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Dockets Management Staff (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Rm. 1061
Rockville, MD 20852

Re: Department of Health and Human Services, Food and Drug Administration [Docket No. FDA-2018-N-1072]: International Drug Scheduling; Convention on Psychotropic Substances; Single Convention on Narcotic Drugs; Cannabis Plant and Resin; Extracts and Tinctures of Cannabis; Delta-9-Tetrahydrocannabinol; Stereoisomers of Tetrahydrocannabinol; Cannabidiol; **Request for Comments** (FR Doc. 2018-07225).

Re: ***Re-Scheduling of Cannabinoids in USA***
- Tetrahydrocannabinol and Cannabidiol Related Arteriopathy, Genotoxicity and Teratogenesis

I am very concerned about the potential for increased cannabis availability in USA implied by full drug legalization; however, a comprehensive and authoritative submission of the evidence would take weeks and months to prepare. Knowing what we know now and indeed, what has been available in the scientific literature for a growing number of years concerning a myriad of harmful effects of marijuana, marijuana containing THC should not be reclassified. These effects that are now well documented in the scientific literature include, alarmingly, harm involving reproductive function and birth anomalies as a result of exposure to or use of marijuana with THC.

In addition to all of the usual concerns which you will have heard from many sources including the following I have further particular concerns:

1) Effect on developing brains [1-15]
2) Effect on driving [16-26]
3) Effect as a Gateway drug to other drug use including the opioid epidemic [27-30]
4) Effect on developmental trajectory and failure to attain normal adult goals (stable relