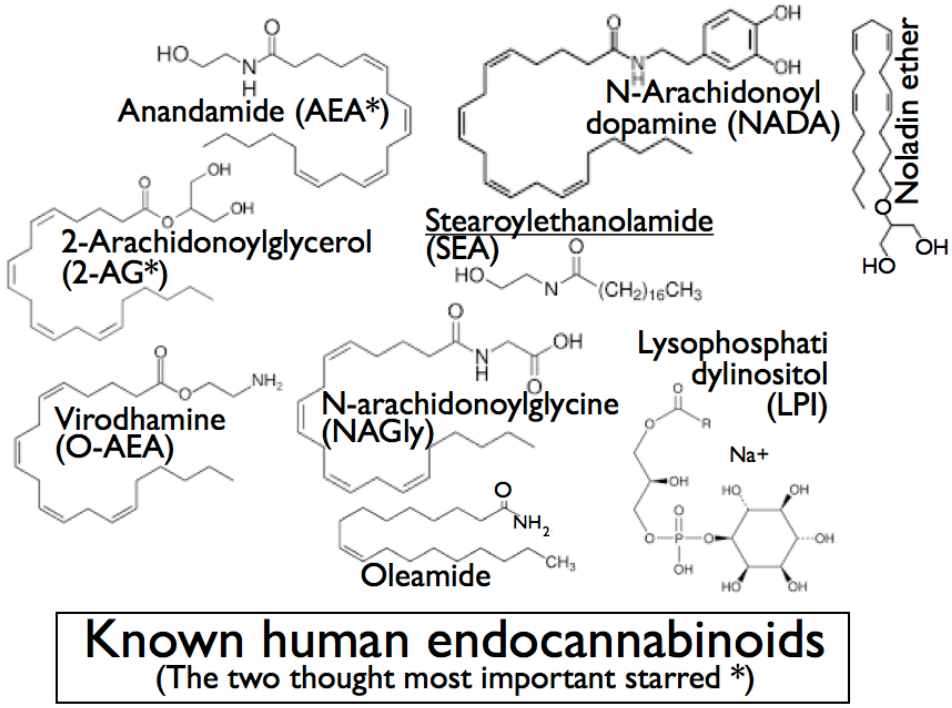
1. The endocannabinoid system

At least nine **endocannabinoid** (EC) molecules (fig.1) are presently known. (And arguably more, e.g. Kogan & Mechoulam 2006 give two anandamide variants in their fig.1.) The first draft of this paper (2013-2015) had only said "five," because fewer were known at that time. These five {AEA, NADA, 2-AG, Virodhamine, NAGly}, as well as perhaps noladin ether, all contain an identical "20-carbon-plus-E" substructure where E denotes a variable non-hydrogen electronegative atom (N and/or O). The later three {SEA, Oleamide, LPI} do not, and have less binding to CB1 and CB2 and hence presumably are less important (although LPI may have importance for binding to GPR55). The prefix "endo" signifies that the human body synthesizes them by itself; it also "receives" them at CB1 and CB2 "receptor" molecules on cell surfaces, causing those cells to do something, or not, in response to the chemical "signal."



Many ***phyto*cannabinoids** also are known, meaning molecules produced by *plants* which can stimulate the CB1 and CB2 receptors in animal cells, and/or interfere with animal endocannabinoid degradation pathways. (They also conceivably could work by affecting synthesis pathways, but I know no examples of that. Degradation and receptors can happen outside your cells, but synthesis happens inside, making it more difficult for any exogenous chemical to affect the latter.) The most famous phytocannabinoid-producing plant is marijuana (*cannabis indica* and *sativa* females) which produce over 140 phytocannabinoids, of which the three that have drawn the most attention for drug purposes (also the three most prevalent inside marijuana plants) are THC, CBD, and CBG, pictured in fig.2. Marijuana plants also produce many other chemicals, e.g. terpenoids (the largest component) such as β-myrcene, which *modify* the drug-effects of its cannabinoids, even though not themselves cannabinoids; and its cannabinoids also modify each other's drug effects, and further can interact with third-party drugs. For example THC and CBD are thought to synergize (which is why both are present in the commercial drug "Sativex" aka "Nabiximols"), and also marijuana enhances the pain-killing effects of opiate drugs (Cichewicz 2004, Abrams et al 2011).

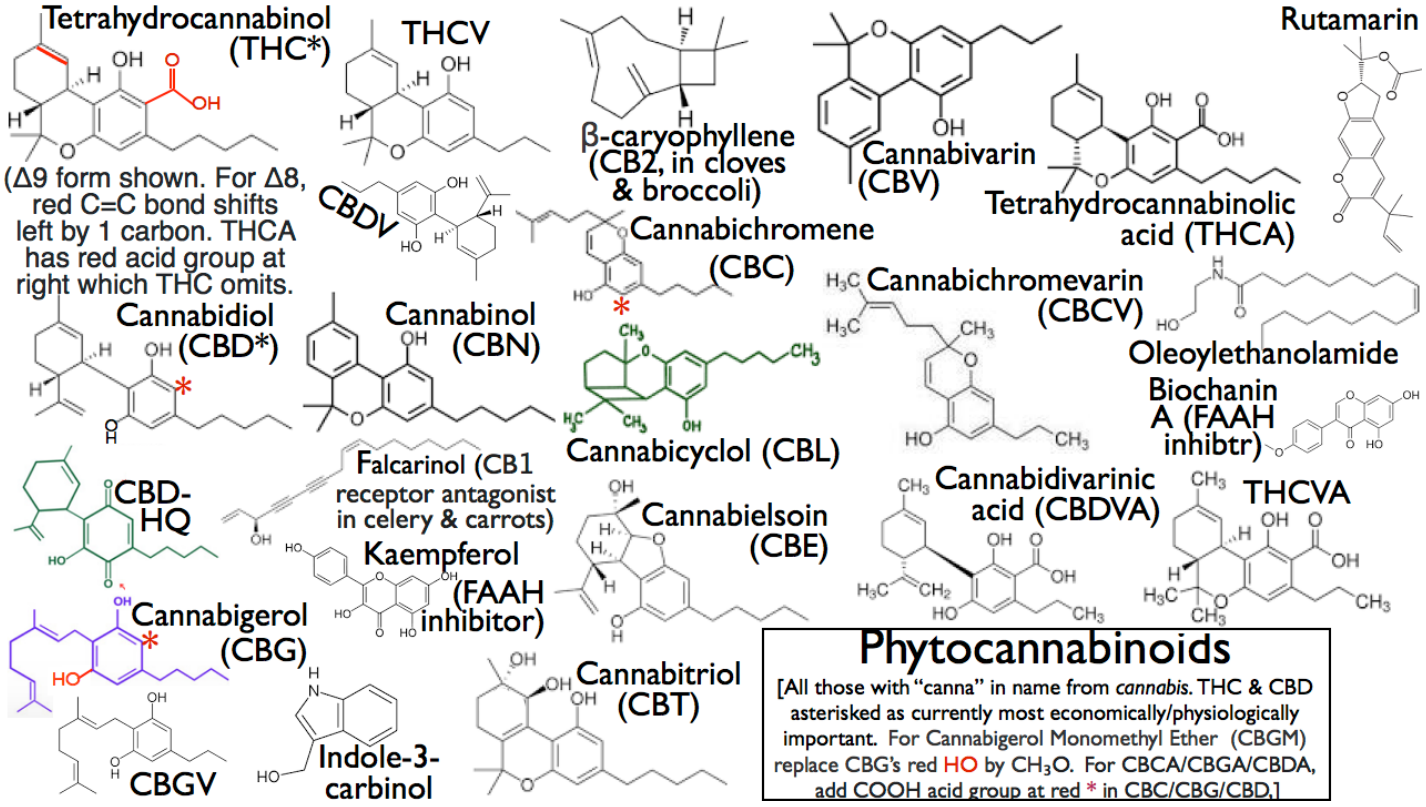
Archaeological evidence from neolithic cave paintings and items preserved in, e.g, tombs, shows that marijuana has been used to make rope, textiles, and drugs for at least 10000 years. Marijuana has been a component of traditional Chinese medicine at least since 2700 BC. In ancient Persia (1500-400 BC; now Iraq) the Avesta religious text of Zoroastrianism ranked cannabis as the most important among all medicinal plants. It also was important in Ayurvedic medicine in India starting in 1300 AD or before. In Exodus 30:23-25 in the Bible, God instructs Moses to concoct an "anointing oil" whose recipe includes "250 shekels" of an ingredient called "sweet calamus" in the King James English version but *kaneh bosem* ("aromatic cane") in Hebrew, which probably was *cannabis*. In the West, the German abbess and polymath Hildegard von Bingen (1098-1179) briefly discussed hemp's medicinal effects in her Physica. The 1851 US Pharmacopeia listed "Extractum Cannabis" in Latin, "Extract of Hemp" in English, on p.50 (described as "An alcoholic extract of the dried tops of Cannabis sativa-variety Indica"; it remained until 1942) and it was recommended in Osler & McCrae 1915 (then the leading medical textbook) as the best treatment for migraine headaches (commercially sold in the 1919 Eli Lilly catalogue for that purpose), and indeed still remains the best available medicine for migraine as of 2022 according to the review by Okusanya et al. It seems plausible/obvious that any medicine with this much historical use in this many places and times, probably was not entirely bunk. But one should be cautious, since, e.g, Osler & McCrae also recommended such wonderful medicines as strychnine and arsenic – both of which undoubtably can be effective (e.g. Gitzelmann et al 1978, Paul et al. 2022), but have major safety issues.

The same plant family also produces "hemp fiber," used to make ropes, especially-durable paper, and cloth (probably including the very first US flag) for thousands of years, and "hemp seed," a nutritious "superfood." All that makes *cannabis* a remarkably useful plant family, which was why King James I mandated that the original 13 US colonies grow it (first crop: Jamestown 1611), and also the reason for the US government's "hemp for victory" program which devoted 1200 km^2 of agricultural land to growing it during World War II. In

particular, George Washington grew hemp at all five of his farms on "Mount Vernon" throughout his lifetime 1732-1799, and his diary entries for 12-13 May and 7 August 1765 make it clear he wanted the drug, not just the hemp fiber. At that time you could be jailed for *not* growing cannabis, in quite remarkable contrast to the situation 2.2 centuries later, when in 2011 Lee Carroll Brooker and in 2017 Allen Russell were sentenced to *life imprisonment with no possibility of parole* for possessing marijuana plants (total weight 1.3 kg) growing in his yard, and 43.7 grams (1.5 oz, approximately the weight of a golf ball) of buds, respectively. Mark Young received the same sentence in 1992 even though he didn't have *any* marijuana; he simply *introduced* three buyers to two sellers. Although these sentences were longer than the 17.5-year median imprisonment served by *murderers*, US drug chief H.J.Anslinger in an interview with *Newsweek* (15 Jan.1945, p.72) recommended making them standard, and indeed suggested the *death* penalty for drug sales (NY Times, 8 Sep.1951).

> Brooker was a disabled army veteran who took marijuana to relieve his symptoms. Their state supreme courts later refused to reduce these sentences, and in Brooker's case also the US federal supreme court. Numerous other US states starting with California in 1996 had *decriminalized* marijuana in a remarkable blatant flout of federal law – but unfortunately for Brooker and Russell, they lived in the wrong states.

Those sentences greatly violated the principle enunciated by Jimmy Carter (1924-2024; US president 1977-1981) that "penalties against possession of a drug should not be more damaging to an individual than the use of drug itself; and when they are, they should be changed." (Drug abuse message to Congress, 2 Aug.1977; Carter wanted to decriminalize possession of small amounts of marijuana, but failed to make that happen.) An unrelated less-famous plant which also produces at least 40 phytocannabinoids is the South African "woolly umbrella" flowering daisy family member *Helichrysum umbraculigerum*, best known for smelling like curry. These two kinds of plants arose relatively recently and apparently independently (*cannabis* about 36 Myr ago near the Altai Mountains in central Asia) – i.e. are much younger than the endocannabinoid systems in animals. More phytocannabinoids are found in rhododendron and radula plants and some fungi. Their phytocannabinoids presumably serve animal-manipulation and/or anti-oxidant purposes useful to these plants. It is less well known that many other plants also produce phytocannabinoids, including some historically used for medical or food purposes. These include: Indole-3-carbinol found in brassica vegetables like broccoli; the coumarin derivative rutamarin from the medicinal herb *ruta graveolens* (rue); β-caryophyllene in black pepper, rosemary, basil, cloves, carrots, and the beer-ingredient hops (also present in cannabis); the FAAH inhibitors biochanin A and kaempferol found in broccoli and red clover respectively, and N-linoleoylethanolamide and N-oleoylethanolamide (as well as anandamide itself) found in chocolate (*Theobroma cacao*). Also, many cannabinoids have been synthesized which do not arise in nature.



There also is a **network of other biomolecules** involved in the human endocannabinoid "system." These include:

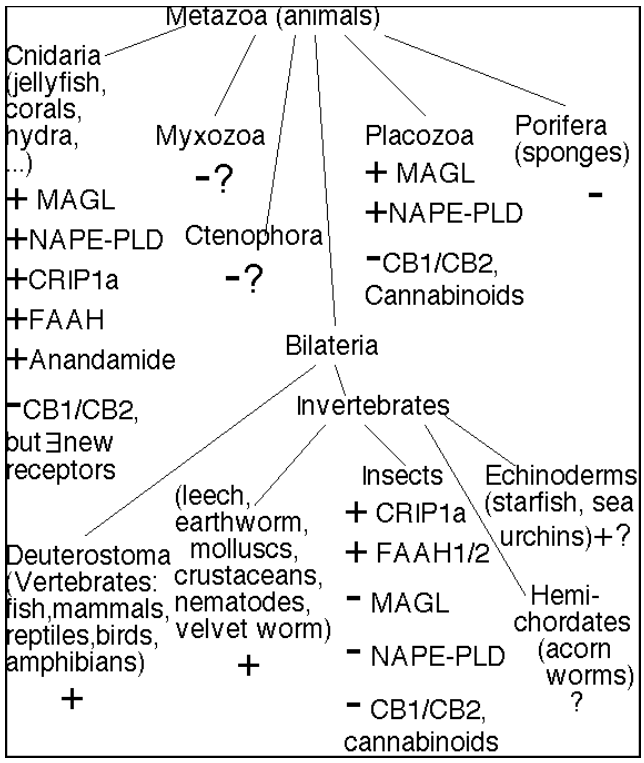
- The CB1 and CB2 receptors (which allow cells which have them on their surfaces, to sense the presence of cannabinoids). CB1 and CB2 are among the most common (perhaps *the* most common) chemoreceptors in the human body.
- FAAH (Fatty Acid Amide Hydrolase) an enzyme which breaks down the anandamide endocannabinoid; also FAAH2,
- NAPE-PLD (N-AcetylPhosphatidylEthanolamine-hydrolysing PhosphoLipase D), also called DAGLα (DiAcylGlycerol Lipase alpha), an enzyme which helps synthesize anandamide; also DAGLβ,
- MAGL (MonoAcylGlycerol Lipase) an enzyme which breaks down the endocannabinoid 2-AG,
- CRIP1a (Cannabinoid Receptor Interacting Protein) which binds to the last 9 amino acids of the CB1 receptor protein,
- COX-2 (CycloOxygenase-2) important enzyme whose action is inhibited by at least some cannabinoids.

It would not surprise me if additional receptors, enzymes, endocannabinoids, and/or additional interacting molecules also exist and play roles, beyond the ones presently known. E.g. GPR55, GPR119, GPR40, GPR18, and TPRV1 are possible additional receptors. [CB just stands for cannabinoid. "GPR" and "GPCR" stand for "G protein receptor" and "G protein-coupled receptor"; Both mean receptors that are bonding sites for G proteins. GPRs are the largest family of signal transducers, with about 800 kinds. These receive hormones, neurotransmitters, odors, etc. and can be located all throughout the brain and body. There are ≈800 GPRs and GPCRs constituting about 4% of all human genes. Both CB1 and CB2 are transmembrane G-protein-coupled receptors.] The endocannabinoids are ultimately made from ω3 and/or ω6 fats, presumably yet another reason those fats are essential dietary needs.

Properties of some important phytocannabinoids. I originally wanted to have a table showing melting and boiling points, LD50, and pharmacologic halflives of various important phytocannabinoids e.g. CBC, CBN, CBD, Δ9THC, CBG, caryophyllene. However, I gave up after finding that numerous so-called sources disagree, sometimes vastly, about LD_{50}s and boiling points; also melting points can differ greatly for racemic mixtures versus pure-stereoisomer natural products; and the simple exponential-decay model for "pharmacological halflife" seems often incorrect (more correct is a sum of several exponentials, in which case there would be several halflives). An effort to examine original sources did not help because they almost never published melting or boiling points. So suffice to say that melting points usually are between -50 and +150°C; acids such as CBNa usually decarboxylate (R-COOH → R-H + CO_2) between 70 and 150°C; LD50s are usually over an order of magnitude smaller for intravenous than for oral dosage mode, and for oral dosages are usually 1-20g/kg; and halflives usually lie between 1 and 100 hours.

My interest was initially piqued by my serendipitous co-discovery (Smith & AW 2010) that achalasia, a rare disease (60-100 cases per million) in which peristalsis (the patterns of muscular contractions that move food down the esophagus into the stomach) is severely disrupted, preventing eating by causing effective blockages and/or vomiting – in some subset of cases is dramatically *cured* by swallowing about 1 large drop of homemade oil extract of marijuana 5 minutes before a meal (effects last about 60 hours, then need to take another dose). This, in the achalasics for which it works, is tremendously more effective, simpler, and cheaper than any other therapy. And its only side effect seems to be "increased appetite" (the dose is too small for psychoactivity). 15 years later, during work on the present paper, I found out that the same discovery (based on an almost identical patient) also was made by Patricia C. Frye, MD, see pages 81-82 of her 2018 book (although she only had one patient and did not recognize the 3 achalasia subtypes).

At first I regarded this as just another of the ≈1000 random inexplicable facts about cannabinoids. But the incredible effectiveness of this treatment seemed to be trying to tell us something important. *Why* should peristalsis be majorly affected by cannabinoids? Naively, it would seem that a simpler and more reliable design would be just to use ordinary muscles and neurons alone.



And it is now known from DNA sequencing and receptor assays that the endocannabinoid system has been conserved by evolution since **very ancient** times. Figure 3 approximates part of the "tree of life" annotated with "+" for animals known to have an endocannabinoid system, "-" for animals which do not, and +/- for lifeforms in which conflicting indications have been reported, e.g. they seem to have some but not other parts of the system. The animals with a full endocannabinoid system are a superset of the chordates and cnidaria but include only a subset of the *bilateria* (including all vertebrates; this suggests that the first such system arose 520-600 Myear ago). For comparison, the CNS "dopamine" system (stimulable by opiate drugs) also appeared probably a bit later during this same epoch (Yamamoto & Vernier 2011). But some parts of the system seem present even in some of the most ancient animal lines – and even *arabidopsis*, a *plant*, contains FAAH – suggesting those parts may be as old as 1 Gyear. (Units: Myear=10^6 years, Gyear=10^9 years.) Some invertebrates have new kinds of cannabinoid receptors, such as CiCBR discovered in the urochordate sea squirt Ciona intestinalis and BfCBR in the cephalochordate lancelet *Branchiostoma floridae*, and some unknown ones in the sea urchin *Strongylocentrotus purpuratus*, the leech, molluscs, cnidarians, and echinoderms – suggesting there might be somewhat different "parallel design" endocannabinoid systems in some branches of life far from ours (Matias et al 2005, Elphick 2007, Schuel et al 1987, Chang et al 1993, Stefano et al 1996, De Petrocellis et al 1999). But the fruit fly *Drosophila melanogaster* and the tiny worm *C.Elegans* both lack any Cannabinoid receptors that are orthologs of the known ones. In any case, the animals which have the system include members which seem extremely different. All that would not have happened unless the endocannabinoid system were **important for survival**$^{+1}$. [However, it is not *essential*$^{+2}$: "CB1/CB2 double knockout mice," and FAAH knockout, and DAGLβ knockout, mice, all have been bred, and survive, albeit they've all been observed to be handicapped/diminished in numerous ways in hundreds of papers.] So it must play some crucial and probably highly general role. But what?

Superscript^{+K} notation: Denotes "this is the Kth item of **evidence**," and the + sign denotes it supports the Hypothesis; minus sign (-) would be for evidence opposing the Hypothesis; and star (*) for weaker items of positive evidence (e.g. worth only half what a normal evidence item is worth).

2. Interlude: 80 years of lies about marijuana

> "Two things are infinite: the universe and human stupidity. And I'm not sure about the universe."
> – attributed, probably falsely, to Albert Einstein.

There have been **heroes** in the history of medicine: Ignaz P. Semmelweiss (1818-1865), Louis Pasteur (1822-1895), Joseph Lister (1827-1912), Alexander Fleming (1881-1955), and Frederick Banting (1891-1941). But unfortunately **villains**, such as Sigmund Freud (1856-1939) and Cyril L. Burt (1883-1971) caused enormous harm by scientific fraud (e.g. fabricating nonexistent "patients" who "proved" their "scientific" theories...); and Donald J. Trump (1946-), acquired and wielded enormous power to deny medical reality, for reasons of self-interest. I.e. Trump, motivated by the fact his hotel and resort businesses were likely to suffer as the result of the COVID-19 pandemic, declared it a "Democrat hoax," and worked against efforts for "social distancing" and mask-wearing, spectacularly mismanaging the epidemic while publicly touting ridiculous "therapies" such as hydroxychloroquine and internal use of dangerous disinfectants like "Lysol." (Astonishingly, Trump actually had himself *secretly* vaccinated against COVID because he did not want to publicly admit vaccines were a good idea, and thereby admit the validity of claims by his political opponents that COVID was dangerous. In reality it was the worst pandemic in 100 years.) The result was 1.19 million confirmed US COVID-19 deaths by 2022, exceeding any other country. Had Trump simply copied the common-sense policies and non-lying of South Korea – a country with less warning time, resources and expertise, but otherwise similar – he presumably would have matched its 5× lower COVID death rate. Then the USA would have had only 236k COVID deaths, i.e. Trump was primarily responsible for **0.96 million** deaths among his own people. That ranks Trump safely among the worst 10 human beings within his adult lifetime (i.e. the last 60 years), although behind Kim Il Sung (N.Korea) and Pol Pot (Cambodia), credited with 1.6 and 1.7M deaths respectively. Trump is, in fact, a multi-time superb example of exactly why it is bad for political leaders to have large commercial conflicts of interest.

In the case of **cannabinoid-related** medicine vis-a-vis the USA, unfortunately three **villains** dominated:

1. Harry J. Anslinger (1892-1975) the first commissioner (1930-1962) of the U.S. Treasury Department's Federal Bureau of Narcotics, a predecessor of the Drug Enforcement Administration (DEA, created 1973).
2. Robert L. DuPont, MD (1936-), the first Director (1973-1978) of the U.S. National Institute on Drug Abuse (NIDA), and later drug-advisor to Attorney General Jeff Sessions.
3. Richard M. Nixon (1913-1994), US president from 1969 until resigning in disgrace in 1974, and Ronald W. Reagan (1911-2004), US pres. 1981-1989, who continued Nixon's policies.

If there is anyone who can be claimed to be a "hero," it would be Israeli chemistry professor Raphael Mechoulam (1930-2023), who discovered or co-discovered THC, CBD, Anandamide, and 2-AG after CB1 was found in the rat brain by Devane et al 1988. (Munro et al 1993 then identified CB2 by sequence homology.)

Anslinger first acquired high power in the U.S. "Bureau of Prohibition" which was in charge of stopping alcohol, which the USA had made illegal during 1920-1933 in what turned out to be one of most spectacularly unsuccessful public health campaigns in human history. In its defense, though, even in year 2025 alcohol remains the third-leading patient-controllable health-damaging factor in the USA after tobacco and obesity. [US deaths attributed to tobacco 15.5%, obesity 11.7%, and alcohol 5.8% according to CDC estimates and Allison et al 1999.] Today's USA makes those legal while banning less-addictive drugs that cause far less damage like marijuana. After prohibition's repeal, Anslinger's >2000 enforcement agents needed jobs, and he needed them to avoid losing power. Anslinger's solution: Demonize marijuana, and therefore (conveniently) also Asian and Mexican immigrants and Negroes whom he associated with its importation and use. (Anslinger quote: "Reefer makes darkies think they're as good as white men.") He led a successful campaign to make marijuana illegal and under federal control (which happened in 1937); then in 1952 the "Boggs act" mandated 2-10 year imprisonment (plus fine equivalent to about the average annual income) for possessing marijuana (same penalty: heroin); then in 1970 as part of "Nixon's war on drugs" *every* use of cannabis was criminalized, including all commercial fiber, food, and medical uses, and it was placed on "schedule 1" – *defined* as unsafe drugs, likely to be abused, with "*no* accepted medical use," e.g. heroin. Marijuana still resides there as of early 2025, despite a second branch of the same US government, the Food and Drug Administration (FDA) approving marijuana's two top bioactive constituents, under the pseudonyms "marinol/dronabinol" (1985) and "epidiolex" (2018), to be sold as "safe and effective" drugs! (Unfortunately as purified mono-ingredients these

two drugs lose whatever benefits are widely suspected to come from *cannabis*' modifier-ingredients.) Meanwhile a third branch of the US government – Department of Health & Human Services – actually filed a *patent* (#6630507) in 1999 for "a new found property [making] cannabinoids [such as CBG] useful in the treatment and prophylaxis of wide variety of oxidation-associated diseases" and neuropathies, which then was approved by a fourth US government branch: the patent office. Anslinger claimed based on a small amount of cherrypicked and intentionally falsified anecdotal evidence that marijuana somehow inspired crime. His propaganda campaign was aided by newspaper baron Wm.R.Hearst (1863-1951) and films such as 1936's Marihuana: weed with roots in hell and Reefer Madness, 1942's The Devil's Harvest, and 1949's She Shoulda Said No! (Wild weed). Marijuana was

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> a deadly, dreadful poison that racks and tears not only the body, but the very heart and soul of every human being who once becomes a slave to it... a short cut to the insane asylum... Hasheesh makes a murderer who kills for the love of killing out of the mildest mannered man...
> – MARIHUANA MAKES FIENDS OF BOYS IN 30 DAYS: HASHEESH GOADS USERS TO BLOOD-LUST, San Francisco Examiner (31 Jan.1923) by longtime Hearst writer Winifred Black, who wrote under the pseudonym "Annie Laurie."

Her later Feb.1928 series explained that marijuana was known as the "murder drug" in India: a person under its influence would "catch up his knife and run through the streets, hacking and killing every one he [encountered]." She further informed that one could "grow enough marijuana in a window box to drive the whole population of the United States stark, staring, raving mad." Anslinger himself wrote "Marijuana: Assassin of Youth," published in the July 1937 *American Magazine* and Feb.1938 *Reader's Digest*, coordinated with the release of a 1937 film with the same title.

He wrote on p.7 of his government report *Traffic in Opium and Other Dangerous Drugs* (U.S. Govt. Printing Office 1939) that "The great danger of marijuana is... the fact that its continuous use leads direct to the insane asylum." Anslinger explained how he knew that in his 1943 letter to the editor of JAMA, apparently the closest Anslinger ever came to a scientific publication. (Anslinger billed himself as the world's foremost expert on drug abuse. He did not even have a college degree, although falsely claiming on resumes to have a law degree from Univ. of Maryland law school.) In this letter Anslinger complained that it was "very unfortunate that [Allentuck & Bowman 1942] should have stated so unqualifiedly that the use of marihuana does not lead to physical, mental, or moral degeneration, and that no deleterious effects from its continued use were observed." (A&B also found marijuana less addictive than either alcohol or tobacco, and recommended using it as a partial replacement for opiates as part of a strategy to end opiate addictions with less "withdrawal.") Anslinger then offered 12 quotations "proving" his contention that (to repeat the clearest of his 12) "it is proved beyond doubt that prolonged use of Indian Hemp leads to insanity." Anslinger attributed that particular quote to Dhunjibhoy 1930. So I checked it out: Anslinger's particular quote was *not* present in Dhunjibhoy's paper. Dr.Dhunjibhoy was the first president of the Indian Psychiatric Society and Superintendent (1925-1941) of the Ranchi Indian Mental Hospital. But p.264 of Dhunjibhoy 1930 did make the following similar but considerably weaker claim: "It is proven beyond doubt that the hemp drug is a direct cerebral poison. I put this drug above alcohol, opium, and cocaine with regard to injurious tendencies in the causation of insanity in India." But that was not justified by evidence in the paper, but rather simply *asserted*. Dhunjibhoy nowhere described how he knew which insanities were caused by which causes. Consider the alternative near-opposite hypothesis that marijuana actually has a *curative* effect on insanity; and those people, recognizing their deteriorating mental state, tried to self-medicate to rescue themselves, but despite the beneficial effects of marijuana nevertheless eventually went insane. That alternative is equally supported by Dhunjibhoy's evidence! Mehndiratta & Wig 1975, after citing Dhunjibhoy 1930, described an *actual* study (*not* merely an unsupported assertion) of 25+25 heavy cannabis smokers and bhang drinkers who'd all been doing it for at least 4 (average 12) years, versus 25 controls who'd never used (all Indian); their results clearly refuted Anslinger's falsified quote. (See also Freedman & Rockmore 1946's study of 310 US army soldiers who'd used marijuana for 7.5 years average, finding "no mental or physical deterioration.") Anslinger also offered, as the second clearest of his 12 quotes: "it may be accepted as reasonably proved that hemp drugs do cause insanity" attributing that to the 1894 Indian Hemp Drugs Commission Report but failing to mention in which of its 8 volumes, totalling over 3000 pages, or on which page, that quote could be found. Meanwhile Anslinger left unmentioned these other quotes from that same report (v1, p.264):

- "It has been clearly established that the occasional use of hemp in moderate doses may be beneficial."
- "In respect to the alleged mental effects of the drugs, the Commission have come to the conclusion that the moderate use of hemp drugs produces no injurious effects on the mind... [and] no moral injury whatever."
- "[But] *excessive* use may certainly be accepted as very injurious, though it must be admitted that in many excessive consumers the injury is not clearly marked. The injury done by the excessive use is, however, confined almost exclusively to the consumer himself; the effect on society is rarely appreciable. It has been the most striking feature in this inquiry to find how little the effects of hemp drugs have obtruded themselves on observation."

The reality is that *if* long-term excessive cannabis use causes insanity, *then* it does so **order 1% or less** of the time, making it statistically difficult to see that effect against this *background*: A fraction **1/439** of the year-1917 USA population was confined in insane asylums according to the US census dept. (plus presumably many more were not in asylums), and presumably mostly for reasons unrelated to marijuana. So to verify Djunhibjoy's theory you would need somehow to find 5000-10000 long-term excessive cannabis users and an equal number of matched controls then track their mental heath for 20 years. We'll discuss the studies that came closest to that ideal later. For now, I'll just quote from the reviews by Burns 2013: "Researchers and clinicians remain divided [on] whether or not cannabis is an independent cause of psychosis and schizophrenia" and by Hollister 1998: "the possible causative role of cannabis in chronic psychotic or affective disorders [is] unconvincing."

When Walter Bromberg (Senior Psychiatrist at Bellevue Psychiatric Hospital, and Director of the Court of General Sessions' Psychiatric Clinic, both in New York) reviewed 2216 felony criminal convictions (later expanded to 16584 criminals), finding *zero* clearly connected to the influence of cannabis, and brought this forcefully to Anslinger's attention. Anslinger ignored him. Gavrilova, Kamala, Zoutman 2019 found that US states, by legalizing medical marijuana, actually *reduced* violent crime and did not increase property crime. Later, Anslinger also *almost* entirely ignored the opposition of 29 of 30 American Medical Association (AMA) pharmacists and drug industry representatives to his proposals to ban cannabis (one called them "Absolute rot. It is not necessary. I have never known of its misuse."). But *not* entirely – Anslinger used the arguments of that one dissenter! The AMA then sent its counsel Dr. William C. Woodward to congress to oppose its planned 1937 cannabis ban; he testified, prophetically, "There are potentialities in this drug that should not be shut off... [but rather] the medical profession and pharmacologists should develop the use of this drug as they see fit." Congress disregarded him.

When New York City mayor Fiorello LaGuardia (1882-1947) organized a committee of experts to study the city's alleged marijuana problem and what to do about it, their 1944 report concluded that marijuana had "low cost," was not "addictive in the medical sense of the word," "does not lead to morphine, heroin or cocaine addiction," "is not the dominating factor in major crimes," is not "associated with juvenile delinquency," and "the publicity concerning the catastrophic effects of marijuana smoking in New York City is unfounded." Anslinger denounced it and attempted to stop all future such research in the USA unless conducted under his direct control.

Anslinger's lifelong anti-cannabis campaign from one of the most powerful positions in the US government devastated cannabis research for 80 years, completely destroyed the USA's hemp fiber and hempseed industries, and (as we shall see) harmed millions. Ironically, Anslinger actually *was* an illegal drug dealer, supplying morphine to the powerful drug-addicted US Senator Joseph R. McCarthy (1908-1957) in an apparent effort to curry favor. And while Anslinger's claims that marijuana causes insanity had rather been contradicted by Clouston 1871 [who claimed co-administering "Indian hemp" cannabis and KBr seemed to *help* 41 out of 51 insane people], ironically Anslinger himself eventually was hospitalized for insanity.

DuPont, while in the US government simultaneously owned commercial interests likely to benefit enormously from criminalizing cannabis. In 2012 he described marijuana as "the most dangerous drug," parroting an earlier claim by US president Ronald Reagan. (The DuPont Chemical corp. was the world's largest manufacturer of nylon – used, like hemp, to make rope. Also, DuPont lobbied to mandate that *every* recipient of federal financial help, *and* all their children, and everybody suspected of driving while intoxicated, be chemically tested for cannabis use. Bensinger, DuPont & Associates would be ready to expand their commercial drug-testing outside the corporate world to help the government do that!) That quote contrasted with, e.g, Sir J.Russell Reynolds, MD, FRS (personal physician to Queen Victoria, and without any commercial conflict of interest) who wrote in the 1890 *Lancet* that marijuana was "one of the most valuable medicines we possess," based on his "more than thirty years' experience of the drug" (indeed, for "almost all painful maladies" it was "by far the most useful of drugs") while Riley D. Kirk, PhD, wrote in her 2025 book Reefer Wellness that "when cannabis is consumed at the right doses with intention and education, it is far safer and far more efficaceous than any other medicine." (How is it even *possible* for accredited MDs/PhDs to publish such absurdly contradictory claims?) DuPont's claim also contradicted the facts that marijuana's lethal/effective oral-dose ratio exceeds 40000 with *zero* clear cases of human overdose deaths.

> (The psychoactive effective oral dose of THC is 50-200 µg/kg in humans according to Mechoulam 1970; the oral LD50 for rat is 800-1900 mg/kg according to Thompson et al. 1973, but is higher in dogs and monkeys: enormous doses up to 3g/kg and 9g/kg were tried with zero fatalities in dogs and monkeys respectively. Thompson et al. 1974 then found that 25% of rhesus monkeys fed 500mg/kg of THC in oil daily for 1 month would die. But only 45 mg/kg/day for a month killed 50% if it instead was administered intravenously – a dosage mode not used in practice. CBD is 4× less toxic than THC: 212 mg/kg daily doses of intravenous CBD for 9 days kills 50% of rhesus monkeys according to Rosenkrantz et al. 1981.)

That zero contrasts with the following rough annual USA death counts from overdoses of these common drugs (all obtainable without prescription): acetaminophen 500, aspirin 6000, antihistamines 90, ethanol 2500 and the following rough lethal/effective dose ratios: ethanol=13, acetaminophen=43, aspirin=43, secobarbital=50, caffeine=120, morphine=310, Diphenhydramine hydrochloride ("Benadryl" antihistamine) 400. DuPont in his same 2012 piece also tried to make his readers believe cannabis causes **lung cancer**. That may have seemed plausible a priori (given that smoking tobacco has been well established to cause lung cancer) but in fact:

1. A 2008 study by Berthiller, Straif, et al of 430 lung cancer cases and 778 controls, all men from Tunisia, Morocco, or Algeria, found *all* those who had ever smoked cannabis were tobacco smokers (often smoked mixed) – making it rather hard to disentangle the two! They found that being a tobacco-but-never-cannabis smoker increased your lung cancer risk 10.9× versus nonsmokers (95% CI: 6-19.7), while the risk-ratio for smoking *both* instead was 18.2 (95% CI: 8-41). Note: this 10.9→18.2 increase was below the threshold for statistical significance (although their sample was large enough to easily detect the risk-increase from tobacco alone) but plausibly would have risen above threshold if their study had been 10× larger.
2. The study by Zhang et al 2015 based on a 5× larger sample – 2159 lung cancer patients and 2985 controls from USA, Canada, UK, and New Zealand (International Lung Cancer Consortium) – found "little evidence for an increased risk of lung cancer among habitual or long-term cannabis smokers" because they were unable to show, with any statistical significance, a risk-ratio>1 versus never-smoked.
3. The 2018 review by Ribeiro & Ind concluded (and another 2018 review by Jett et al agreed) "[The available] evidence [all of which they consider 'preliminary'] does not suggest association" between cannabis smoking and lung cancer.
4. The 2024 re-review by Khoj et al (which I have been unable to read) finally claimed to begin to see evidence for that association.

Why would smoking cannabis by itself increase lung cancer risk much less than tobacco (indeed so little it was statistically undetectable before 2020), *but* increase the carcinogenicity of tobacco? Such a contrast is, in fact, a *prediction*[*1] of our upcoming Hypothesis: tobacco smoking might be expected to cause a lack-of-EC chemical signal that something was dangerous in your lungs, inspiring "clean & protect" responses trying to mitigate such damage. By foolishly also dosing yourself with phytocannabinoids, the signal "everything is ok" would instead be transmitted, *preventing* such a "clean up" response, and therefore worsening the carcinogenic damage caused by tobacco. In particular, THC in marijuana is known to be a potent broncho-dilator, exactly why it is a useful drug for asthma (Tashkin et al 1975, Williams et al 1976, Hartley et al 1978).

DuPont's NIDA also controlled the tiny amount of USA cannabis medical research that somehow still was permitted to happen, and unfortunately used that control to further-bias the picture. An example was the case of Dr. Melanie Dreher. In the late 1960s, she was sent to Jamaica on a NIDA grant to find "amotivational syndrome" caused by marijauna. (But couldn't find it.) She then also did a study comparing 30 pregnant cannabis users versus 30 matched women who did not use cannabis. All 60 successfully gave birth then breast-fed their babies. Upon testing the children, no significant differences were found at 3 days of age, but at 30 days, the cannabis babies unexpectedly performed significantly *better* on the Brazelton neonatal scale! By 5 years of age, those differences had retreated to statistical invisibility to the McCarthy Scales of Children's Abilities. Dreher then was told her funding was finished "unless you can find something negative or something wrong with cannabis"! Can cannabis during pregnancy and/or breastfeeding actually improve babies? As we shall explain, the Hypothesis might predict[*2] the former, while the latter makes sense for this second simpler reason: anandamide is known to be secreted in mother's milk to "reward" babies for more suckling (Fride 2004a; Fride, Braun et al. 2007; Mechoulam, Berry, et al 2006).

After **Nixon** died in 1994, his close advisor, white house counsel John D. Erlichman (1925-1995), who had served 1.5 years in prison for his role in Nixon's "watergate" corruption (while Nixon avoided punishment due to a carefully negotiated deal between him and his VP Gerald R. Ford to grant him "a full, free and absolute pardon") gave an interview to journalist Dan Baum, in which Erlichman explained the real motivation behind **Nixon's "war on drugs"** (Baum 2016):

> You want to know what this really was all about? The Nixon campaign in 1968 and the Nixon White House after that had two enemies: The anti-war left and Black people. Do you understand what I'm saying? We knew we couldn't make it illegal to be either against the war or black. But by getting the public to associate the hippies with marijuana and Blacks with heroin, then criminalizing both heavily, we could disrupt those communities. We could arrest their leaders, raid their homes, break up their meetings, and vilify them night after night on the evening news. Did we know we were lying about the drugs? Of course we did.

Indeed, when Nixon organized the expert "Shafer Commission" to study the USA's marijuana problem and provide the underlying scientific justification and guidance needed for his "war on drugs," their 1972 report recommended *decriminalizing* marijuana! Nixon ignored all their recommendations.

You can't make all use and research on one of the historically most important agricultural crops and "one of the most valuable medicines we possess" illegal, spread and coerce enormous lies about it, officially declare it to have "no medical use," and nearly shut down medical research on one of the oldest and most prominent biochemical signaling systems in the human body for 70 years, without causing huge damage. To **assess that price**, consider the facts that

a. According to NIDA, **opioids** (both natural and synthetic) caused the deaths of about 83k US residents during 2022, while diazepines killed about 10k. In 2014 it was estimated that 2 million people in the US were addicted to opioids.
b. Tumati et al 2022 found that older Canadians, by using cannabis to relieve pain, often were able to **reduce their doses** of more dangerous painkillers: "35% (self) reported reduced dose of opioids, and 20% reduced dose of benzodiazepines." Nielsen et al 2017 quantified how much opioid dosages could be lowered by adding (the far less dangerous) THC, finding the median effective morphine dose could be reduced by a factor of 3.6, while for codeine the factor was 9.5. And Cooper et al 2018 found in a double-blinded placebo controlled study that "Cannabis enhances the analgesic effects of subthreshold oxycodone, suggesting synergy." This kind of synergy, with the two painkilling drug effects acting *multiplicatively*, makes perfect sense[+3] under our Hypothesis: marijuana reduces the *source* of the pain (EC shortage in painful body part) while opiates diminish the final *reception* of the pain (inside your brain).
c. Bachhuber, Saloner et al 2014 **compared** the US states with laws legalizing medical cannabis, versus the states where it was illegal. They found "States with medical cannabis had **24.8% lower** mean annual opioid overdose mortality rate (95% CI: -37.5% to -9.5%)."
d. Bradford 2016 estimated that medical marijauna would save the USA $165.2 million in medicare **costs** for other more-expensive drugs in the year 2013 – financially equivalent to saving perhaps 100 additional lives.

Given these facts, we see that if the USA had *not* demonized and criminalized cannabis, but rather correctly handled it, then it would have saved ≥20000 lives just in the year 2022 solely from this effect. (I consider it an **outrage** that opiates are not standardly used combined with cannabinoids; and that dosing methods for cannabinoids have not been developed for *local* rather than whole-body use.) Crudely multiplying by 50 produces the estimate that the 80-year marijuana blackout (for which Anslinger, DuPont, and Nixon bear primary responsibility) caused **≥1 million US deaths**. And those deaths were only part of the price:

e. According to the 8th edition of the World Prison Population List, the incarceration rate of the "land of the free" (USA) peaked in 2008 at 765 per 100k population (**2.3 million imprisoned**), above every other country in the world at that time (second place: Russia with 629). For comparison, in 2025 the *median*-incarceration-rate countries were Spain and Scotland with 113 and 112 per 100k. A big part of the reason was the "war on drugs": 43% of year-2025 US inmates got there for drug offenses; contrast that with the year 1940, when Anslinger's anti-marijuana campaign had only just gotten started, when the USA's incarceration rate was only 201/100k. Between 1985 and 2000 the USA arrested 31 million people on drug-related charges, approximately 10% of its population.

And, by design, the USA's treatment of drug offenses was very racist. According to the NAACP, "One out of every three Black boys born today can expect to be sentenced to prison, compared to 1 out of 6 Latino and 1 out of 17 white boys" and "African Americans and whites use drugs at similar rates, but the imprisonment rate of African Americans for drug charges is almost 6× that of whites." Wealth and power also mattered. A blatantly obvious example came with the *Rolling Stone* exposes Trump's White House Was 'Awash in Speed' – and Xanax handed out by White House physician Ronny L. Jackson (later a congressman and himself witnessed being drug-intoxicated; 3 Mar.2024 story by N.Schachtman & A.Suebsaeng; the white house drugs they mentioned were modafinil, alprazolam, and zolpidem, amounting to many thousands of pills, plus morphine, hydrocodone, diazepam, lorazepam, fentanyl, and ketamine) and Trump's White House Pharmacy Handed Out Drugs Like Candy (by N.C.Ramirez, 24 Jan.2024). None of these White House drug abusers and dealers were ever imprisoned or even prosecuted. And the sons of White House Chief of Staff James Baker and antidrug Congressman Dan Burton (who'd introduced a bill calling for the *death penalty* for drug dealers) magically got zero prison time for their drug convictions.

My personal history. I am a PhD mathematician, *not* an MD or biochemist – although I believe I know more about biochemistry and physiology than the vast majority of mathematicians. I invented the present paper's Hypothesis in 2013, perhaps aided (?) by mathematician-style logic or pattern-recognition skills not as greatly emphasized by biochemists or MDs, and also aided by my (highly serendipitous) co-discovery of a very large curative effect of marijuana oil-extract for a substantial subset of achalasia patients. Biology and medicine are, and should be, almost wholy experimental/observational; they cannot be as theoretical a science as physics and math. That adds extra importance to the comparatively rare cases where an overarching/guiding theory can and does enter the picture. This is one. I had written a first draft of this paper by 2015. I circulated it to a number of cannabinoid experts. R.Mechoulam encouraged me. Attempts to find an MD collaborator failed; US criminal laws and extra-horrendous bureaucracy surrounding marijuana were probably a goodly part of the reason. The need to overcome my lack of high-level training, combined with my inability to find a collaborator who had it and access to patients, and/or laziness, delayed the final version of the paper until 2025. The explosion of research papers about cannabinoid medicine (related to legalizations) during 2010-2025 was very helpful; originally I'd had to rely to a much greater extent on "underground science." (Although, frankly, during 1955-1990 the "official" science/medical community mainly played the role of "cowardly liars" about cannabinoids and were vastly outperformed by "underground scientists" and amateurs.) An invitation from the journal *Physiologia* encouraged my final effort.

3. The Hypothesis

A lot of computer software has "error conditions." It's a big issue in computer language design and use. And consider NASA spaceprobes like New Horizons, as the closest

technological analogue at present to autonomous life. ("Autonomous" because it takes many hours for signals to reach Earth, so the probe has to make decisions on its own; it would be too late if it waited for Earth controllers.) Such probes are nowadays engineered with "safe mode" aka "panic mode." It works like this: the software continually checks status – "is everything ok?" Sanity checks of all kinds are performed. If has imperfect notions of when things are screwed up. It is too dumb to understand why and wherefore, it just gets a notion that "things are screwed up, and that could be dangerous." Whereupon it switches the probe into panic mode. Which is: *stop* doing everything you are doing that could possibly get us into trouble. Just shut all that down, and concentrate on just saving power and making sure the radio dish is pointed at Earth. Transmit data to Earth and hope they can figure out what is wrong and then download instructions to fix it.

This "safe mode" is believed to have saved many space missions. But it also can be harmful. For example New Horizons panicked just a few days before its 2015 Pluto flyby, which if it had happened *during* the flyby would have been very harmful to mission success!

So my hypothesis is this also happens inside live animals. Because it is highly beneficial for animals, not just NASA spaceprobes – and for the same reason. Cells in parts of your body keep doing some sort of sanity checking, and reporting, *by emitting* cannabinoids, that "everything is ok. Status ok." (Actually, the common computer-programmer jargon "sanity checking" might more accurately in a biochemical context be called a check of "correct functionality" or "health.")

> Nevertheless, despite this system *helpfully increasing* survival chances, it is not *essential* – as evidenced by the historical fact that many spaceprobes managed to accomplish their missions before the "safe mode" concept.

And if they stop emitting EC (and note: it had to be this sign: stopping=*ab*normal, which is another fact that supports our Hypothesis)[+4] that means "PANIC! Something dangerous may have gone wrong with this body part." And if enough of that signal happens, then your body decides to switch that part into "safe mode," which in the case of the upper digestive system means "vomit, stop trying to digest, and stop performing normal peristalsis."

Which could easily save an animal's life.

4. Predictions derived from the Hypothesis; confrontation with Evidence (simple look)

Q. Why cannabinoid chemicals? And how did this all evolve?

A. It did not greatly matter originally what the chemical was. *Any* chemical "C" that is pretty uniquely identifiable by receptors, and is complicated and peculiar enough so that it would not arise by chance contamination, and which has about the right decay rate, and which is fat-soluble, would have been suitable for the proposed normalcy-reporting mechanism. If complicated to biosynthesize and export outside the cell, then so much the better, because then there would be more ways its synthesis and export could fail, which would automatically cause non-synthesis and/or non-exportation to be a more-sensitive detector of abnormality.

So it would have been very easy for this mechanism to arise originally. For some other reasons, something's cells were making and exporting chemical C. Then automatically the existence of C signified normalcy. It then became beneficial to develop ability to sense C and hence sense normalcy/not and hence be able to do something about it. Once that system was well established, finally, it became beneficial to refine the system via additional receptors (CB1 is more used by neurons and CB2 by immune cells), fine-tuning the degradation rates and endocannabinoid mobilities, and adding additional endocannabinoid molecules. Note the human CB1 and the CB2 receptors possess approximately 44% amino acid similarity, indicating they were originally one and later in evolutionary time split into two types, compatibly[+5] with our Hypothesis. Presumably originally there was only one receptor and only one endocannabinoid.

Warning re confusion-inducing sign issue: The cells in people who are heavy marijuana abusers for a long time, not surprisingly *adapt* by reducing their numbers of CB1 and CB2 receptors. Hence if that person then stops dosing himself with marijuana, his cells will *perceive* the situation as "cannabinoid levels appear to be low" (even though, really, the levels would be normal). Our Hypothesis therefore, would predict that many such people by *stopping* marijuana abuse, would feel "withdrawal" symptoms. This prediction is correct (Livne et al 2019)[+6]. But this poses a problem for us as judges: the symptom of taking *too much* marijuana can in this way actually be equivalent to the symptoms of having *too low* endocannabinoid levels. Opposite sign! We need to be *careful* to distinguish "real" effects caused by a one-time marijuana dose, versus the adaption countereffects from longer term heavy marijuana abuse.

Another remark on cannabinoid evidence generally. Due to legal and fear-related idiocy, cannabinoid research was horribly impeded and snarled for about 60 years, causing a near blackout in the scientific literature about medical marijuana. On the other hand, there (a) has been something of a renaissance due to the discovery of the endocannabinoid system, and (b) partial legalization and (c) due to the high popularity of marijuana as a recreational drug, many observed facts are available both collected by "underground scientists" and as anecdotal evidence. We shall try to employ only the most-accepted among the latter.

Keep those warnings in mind; we now return to our main exposition.

Q. Why did chemical C have to be fat- but not water-soluble?

A. Because if it had high water-solubility, it would be too mobile. The Hypothesized purpose is an abnormality detector for *specific body parts*. If C quickly migrated all over your body, it would be useless for that purpose. Actually, presumably even better than "fat soluble" is a chemical which prefers lipid-water *interfaces* by having both lipophilic and hydrophilic groups, but not enough of the latter to be too water-soluble. Even better still, keep it bound much of the time to certain specialized "fatty acid binding proteins" (FABPs). That presumably would make it even less mobile. This prediction is *confirmed* by reality for the first five[+7+8+9+10+11] known endocannabinoids, plus see Elmer, Kaczocha et al 2015 about[+12] FABPs.

Also, the Hypothesis would predict the cannabinoids are *not* stored, e.g. in vesicles, but rather continually synthesized without storage. (The Purpose is to detect abnormality *now*, not problems that happened some time in the past when the storage happened.) This prediction presently appears[+13] correct. (E.g. Senst & Bains 2014: "These lipid-derived molecules are thought to be recruited in an 'on-demand' fashion" citing Piomelli 2003; "unlike other synaptic messengers such as the neurotransmitters acetylcholine and dopamine, endocannabinoids are not presynthesized and stored in vesicles but are produced 'on demand' according to Cabral & Griffin-Thomas 2009.)

Q. Why must chemical C decay at the "right" rate? (Which is what?)

A. To be best for its Hypothesized purpose, the decay timescale should be comparable to or less than the minimum among the synthesis and mobility timescales. This prediction apparently has never been tested by actually measuring the decay and mobility times of endocannabinoids in vivo. But it would be possible to do so using isotope labeling techniques, and various related timescales have been measured (discussion soon).

Incidentally, the endocannabinoid system (our Hypothesis hereby proclaims) is intended to detect "error states" which act at those timescales, i.e. the same timescales as typical biochemical processes. It is *not* suitable for, say, processes like being burned, which can happen in under 1 second and which therefore demand an equally rapid corrective response (e.g. reflexively yanking your hand away from hot object). Such fast detection and responses need to be engineered using neurons and muscles, *not* the slower cannabinoid synthesis-export-detect-respond system. It is, however, a difficult engineering problem for evolution to solve, to handle all potential problems in the same way as the burn reflex. That would require developing a very large number of neuronal detectors for different possible problems. It is a much simpler engineering problem for evolution, if *any* kind of cell (neuron or not) can serve as an "abnormality detector" and then only one or a few kinds of neurons are needed to read the standardized endocannabinoid status-signal indication "normal/abnormal."

Indeed, we can argue that a purely neuronal solution for everything would not merely have been a "difficult" engineering problem, but actually "*impossible*." Because animals need to detect abnormalities happening inside *non*-neuronal cells (e.g. if those cell types get infected by a virus, or poisoned). That inherently would not be possible if neurons were to be the sole detectors of abnomality. It only is possible if the cells themselves emit a "status ok" signal, and this signal needs to be a chemical since by definition there is no other option for non-neuron cells.

Note from figure 1 that indeed all the endocannabinoids are fairly complicated and unusual molecules, and indeed are detected by CB1 and/or CB2, agreeing[+14+15+16+17+18] with the prediction.

The first endocannabinoid discovered, anandamide, was noted by R.Mechoulam (the leader of the discovery team) and E.Fride, to be "labile," meaning chemically unstable. (Perhaps better words would be "short-lived" or "ephemeral.") E.g., in the presence of water, it hydrolyzes into arachidonic acid and ethanolamine. Even in ethanol instead, they observed that anandamide in a jar at room temperature will decay on a timescale of several days. (It could, however, be preserved for at least a few months via refrigeration to

-20°C.) But in vivo one would expect the lifetime of anandamide to be much shorter than in water in a jar, because of the ubiquitous presence of the degradation-catalyzing enzyme FAAH. Deutsch & Chin 1993, who discovered FAAH, noted it was present in "the brain and the majority of cells and tissues tested" and that anandamide would not accumulate in cell cultures because it was continually degraded by amidase residing mainly on cell membranes. Deutsch & Makrivannis 1997 found that in ground up tissue, degradation of anandamide proceeded at such a rate that after 1 hour, only 1% of the anandamide remained (judged by radioactive labeling methods); this corresponds to a "halflife" in pseudo-vivo of about **9 minutes.**

The next endocannabinoid to be discovered was 2-AG. It also is labile, according to Savinainen et al 2003, and in vivo its decay again is expected to be far more rapid than in a jar because it not only is degraded by FAAH at a comparable rate to anandamide, but also is degraded by MAGL. Goparaju et al 1998 found 2-AG is degraded "about 4-fold faster than anandamide" in pseudo-vivo, which would suggest its halflife is only **2 minutes** in vivo.

It also has been claimed in print, but those claimers did not cite any specific evidence, that *all* endocannabinoids "are short-lived" (Martin A. Lee) and they all are "highly labile yet ubiquitous in the brain" (Senst & Bains 2014)[+19].

Another point[+20]. is this: Neurons usually transmit information (to other neurons, or muscles) in one "forward" direction, i.e. from the cell-body toward and along the axon. When cannabinoids stimulate CB1 in neurons, that is the only known way to make neurons also transmit information "retrograde" (Ohno-Shosaku & Kano 2014; Dudok, Fan, Farrell, Malhotra, et al 2024). Which is exactly the behavior the Hypothesis would predict would often be useful for "doing something" about a problem with a body part!

With that explained, we now are ready to present a short summary of the predictions derived from our Hypothesis. Namely: The Hypothesis predicts that cannabinoids ought to suppress (since *lack* of endocannabinoids ought to cause) all of the following:

General-purpose responses for *general* body parts (or whole body) to perceived abnormal problems (that are normally not invoked in the absence of those problems). I have not included a "sleep & fatigue" line in the table because those phenomena do not satisfy my "normally not invoked" demand. Nevertheless, sleep and fatigue (or their absence) might well be useful responses to evidence that something is wrong with your body, and hence also would be predicted to be affected by marijuana.

#	Response (to lack of EC)	Its utility	Downside(s) if that response was a mistake
1	Pain	Inspires useful behavior changes relevant to painful body part	uselessly annoying
2	Itch ("pruritus")	Inspires useful behavior changes relevant to itching body part	uselessly annoying
3	Inflammation	Overall useful, but...	"Allergic reactions." Inflammation sometimes causes rather than solves problems.
4	Immune responses	Overall useful, but...	"Autoimmune diseases," e.g. Myasthenia gravis, Fibromyalgia, septic shock, multiple sclerosis, Diabetes Mellitus type I, Lupus, rheumatoid arthritis.
5	Muscle movements	Useful & necessary for preventing, e.g, "bedsores," a life-threatening condition	tics, spasms, spasticity, epilepsy, tremors, restless leg syndrome
6	Fever	Overall useful general response to infection, but...	Can be dangerous if mistaken or gets too hot
7	Increased blood pressure	Useful for supplying more blood, hence nutrients, oxygen, immune cells, to repair/fight damage but...	risks stroke
8	Anxiety, Depression, Stress, Sleeplessness	Mood/mind/behavior changes hopefully inspiring brain to think of ideas useful for solving your problem (although actually it is not obvious a priori which sign effect is desirable for "depression")	Uselessly annoying and in severe depression cases even life-threatening

General-purpose responses for *specific* body parts to perceived abnormal problems.

#	Body part	Response (to lack of EC)	Its utility	Downside if response mistaken
9	Upper digestive system	Vomiting, non-peristalsis, loss of appetite	Can save life if ingest poison	Problematic; anorexia, achalasia
10	Lower digestive system	Diarrhea, "irritable colon," Crohn	Could save life if intestinal blockage, infection, parasites	Problematic
11	Uterus	(If pregnant) spontaneous abortion aka "miscarriage"	Can save mother's life, increase Darwinian fitness (especially if baby was doomed anyhow)	obviously Darwinianly bad
12	Lungs, bronchi	Shallow/restricted breathing, reduce diameter	Could save life if infection, polluted air	Asthma
13	Brain	*Remember* stress/problem times better than usual times; pay more *attention*; activate microglial "cleaning" cells	More likely to be Darwinianly helpful	?

Re the importance of these effects, consider the top five reasons people say they took "medical marijuana" according to the survey by Boehnke et al 2019 (in descending order):

a. **pain**
b. **spasticity** in multiple sclerosis
c. **nausea & vomiting** from chemotherapy
d. post traumatic stress syndrome / **anxiety**
e. relief of cancer symptoms.

The similar descending list found by the independent Australian survey by Swift, Gates, Dillon 2005: chronic pain, depression, arthritis (presumably pain?), nausea, weight loss, insomnia.

Summary. We'll look into this in more detail later, but for now, suffice it to say that ***every* prediction** in the above two tables – with the possible exception of row #11 (uterus) for which the evidence is less convincing(*) – is **correct**: cannabinoids *do* produce an effect, and every time with the predicted *sign*. We'll soon back that up with literature citations.

> *** Asterisk:** In principle one could compare endocannabinoid concentrations in placentas from spontaneous versus elective surgical abortions to answer this question; but in practice that might not be feasible due to the short in vivo lifetimes of endocannabinoids. And indeed Trabucco et al 2009 found twice as much NAPE-PLD mRNA expression, less CB1, and less FAAH in first trimester elective abortion placentas versus ones from spontaneous miscarriage. The first one, and perhaps two, of those findings seem compatible with my Hypothesis, but not the third. Maccarrone, Valensise, et al 2000 found in humans that the likelihood of miscarriage increases if uterine anandamide levels are either too high or low. The latter finding seems compatible with my Hypothesis, and perhaps the former might be explicable as a adaption effect. Also recall Dreher's findings; those make sense if we suppose that a mother should (Darwinianly) be less-willing to invest resources in a fetus that, based on low ECs, she is likely to miscarry anyhow – or that, even if successfully born, is likely to be too unhealthy to survive to adulthood. If so, improved babies should result (within the subset of pregnancies that were always going to result in successful births), when mothers artificially dose themselves with cannabis. But that improvement might come at extra cost and risk to the mother, and would also incur the risk that cannabis chemicals would interfere with fetal development, leading to the opposite of "improved" children and the birthing of babies that normally would have been spontaneously aborted.

Even if we (to be conservative) ignore the *production* of an effect, and focus only on its *sign* (and even if we ignore the uterus line as attached to insufficient evidence), that is 12 sign-predictions in those two tables, every one correct, i.e. equivalent to tossing a coin 12 times, miraculously getting "heads" every time. In other words, yielding **confidence≥1-2^{-12}>99.97%** (versus the null hypothesis) that the Hypothesis is correct. (If we also took into account that they produce an effect versus not, then we might want to increase that to 1-3^{-12}>99.9998%, but in the interests of being conservative, I have not done that. Also, note that most of the table rows are supported by not not just one, but rather several independent-seeming kinds of evidence, a fact we again have not used, again meaning my confidence numbers should be very conservative.) Put those 12 together with the other 20 items of "+" evidence (all pro-hypothesis) that we've already enumerated That suggests we should boost that claim to **1-2^{-32}>99.99999997% confidence** even if, to be conservative, we ignore all "*" lower-quality evidence. Even if we pessimistically forecast that the uterus evidence somehow will come out 100% against us (one "-") – which it won't – then that still is like tossing 32 coins and getting 31 heads – still **>99.9999992% confidence**-level astonishing.

Literature citations relevant to table rows 1-13:

1. Reinarman et al 2011. Tumati et al 2022. Bachhuber, Saloner et al 2014. Cooper et al. 2018. Nielsen et al. 2017. Boehnke et al 2019. Swift, Gates, Dillon 2005. Urits, Charipova, et al. 2021. Ware et al. 2010. Nurmikko et al. 2007.
2. Shao, Stewart, Grant-Kels 2021.
3. Ashton 2007. Burstein 2015. Cabral & Rogers 2015. Cabral & Griffin-Thomas 2009. Gaffal et al. 2013. Karmaus, Chen, et al. 2011. Karmaus, Wagner, et al. 2013. McCoy 2016.
4. Friedman, Newton, Klein 2003. Habib & Avisar 2018. Giorgi et al 2020 and 2021. Paolicelli et al 2016. Da Silva, Christianetti, et al 2024. Rodriguez Mesa et al. 2021. Anson 2014. And (as a typical example of "underground amateur science") Walker 2014.
5. Koppel 2015. Eapen et al 2025. Filippini, Minozzi et al 2022. Lattanzi, Trinka et al 2021 (and literature they review). Ghorayeb 2021. Urbi et al 2022. Reynolds 1890. Boehnke et al 2019. Muller-Vahl et al. 2002, 2003. Studies reviewed in §3.4 of Ben Amar 2006. The THC+CBD drug "Sativex" is approved for treating MS spasticity in Canada, UK, Spain, Czech Republic, Germany, and Poland. Bilbao & Spanagel 2022 also find CBD has a significant beneficial effect on Parkinsonianism.
6. Kosersky, Dewey, Harris 1973. Porter et al 2002. Ross 2003. Hsiao et al 2015. Andres, Passaglia, et al. 2025.
7. Vernail, Bingaman, et al. 2022.
8. L.Wang et al 2011. Murillo-Rodriguez et al 2011. Bergamaschi et al 2011. Davis, Pedersen, Tucker 2023. Neumeister, Normandin, et al. 2013. Boehnke et al 2019. Swift, Gates, Dillon 2005.
9. Doblin & Kleiman 1991. Smith & AW 2010 (finding confirmed by P.C.Frye). McLaughlin, Winston et al 2005 for a CB1 antagonist. Goyal, Singla, et al. 2017. Rogers & Pacanowski 2023. Boehnke et al 2019. Swift, Gates, Dillon 2005. Jones & Kirkham 2012. THC ("Marinol") has been approved for treating chemotherapy-related nausea/ vomiting by the United States FDA.
10. Choi, Abougergi et al. 2022. Desai, Mbachi, et al. 2020. Camilleri & Zheng 2023. Naftali, Mechulam, et al 2014.
11. Wang, Xie, Dey 2012 found that EC-underreception induced preterm birth in mice; Feduniw, Krupa, et al 2024 in humans.
12. Tashkin et al 1975. Williams, Hartley, Graham 1976. Hartley et al 1978. Lewandowska, Rybacki, et al. 2025.
13. Urits, Charipova, et al. 2021. Hidalgo, Vazquez-Martinez, et al. 2022. Palmisano, Ramunno, et al. 2024. Pintori et al. 2021 (for CB1 *ant*agonist JWH-018).

5. More detailed/complicated look at the evidence (and those citations)

The core of this paper is now complete, and I think the reader should already be highly convinced of the Hypothesis. The remainder of this paper will more-randomly explore the Hypothesis and related phenomena either hopefully more clearly, or more deeply in a less-simple and sometimes speculative way, sometimes looking at biochemical mechanisms, and will find exceptions and complications. This kind of exploration could continue almost indefinitely and I had to force myself to stop and substantially cut back in order to complete the paper in finite time. Our (+,-,*) evidence superscript **counters** (current values: +20, *2, -0 not including all the evidence in those tables) will now be **restarted** at 0.

Q. What body parts should be affected?

A. The three most complicated and mysterious systems in the human body, which can get into an enormous number of possibly bad and dangerous states in ways that can threaten your life – but which can hope to try to fix the problem by intentionally changing their state in response – are the brain, immune, and digestive systems. (By comparison, the heart is simple, it just pumps. Even the liver is "simple" in the sense its cells are thought to work largely independently of each other, and the liver has little "choice" about what it does.) These are *precisely*$^{+1+2+3}$ the three systems which seem to exhibit the most cannabinoid activity.

Q. How should the **digestive system** be affected?

The "normal" state of digestive system is: if there is food inside, then transport (via peristalsis) and digest it. If there isn't, then do nothing – but if the system regards itself as in good working order then that should help stimulate the life-form to seek more food. If, however, you ate something poisonous or risky, it would be best to detect that and trigger "safe mode" or "panic mode" – which is "stop digesting and start vomiting." The trouble is, there are an effectively infinite number of possible poisons. It is not feasible to develop special chemical detectors for them all, nor even for any substantial fraction. Instead, the Hypothesis is that the very *fact* that you are being poisoned, is detected, because poisoned dead/ dying/hurt cells are no longer able to synthesize and export endocannabinoids as though the situation were normal. This lack of endocannabinoids triggers safe mode.

Now, it is a well known fact (which indeed was the topmost original impetus for the "legalize medical marijuana" movement) that

A. Cancer chemotherapy drugs, although there are many varieties, almost all are poisons which are more-poisonous for fast-growing cells (such as cancer, hair, and digestive cells) than for slow-growing cells.
B. Chemotherapy usually induces nausea and loss of appetite.
C. Marijuana reduces nausea and restores/creates appetite. (Doblin & Kleiman's 1991 Harvard survey of 2430 US oncologists got a response rate of 43% and found that 44% of the respondents had recommended marijuana to their cancer patients for this purpose *despite* its illegality in all 50 US states!)

These three facts all agree^{+4+5+6} with the Prediction. It also is the case that many commonly-encountered "spoiled foods" containing dangerous toxins and/or bacteria – as well as eating certain artificial chemicals – cause Nausea^{+7}. And that marijuana oil extract cures a subset of achalasia patients by restoring^{+8} normal peristalsis (Smith & AW 2010). The Hypothesis predicts that there ought to be at least three types of achalasia (indeed three types of virtually *any* cannabinoid-related syndrome), only one of which would be cured by marijuana:

a. The cannabinoid is not synthesized by your body, or no longer transmitted to esophageal neurons,
b. it is no longer received,
c. it is received but whatever the reception is supposed to make happen, does not.

My point is that a,b,c constitute three possible underlying causes for achalasia. If they are genuine, then type-a would be expected to be cured by marijuana, while types b,c would be expected *not* to be thus-cured. This prediction is correct – there *are* at least 3 types of achalasia, identified by Pandolfino et al 2008, which Rohof, Salvador et al 2013 then confirmed respond differently to treatments. (And Smith & AW 2010 confirms that only *some* achalasics are cured by marijuana oil; others appear unaffected.) Their classification into 3 types was based on "3 distinct patterns of aperistalsis are discernable with high-resolution manometry (HRM)":

I. achalasia with minimal esophageal pressurization (21%)
II. achalasia with esophageal compression (49%; this is the type most amenable to treatments)
III. achalasia with spasm (29%; the least treatable type)

I have not, however, seen any study directly measuring endocannabinoid levels in the digestive system and how they change when one eats the "right" or "wrong" substances, or is exposed to chemotherapy drugs. Such a study should be feasible in lab animals.

The Cannabinoid CB1 receptor antagonist "AM 251" induces food avoidance and behaviors associated with nausea^{+9} in rats (McLaughlin, Winston et al 2005; see also the drug candidate "resunab" formerly being trialed).

Another possibly-useful panic response to digestive abnormality is: diarrhea. Therefore, our Hypothesis would predict that low endocannabinoids can cause diarrhea, while marijuana can alleviate it. At least some subset of "Crohn's disease" and "inflammatory bowel disease" cases indeed *are* alleviated by marijuana^{+10} (Naftali et al 2014).

Now suppose you are **pregnant**. The fetus is known to be considerably more sensitive to environmental chemicals than the mother. For example, thalidomide is a famous teratogen disrupting fetal development and causing severe birth defects. But it is harmless to the mother. Many plants contain substances toxic to many animals (for example avocados are toxic to cats and dogs) and it's chemical warfare out there. Therefore, it is, evolutionarily speaking, a good idea to *alter the threshold* signifying "abnormal" digestive-system state, so that pregnant women are more likely to vomit than nonpregnant people. (Prediction confirmed: "morning sickness.") We now deduce the subsequent predictions that

A. Marijuana should alleviate morning sickness. (I'm unaware of any scientific study of this, and indeed think it would be unethical to do one on humans, but^{+11} googling this question instantly yields many pages of "hits" offering anecdotal evidence that "yes, prediction confirmed.")
B. Consuming Marijuana during pregnancy should, however, increase the rate of birth defects (i.e. noticeable deviations from mean) in the children. And there indeed have been claims of this: Cannabis – yet another teratogen? was an unsigned 1-page article on p.797 of British Medical J. 1,5647 (Mar.1969) based on experiments by Persaud & Ellington 1968 giving female rats 6 intraperitoneal injections of, in total, about 4.5mg cannabis resin early in their pregnancies (this caused a large number of fetal defects versus control rats who got saline injections); and van Gelder et al 2014 based on "correcting for under-reporting of cannabis use." Irner 2012 reported "an association with

deficits in language, attention, areas of cognitive performance and delinquent behavior in adolescence" in humans exposed in utero to cannabis. The 2011 review of rodent studies by Campolongo et al. said there was "... increasing evidence from animal studies showing that cannabinoid drugs ... induce enduring neurobehavioral abnormalities in the exposed offspring." If those claims are valid they confirm[*1] the Hypothesis, although this could have been the direct result simply of teratogens possibly being present in marijuana, rather than the indirect result of our Hypothesis; and reviews by Sujan et al 2023 and Thompson et al 2019 both call for more research because what is presently known is inadequate. The Sujan review, however, idiotically "excluded animal studies [because our] focus is strictly on human outcomes." Because birth defects are rare, and people willing to participate in cannabis/pregnancy studies also rare and likely to be a biased misreported sample, and many such studies would be unethical, it is very difficult to study this in humans.

C. Pregnancy-related hormones must interact with endocannabinoid receptor, degradation, and/or synthesis to cause (A). Furthermore, by the same reasoning, sex hormones and developmental hormones should also interact with these things. (E.g. you are more likely to get pregnant if you are a woman rather than a man or child. You may be more sensitive to food poisons at some rather than other life/developmental stages. Therefore these things should act to *alter* "abnormality thresholds" for your digestive system.) In particular presumably the most sensitive life-stage is babyhood, which would therefore be predicted to be the one with the most[+12] vomiting. Also, endocannabinoid levels would be predicted to vary according to menstrual cycle phase – which indeed happens[+13] (El-Talatini, Taylor, Konje 2009 & 2010).

The predictions in (C) are, in fact, known to be correct in many cases[+14+15] (e.g. Winsauer et al 2012 & 2015).

Q. How should **neurons** be affected?

A. Well, neurons could trigger pretty much any behavior, and presumably it will be a behavior corresponding to "safe mode" aka "panic mode" for that body part (if such a behavior has an identifiable meaning). But in the absence of any special-purpose response, a *general* purpose useful response predicted by the Hypothesis would be generating *pain*. If some body part is detected by your cannabinoid system to be sick/wrong, then have neurons generate pain in/near that body part, and hope the animal will then treat that body part with extra care, or think of something useful to do about it.

And sure enough, surveys of medical marijuana users have found[+16] that the most frequent application they try to use it for, is to alleviate chronic pain, for example back pain or arthritis pain. This also has been supported by randomized controlled trials (Ware et al 2010, Nurmikko et al 2007). Also marijuana has been found by some sufferers to be a highly effective cure/preventative[+17] for migraine headaches (Reynolds 1890; Osler & McCrae 1915; Russo 1998; Fishbein 1942; the review by Okusanya et al 2022 claimed "Medical cannabis... was 51% more effective in reducing migraines than non-cannabis products.")

Another interesting phenomenon which I speculate perhaps sometimes is caused by endocannabinoids is "radiated" pain (also called, or related phenomena called, "referred" or "reflected") pain: patients perceive pain in locations different from damaged areas. The most famous example is heart attack victims who feel pain in their neck, shoulders, back, jaw, and/or arm. This could be caused by neuron "crosstalk." But that fails to explain why there can be a *delay* between the pain stimulation and the perception of referred pain. If the two locations are nearby, it perhaps could be caused by the *migration* of endocannabinoids (or other chemicals). Note: if ever there were a body part you'd think would cause especially high chemical migration, the heart would be it.

Also, it is highly useful (under our Hypothesis) for neurons receiving EC signals to be able to transmit information *retrograde*. That indeed happens (Ohno-Shosaku & Kano 2014, Dudok, Fan, Farrell, Malhotra, et al 2024)[+18].

Q. How should the **brain** be affected?

A. First of all, if there are high levels of (endo)cannabinoids, that is predicted to make you feel *happy*[+19], plus generally not inclined to do anything that changes your situation (lassitude)[+20]. Why? Because when your endocannabinoid system is detecting that status is ok and everything is fine, that means a good move for you, is to keep things that way, and strive to reattain this state in future (i.e. "happiness").

Of course, those predictions *are* well known to generally be true, which is why marijuana is a popular recreational drug.

Conversely, the Hypothesis would predict that low brain endocannabinoid levels should produce *anxiety* and repress *sleep*, hopefully stimulating you to try to do something unusual that might fix the problem. Sure enough, surveys of medical marijuana users find the second most popular use of marijuana self-medications is to diminish anxiety[+21] and cure sleep problems[+22] and this is supported by randomized controlled double-blind studies (L.Wang et al 2011, Murillo-Rodriguez et al 2011, Bergamaschi et al 2011, etc).

Second, another good general purpose brain "panic mode" response is to "activate microglial cells." Microglial cells are believed to act as the brain's "clean-up brigade," that tries to clean up and remove intercellular debris. That could include Alzheimer's disease "amyloid plaques." Attempts to grow neurons in vitro fail (i.e, they die) unless accompanied by glial cells as "helpers." Anyhow, this Prediction is correct: cannabinoids indeed suppress, and their lack (or dosing you with CB-receptor antagonists) stimulates, glial cell activity[+23] (Palmisano, Ramunno, et al. 2024; Pintori et al. 2021).

Suppose we now return to the "marijuana⇒insanity hypothesis" (MIH; this is a much weaker version of what H.J.Anslinger throughout his life falsely propagandized to be a "proven fact"): long term heavy marijuana abuse increases your chance of eventually becoming insane. Anslinger's "scientific" method consisted of falsifying and cherrypicking evidence, while ignoring all evidence contrary to whatever he wanted. Nevertheless, Anslinger 1943 did succeed in digging up 12 authorities during 1838-1937 who supported this hypothesis, many of them based on observations in the countries of India and Tunisia, where at that time marijuana use was both legal and very common to a degree unparalleled anywhere else. Because India criminalized marijuana in 1985 and Tunisia in 1992, no comparable observations are possible today.

Anyhow, *my* Hypothesis would ***predict* the marijuana⇒insanity sub-hypothesis**. Why? Because if you continually flood your brain with exogenous phytocannabinoids, then it *always* is getting the "everything is ok" signal, causing your glial cells to lack *guidance* in their (known to be essential) repair and clean-up activities. The situation is analogous to: if the British during World War II, had switched off their radar. Quite probably, if they had done so, their air defenses would have been less effective, so much that they probably would have lost the war. Similarly, without guidance, your glial cells will perform their defensive duties less effectively, causing them to less-effectively repair continually occurring brain damage, which over many years should be expected to increase your chances of eventually becoming insane.

Is the MIH prediction correct? The reviews by Sorkhou, Dent, George 2024, West & Sharif 2023, Murrie, Lappin, Large, Sara 2020, Gage, Hickman, Zammit 2016, and Ortiz-Medina et al 2018 all are in favor[+24] of "yes," with the lattermost estimating marijuana abuse "doubles the risk of developing psychosis in vulnerable people."

Furthermore, for approximately the same "removed guidance" reason (except now *not* restricted to inside the brain) I would predict that heavy long-term marijuana abusers should have **shorter life-expectancy**. Two attempts by S.Sidney et al in 1997 using ≈65000 Kaiser Permanente patients whose lifetime marijuana use was self-assessed by questionaire, were unable to find statistically significant connections between marijuana consumption and either mortality or cancer. Nevertheless I would guess this prediction probably is valid[+25] given that

- Jeffers et al 2024 finds that "Cannabis use is associated with adverse cardiovascular outcomes, with heavier use (more days per month) associated with higher odds of adverse outcomes."
- Gallagher et al 2024 found that heavy cannabis users had a higher risk of any head or neck cancer (risk ratio 3.49; 95% CI 2.78-4.39).
- In most years, cancer and "adverse cardiovascular outcomes" are the top two causes of death.

Low cannabinoid levels have been correlated with improving *memory* (and marijuana use reduces memory performance)[+26] which makes sense under our Hypothesis – it is worthwhile to remember more about a time when some part of your body was in danger. Similarly, at those times it is useful to be more *attentive* – and marijuana use reduces attentiveness[+27].

Furthermore, CBD is claimed to have a beneficial effect reducing the frequency of epileptic seizures with otherwise drug-resistant forms of epilepsy e.g. Lennox-Gastaut syndrome, and "Dravet's syndrome" in children. Press et al 2015 found 33% of patients found seizure counts reduced by over 50% by using oral cannabis extract, with an additional 24% reporting some improvement. The European Medical Agency, United States FDA, and Australia all approved "Epidiolex," a cannabidiol extract by the British company GW Pharmaceuticals, for its treatment.

Let me make a speculation about that. Electroshock therapy can be highly effective for certain people with certain mental disorders, and is guessed to act on your brain similarly to rebooting a computer. So suppose epileptic seizures – or something less dramatic but resembling them, perhaps intended to be restricted to certain malfunctioning subregions of the

brain – actually have an evolutionary *purpose* as a kind of self-administered electroshock therapy intended to try to escape your brain (or some component of it) from some kind of state-space trap. (Of course, that also could be the opposite of helpful.) If so, then the best time to trigger that sort of response, would be if and when brain abnormality is somehow *detected*, by means of the usual signal – low endocannabinoid levels. This would predict that cannabinoid drugs would sometimes be able to reduce epileptic seizures. And this prediction is confirmed[+28] by reality.

Multiple Sclerosis patients are helped by cannabis (significant reduction of spasticity, overactive bladder, and incontinence in all of several randomized placebo-controlled double-blind studies of marijuana chemicals as oral drugs, reviewed in §3.4 of Ben Amar 2006; the THC+CBD drug "Sativex" is approved for treating MS spasticity in Canada, UK, Spain, Czech Republic, Germany, and Poland). Tourette's syndrome patients in two randomized, double-blind studies (Muller-Vahl et al. 2002, 2003), were found in both to have their tics reduced by use of oral THC versus placebo.

That makes sense under the view that muscle movements like "tics" and "spasticity" are a useful response to signals something is wrong with body parts (e.g. muscle movements prevent "bedsores," a life-threatening condition)[+29]. Also, this could also be the explanation for the "marijuana cures epilepsy" observations, if "epilepsy" and "tics" are different aspects of the same phenomenon.

Q. How should the **immune system** be affected?

A. If your endocannabinoid system is detecting that you (or some body part) is sick/abnormal, that can mean that an immune response is desirable.

Immediate prediction: marijuana should alleviate allergies. (Because: allergies are the result of your immune system over-responding to unfounded worries that something is bad in some part of your body; maybe that body part is under attack, hence better respond. Cannabinoids should reassure that "everything is ok, stop panic mode" thus alleviating the allergies.) This prediction is true[+30] (Karsak et al 2007, Gaffal et al 2013).

Immediate prediction: reduced endocannabinoid levels should stimulate fever (and conversely, taking marijuana should reduce body temperature) since fever is a well known general purpose infection-fighting response. Confirmed[+31]: Virodhamine and anandamide both lower body temperature in mice (Porter et al 2002; see also Ross 2003 about AEA and NADA acting on the thermoregulation-related TRPV1 receptor). And Hsiao et al 2015 found that treating obese mice with the novel CB1 *ant*agonist BPR0912 causes *increased* body temperature yielding[+32] "significant in vivo efficacy in inducing food intake-*independent* weight loss."

General purpose response: According to wikipedia,

> "Inflammation is part of the complex biological response of body tissues to harmful stimuli, such as pathogens, damaged cells, or irritants. Inflammation is a protective response that involves immune cells, blood vessels, and molecular mediators. The purpose of inflammation is to eliminate the initial cause of cell injury, clear out necrotic cells and tissues damaged from the original insult and the inflammatory process, and to initiate tissue repair. The classical signs of acute inflammation are pain, heat, redness, swelling, and loss of function. Inflammation is a generic response, and therefore it is considered as a mechanism of innate immunity, as compared to adaptive immunity, which is specific for each pathogen. Too little inflammation could lead to progressive tissue destruction by the harmful stimulus (e.g. bacteria) and compromise the survival of the organism. In contrast, chronic inflammation may lead to a host of diseases, such as hay fever, periodontitis, atherosclerosis, rheumatoid arthritis, and even cancer (e.g, gallbladder carcinoma). Inflammation is therefore normally closely regulated by the body."

so our Hypothesis would predict that marijuana suppresses inflammation while low endocannabinoid levels (or CB receptor antagonists) should engender it. Prediction confirmed![+33] (Ashton 2007, Burstein 2015, Cabral & Griffin-Thomas 2009, Gaffal et al. 2013, Karmaus, Chen, et al. 2011.)

More generally, marijuana should act as an immune-system suppressant – true[+34] (see Morahan et al. 1979, table 4 of Friedman, Newton, Klein 2003, and Cabral & Marciano-Cabral 2004) – and it could, and does accomplish that in a horribly large number of ways:

A. THC has been reported to suppress the antibody response of humans and animals (Klein et al. 1998)
B. THC suppresses a variety of activities of T lymphocytes (Kaminski 1998; Klein et al. 2004). And B and T cell proliferation are suppressed by CB2 agonists including THC.
C. THC also has been reported to inhibit natural killer (NK) cytolytic activity and reduce interferon gamma (IFNγ) levels in mice (Massi et al. 2000)
D. AEA inhibits chemokine-elicited lymphocyte migration (Joseph et al. 2004)
E. THC and the synthetic cannabinoids HU-210 and CP55940 all suppress or abolish functional activities of macrophages and macrophage-like cells, including macrophage-mediated cell contact-dependent cytolysis of tumor cells and the processing of antigens (Burnette-Curley et al. 1993; Klein et al. 1991; McCoy et al. 1999, Chuchawankul, Shima et al. 2004).
F. THC and endocannabinoids alter the production of chemokines and cytokines. These chemicals include members with anti-inflammmatory actions (such as IL-4 and IL-10; here IL stands for "interleukin") and also ones with pro-inflammatory actions (such as IFNγ and TNF-α; here INF stands for "interferon" while TNF stands for "tumor necrosis factor"). E.g. THC reduces interleukin-2 release (Ihenetu, Molleman, et al 2003). And CB2-activation indeed depresses TNF-α (Persidsky et al 2015) and THC decreases IFNγ and the T-cell stimulating IL-12. THC decreases levels of proinflammatory cytokines in the adolescent mouse brain (Moretti et al. 2015; Klein, Newton, Zhu, Daaka, Friedman 1995).
G. other phytocannabinoids such as CBD and CBN can also alter the functional activities of the immune system (Cabral, Rogers, Lichtman 2015) although THC has the largest effect (Blevins, Bach, et al. 2022)
H. Karmaus, Chen et al 2011 find that CB1 and CB2 knockout mice have increased inflammation and "cellular immunity" during influenza infection, and this is at least partly due to "exacerbating APC function" (APC=antigen-presenting cell).
I. In murine models of Granulomatous Amebic Encephalitis (GAE) and atherosclerosis, macrophages and macrophage-like cells exposed to THC have been reported to display less migration to sites of infection; however 2-AG (which Sugiura, Kondo et al 2000 suspect is the most important immune-endocannnabinoid and the natural ligand of CB2) *increases* the migration of HL-60 cells according to Kishimoto et al 2003, which could make sense since you want your immune cells to migrate *away* from healthy regions. See Steffens, Veillard et al. 2005, and Ullrich et al. 2007.
J. Cannabinoids have been shown to decrease host resistance to various infectious agents. THC lessens mouse resistance to Listeria monocytogenes bacteria and to the herpes simplex virus-2 (HSV-2). (Cabral & Staab 2005; Morahan et al 1979). Cannabinoids compromise host resistance to Legionella pneumophila, Staphylococcus albus, Treponema pallidum, Friend leukemia virus, and Acanthamoeba.

(Most of above cites came from the review by Cabral et al 2015.)

Again, each of these is really two predictions (1) it should be affected, and, less clearly, (2) with the expected sign. The overall sign should be that the overall effect is, that marijuana will be an immune-system suppressant.

The above list makes it clear that the overall prediction is true[+35] (see also Hegde et al 2010) and many specific subeffects also occur (all or almost all with the expected signs). And marijuana is generally regarded as having anti-inflammatory action (e.g. Ashton 2007), *except* that Karmaus, Wagner at al 2013 found it actually *increased* pulmonary inflammation[-2] in a certain situation in mice. That exception seems like evidence against the Hypothesis, but could perhaps be regarded as pro-Hypothesis evidence as follows[+36]: Marijuana's "bronchodilator" effects have long been known (has been used as a cure for asthma, starting already with the investigations of Wm.B.O'Shaughnessy in 1842). One might postulate that "safe/panic mode" for the **lung** is to breathe shallowly and contract bronchii to prevent nasty gases/smoke from getting in, or bacteria spreading, while "normal operation mode" is just standard breathing. If so, that would both explain marijuana's asthma-curing effects and perhaps also the Karmaus-"exception" as a side-effect.

Q. What is the effect of cannabinoids on the **liver**?

A. They stimulate fat storage (Cooper & Regnell 2014, Purohit et akl 2010) via increased de novo fatty acid synthesis as well as decreased fatty acid oxidation, culminating in the development of fatty liver (steatosis). Cannabis smoking can worsen fatty liver. CB1 antagonists (whose effect ought to be the same as a *lack* of endocannabinoids) increase insulin clearance (Kabir et al 2015) in dog livers. Do these effects make sense in the light of our Hypothesis? I.e. does it make sense that a liver in "panic mode" should want to stop fat storage and stop insulin clearance? First, fatty liver is unhealthy and will eventually cause cirrhosis, which can lead to jaundice and liver failure; so it makes sense a liver in panic mode might want to stop creating more fat. Second, about insulin clearance; that makes sense because of...

Q. What is the effect of cannabinoids on the **insulin** system?

A. CB1 antagonists (corresponding to a *lack* of endocannabinoids) increase "insulin sensitivity" meaning a smaller amount of insulin is needed to stimulate the conversion of blood sugars into stored fat in fat cells and (in the liver) into stored glycogen. This effect makes sense[+37] according to our Hypothesis because high blood sugar can be a life-threatening problem (which is why diabetics have lower life expectancy) and to "play it safe" if your body is in "panic mode" it makes short term sense to solve that problem even though, long-

term, obesity also is a health risk.

Q. What does the Hypothesis predict about **bones**?

A. You will need to know the nomenclature from hell that osteoclasts are a type of bone cell that *reabsorb/remove* bone, while osteoblasts are a type that *creates* bone mineralization. These two kinds of cells are in a perpetual war, or more precisely a process of "creative destruction," which continually re-engineers your bones. The Hypothesis appears to act in the following somewhat non-intuitive manner for bone:

- If situation normal (normal/high endocannabinoid levels), then encourage the creative destruction and feel free to build more bone (osteoblasts and to a lesser extent osteoclasts, both stimulated).
- If situation dangerous (low endocannabinoid levels), then don't make it worse by removing bone (osteoclasts inhibited).
- Overall effect should be: bone becomes stronger (or at least holds steady) where it is in danger, i.e. weak and stressed; but creating new bone is avoided in unhealthy areas of the body, because *that* also might make things worse. (E.g. a "bone spur.")

Those rules admittedly were not my first guess, but seem to make sense. Most, but not all, **evidence** seems to support the Hypothesis provided it is assumed to work as just explained about bones:

Pro-Hypothesis	Anti-Hypothesis
Nikolaeva et al 2015: CB2-knockout mice exhibit greater bone density ($p<0.05$).	Rossi et al 2014: osteoclast activity is "restored" in ovariectomized mice by knocking out TRPV1 receptors, but this increased CB2 receptors as side effect, so it is hard to interpret what this says about our Hypothesis.
Wasserman et al 2015: THC "attenuates" skeletal growth via CB1 receptors.	
Idris et al 2005: CB1-antagonist AM251 (1-3mg/kg/day) prevents ovariectomy-induced bone loss in wild type mice.	Ofek et al 2006: CB2-deficient mice experienced high bone turnover then developed osteoporosis when old (51 weeks). But the latter, which was confirmed by Sophocleous et al 2011, could be attributed to just the cumulative effect, over time, of a defective cannabinoid system, in which case that evidence might actually be regarded as pro-Hypothesis...
Idris et al 2008: CB2-deficient mice were partially protected from ovariectomy-induced bone loss as compared with wild type littermates.	... Indeed Idris et al. 2009 found CB1-deficient mice developed osteoporosis with increasing age due to a defect in bone formation and accumulation of marrow fat...
Idris et al 2008: CB2-antagonist AM630 prevents ovariectomy-induced bone loss in mice in vivo.	...which, remarkably, occurred *despite* the pro-Hypothesis fact that osteoclastic bone resorption remained lower in CB1-deficient mice than in wild type littermates throughout life.
Lunn et al. 2007: novel CB2 selective antagonist Sch.036 prevents bone damage in arthritic mice.	
Idris et al 2005: Anandamide, 2-AG, and CB2-stimulators HU308 and JWH133 all enhanced osteoclast formation, while CB2-antagonist AM632 inhibited it.	
Schuehly et al. 2011: endocannabinoids stimulate osteoclast formation.	Tam et al 2006: CB1 deficient mice on a C57BL/6 background were found to have reduced peak bone mass when compared with wild type littermates.
Ridge et al 2007, Whyte et al 2012: 2-AG and anandamide stimulate bone resorption by human osteoclasts in vitro.	
Tam et al. 2008: an expected increase in bone formation was absent in CB1-deficient mice, but occurred as usual in wild type and CB2-deficient mice.	Rossi et al 2009: AM630 in *humans* at high concentrations (10μM) stimulates osteoclast formation, exactly the opposite effect as Idris et al 2008's in *mice*.
Tam et al. 2006: bone formation rate reduced in young (9-12-week old) CB1-deficient mice	
Idris et al. 2009 and Tam et al. 2006: CB1-deficient mice of both genders exhibited high peak bone mass.	Kogan et al 2015: Cannabidiol enhances fracture healing and stimulates lysyl hydroxylase activity in osteoblasts.
Sophocleous et al. 2012: combined deficiency of the CB1 and CB2 receptors enhances peak bone mass (but increases age-related bone loss).	

All references dated ≤2012 in the above table are taken from the survey by Idris & Ralston 2012. I regard the table as 13 Pro and 2½ (which, to be conservative, I'll round up to 3) Anti-Hypothesis evidence items, so our counters update to $^{+50}$ and $^{-5}$.

Q. What does the Hypothesis predict about **blood pressure**?

A. If some tissue is sick or in trouble as judged by a lack of endocannabinoids, then it would seem to make sense to raise blood pressure to try to feed it more oxygen. And, experimentally, marijuana lowers blood pressure^{+51}. This may be related to nitrogen monoxide (NO) a potent vasodilator whose production is stimulated by cannabinoids, according to Stefano, Liu, Goligorsky 1996.

Q. How should the reproductive system be affected?

A. If your endocannabinoid system is detecting that you are sick/abnormal (or just your uterus is), then that means that it is probably a bad health decision, to get pregnant. Therefore, lack of endocannabinoids is predicted to *reduce female fertility* in humans (and indeed in any animal, especially mammals, in which pregnancy consumes a lot of resources and causes a lot of stress). It could do so in several ways:

A. inhibit oogenesis (egg-creation/release).
B. inhibit fertilization of egg by sperm.
C. decrease libido.
D. inhibit implantation of zygote on uterine wall.
E. increase rate of miscarriage (spontaneous abortion).

Each of those predictions is actually two predictions (1) that it ought to be affected and, less clearly, (2) that the effect would have the predicted sign. Actually, however, the sign predictions are not really reliable, since, for example, it might be desirable to inhibit oogenesis but actually enhance implantation if the net effect on fertility still were negative. My point is: the precise shape of the response curve of fertility to cannabinoids can be adjusted by combining many components, and it is not necessary (or necessarily desirable) for each component to have the sign one naively expects – albeit to make the system more robust (i.e. still working somewhat even if one component malfunctioning), it might indeed seem beneficial for all subeffects to have the obvious sign. In any case the *overall* sign (for total fertility) should be negatively affected by decreased cannabinoid levels. (But recall our warning about adaption-caused "fake signs.") Sure enough, many of these predictions are known to be true$^{+52+53+54+55}$ (Bambang et al 2014; Karasu et al 2011; Sun & Dey 2012; Fride 2004).

More speculatively, if you are male and your endocannabinoid system is detecting that you are sick/abnormal, then that means that it is probably a bad idea for the health of your species, for you to reproduce. (Versus some healthier male.) Therefore, one might predict that lack of endocannabinoids would affect sperm production and/or libido; and that these effects (or at least, the net effect on fertility) should be negative. *But* we could also argue the opposite: the evolutionary logic might instead be that as a sick male, you are likely to die soon anyway (or if just your reproductive system is sick, you are likely to become infertile soon anyway) so might as well try to reproduce first. (And sperm production is a smaller cost than pregnancy is for females, at least usually in mammals, so this will not hurt the male's survival chances as greatly.) So it is not at all obvious what *signs* these effects should have for males, but both arguments predict the *existence* of effects.

True^{+56} (Fasano et al 2009; Pacey et al 2014).

However, there are many cannabinoid↔reproduction effects – too much for me to review here. Many seem to have the "wrong" sign, which seems bad news[-6] for our Hypothesis, at least as far as human reproduction is concerned.

Q. What does the Hypothesis predict for a person with a **bodywide *shortage* of endocannabinoids**? (Or shortage of receptors?)

A. Actually, Ethan B. Russo in 2004/2008 proposed his own hypothesis – that a certain set of human syndromes were exactly caused by that kind of shortage, which he dubbed "Clinical endocannabinoid deficiency (CECD)"! So let us first discuss Russo's theory and how well it has fared versus observation, before returning to our Hypothesis. Russo specifically suggested that

> Migraine, fibromyalgia, irritable bowel syndrome (IBS), and related conditions display common clinical, biochemical and pathophysiological patterns that suggest an underlying CECD that may be suitably treated with cannabinoid medicines.

Ester Fride (2004) also suggested (which Russo agglomerated into his theory) that CECD is the cause of infant growth failure (i.e. height & weight below 3-5 percentile for age & sex) resulting from an inability to ingest food, known as "non-organic failure-to-thrive" (NOFTT) syndrome.

We have already discussed elsewhere herein the observed fact that some migraine and IBS patients are helped by medical marijuana. Fibromyalgia (FM) is a disorder characterized by widespread musculoskeletal pain especially at a set of about 15 painful tender points, accompanied by fatigue, sleep, morning stiffness, and word-finding and memory problems ("fibro fog"), sometimes accompanied by muscle cramping, migraines, and digestive problems. It can be debilitating. It is the most common diagnosis made by rheumatologists. Russo noted that he had once ridiculed FM as a "semi-mythical pseudo-disease." That notion is/was common among doctors because all symptoms were largely subjective and there seemed no identifiable cause of the condition, hence it was widely speculated to be a hoax invented by hypochondriac patients or ones seeking opiates.

7-11 years later, we are happy to report that Russo's theory is looking excellent re fibromyalgia. First of all, a blood test for FM (tested in a blinded study by Behm et al 2012 of 110 FM patients and 91 controls) was invented. The test now is commercially available from EpicGenetics and (according to its head B.Gillis in an interview) has false-negative rate of 7% and false-positive rate of 11%. This *proved* FM *is* a genuine medical condition, *not* a hoax, and that it has something to do with the immune system. The test works by "challenging" a blood sample with each of two mitogens. In response, the blood produces 8 cytokines, whose level-changes are measured. The blood of FM victims tends to produce a lot more of the 8 kinds of cytokines.

(Whether FM is caused by these immune abnormalities, or it causes them, or both have some higher cause, is not known. And while I contend Behm et al's blood test is *valid*, it currently seems to have poor medical *cost-effectiveness*. That issue is irrelevant for our purposes here.) Our Hypothesis (and Russo's) would contend the "higher cause" often is bodywide endocannabinoid or receptor shortage.

Second, Fiz et al 2011 studied 28 FM victims and 28 controls, finding smoked (54%) or oral (46%) or both (43%) marijuana improved the following FM symptoms:

> pain ($p<0.001$), stiffness ($p<0.001$), relaxation ($p<0.001$), somnolence (sleeping, $p<0.001$), overall well-being ($p<0.001$), as well as score on a mental-health test ($p<0.05$)

at the cost of the following side effects (96% of patients reported at least one side-effect, the side effects are listed with their counts in decreasing order):

> somnolence (18), dry mouth (17), sedation (12), dizziness (10), mentally "high" (9), tachycardia (8), conjunctival irritation (7), hypotension (low blood pressure) (6).

Then the National Pain Foundation conducted an online survey (Anson 2014) of 1339 self-selected FM sufferers, finding the following stunning results concerning the patient-perceived effectiveness of drugs:

Drug	Very effective	Helps a little	Does not work
Cymbalta=Duloxetine (Eli Lilly)	8%	32%	60%
Lyrica=Pregabalin (Pfizer)	10%	29%	61%
Savella=Milnacipran (Forest Labs)	10%	22%	68%
Medical marijuana (among the 30% who had tried it)	62%	33%	5%

- The 3 drugs in the top 3 lines of the table are *exactly* the full set of drugs approved by the FDA for fibromyalgia and generate billions of dollars in annual sales. But marijuana tremendously outperforms them all.
- 43% of fibromyalgia sufferers feel their physician is not knowledgeable about the disorder.
- 35% feel their physician does not take their fibromyalgia seriously.
- 82% said they had stopped seeing a doctor because they felt they were treated poorly.
- 96% of respondents were female. This contrasts with the claim, based on a survey of 2445 allegedly-random Germans by Wolfe, Brähler et al 2013, that the frequency of FM in the general population is 2.4% in women and 1.8% in men. The only ways to explain this contradiction are that (a) Wolfe's survey was garbage, (b) The health/diagnosis system that produced the people who believe they have FM, is extremely broken, (c) women FM-sufferers are 18× more likely than men to fill out online survey.

Verdict: as matters presently stand, these results about FM must be considered a giant success for Russo's theory. They[+57] also seem entirely compatible with our Hypothesis.

What about NOFTT? As far as I know, as of year 2015, there has never been any large or medium scale human study about attempting to cure NOFTT with cannabinoids; and I read several "patient guides to FTT" finding none even *mentioned* Fride's cannabinoid theory. However, there have been a few human-infant case reports and some lab animal studies, which both support Fride's theory in a (necessarily quite limited) way. Also, it is known that 2-AG and anandamide are present in mother's milk (but not formula!) which presumably help provide a "reward" chemical signal to sucking infants, help their digestion, and/or help cause them to sleep after being fed.

> "Endocannabinoids have been detected in maternal milk and activation of CB1 receptors appears to be critical for milk sucking... apparently activating oral-motor musculature"
> – Fride's Europ.J.Pharmacology 2004 abstract.

Q. What does the Hypothesis predict for a person with a **bodywide *oversupply* of endocannabinoids**? (Or of receptors?)

A. Presumably such persons would have a large appetite and tend to become obese and develop gastrointestinal problems at a higher than usual rate, but that, if so, presumably could be cured by cannabinoid receptor antagonists. These people might also be less likely to vomit and hence more vulnerable to poisoning; and less likely to get a fever or inflammation, and hence more vulnerable to infection and to cancers. It might, however, be that whole Idea we are advancing is "fail safe" in the sense that having a natural bodywide oversupply of cannabinoids, is almost *impossible*.

Rimonabant, a CB1 *ant*agonist, successfully gained approval[+58] as an anti-obesity drug in Europe, and was marketed by Sanofi. However, it was withdrawn from the market, and never approved in the USA, because its side effects included suicidality and depression. (Sun & Chen 2012. A new CB1 antagonist called NESS-0327 was proposed in 2012 as hopefully providing the beneficial effects of rimonabant without the drawbacks.)

Most generally: our Hypothesis would predict that a **vast array** of symptoms of all sorts of diseases ought to be affected by cannabinoids. This explains the vast number of claims[+59] out there – quite possibly many are untrue, but there are a tremendous number of them – that seemingly nearly every human medical malady is in some way affected by marijuana.

6. Refined hypotheses?

The fact that we've found some evidence *opposed* to the Hypothesis could mean it is wrong, or just that that evidence was erroneous or misinterpreted. But I think it is most likely that our Hypothesis is mostly correct, but not perfect; really, the truth is more complicated and our Hypothesis is an oversimplification of that truth. Landscape artists typically begin by painting a crude approximation of the scene, then add details. Darwinian evolution presumably often behaves similarly. Hence our Hypothesis may have originally been more true in early evolutionary times, than it is today, after all sorts of detailed modifications have been opportunistically added by further evolution.

Here are some **candidate ideas for this more-refined "higher truth":**

- Originally our Hypothesis was essentially true. However, later in evolutionary time, with the endocannabinoid system in place, it became useful to take advantage of the then-enjoyed biochemical capabilities to implement new useful functionalities. For example, exercise is good for you. Therefore, by causing successful exercise to generate *extra* endocannabinoids, causing "runner's high" (sense of well being), organisms would usefully be encouraged to exercise. There is evidence for this[+60] (Dietrich & McDaniel 2004). Exercise has long been regarded as good therapy for depression and anxiety (e.g. Craft & Perna 2004); and this might be a partial explanation for that.
- Although the Hypothesis may have been true at first, later more chemicals interacting in more ways, were added to certain systems (probably especially the brain and immune system, which nowadays are highly complicated), causing their operation to become more complicated with the endocannabinoid system being a smaller part of the final result, with a modified role.
- As still another example, suppose it was useful under certain circumstances for cell-subset A to send a "message" to cell-subset B, causing the B-cells then to do something. This message and action would not necessarily be "panic!" and "switch into safe mode!". Nevertheless, if that body part was not already committed to some already-defined "safe mode" and "panic status" – then evolution was free to try to employ its endocannabinoid machinery in that situation for this new non-panic communication purpose.
- Mammalian reproduction seems the most sophisticated kind of animal reproduction and arose the latest – well after the endocannabinoid system. Therefore, it might be that the usual Hypothesized role of the endocannabinoid system as an error-status-notifier was *overridden* or swamped out by other systems created to enable mammalian reproduction – thus explaining the large amount of conflicting evidence about our Hypothesis vis-a-vis mammalian reproduction. This possibility could be studied by investigating reproduction↔endocannabinoids in *non*mammals.

7. Summary

Over 90% of evidence items support the Hypothesis. While many of the items seem very weak, often as poor as "my coin just came up tails," the net effect is an extremely impressive pattern of pro-Hypothesis evidence. [If 66 coin tosses produce at most 6 heads, we obtain confidence=$1-2^{-66}\sum_{0\le k\le 6} k!^{-1}(66-k)!^{-1}66!$> 99.9999999998%.] In my opinion overwhelming confidence has been obtained versus the null hypothesis.

But of course, I must admit that if some rival hypothesis were invented that would have predicted 66% of our evidence, then the confidence in our Hypothesis versus that rival would be greatly reduced in comparison to our Confidence versus the null hypothesis (all "coin flips" random). But as far as I can tell from review papers and books, etc, no unified hypothesis about endocannabinoids of any kind has ever been advanced, – or at least if it has then those reviews left it out.

Furthermore, several experiments are suggested by this line of thinking, which as far as I know have never been performed, but could be, which would be expected to provide further confirmation, or refutation, or at least a deeper understanding, of our Hypothesis.

How do I feel about **marijuana legalization**? It seems to me it should be very greatly or wholly decriminalized because

1. The cost to society of all that jailing and enforcement effort, probably exceeds the benefits.
2. Powerful wealthy international criminal organizations formed which, e.g, commit many murders; but which probably would not exist if the drugs they make, smuggle, and sell were legal.
3. Criminalization has severely distorted marijuana economics, making it far more expensive – and also causing breeders to alter the plant to make it produce far more THC but far less of other cannabinoids and associated chemicals. Both these effects probably are negative.
4. As side-effects of marijuana criminalization/demonization, cannabinoid research was decimated.
5. The two parts of the hemp industry having nothing to do with cannabinoids – hemp fibers used for, e.g. ropes, cloth (which otherwise plausibly would have been a million-ton/year industry today); and hemp seed, a "superfood" rich in essential fats – both were devastated as another side-effect.

But that stance by me should not be interpreted as support for recreational marijuana use. Instead, it seems to me (just at an intuitive level, albeit I have citeable evidence) that any biochemical system of as fundamental a nature as our Hypothesis makes the endocannabinoid system seem, is *not* something that should be cavalierly toyed with for recreational purposes. That does not seem like a smart idea. [Furthermore, even for medical uses I would prefer if more targeted (i.e. localized) drug-administration methods were devised.] Nevertheless today's data make it seem overwhelmingly likely marijuana is both less harmful and less addictive than tobacco, and less dangerous than aspirin, which are legal in every country.

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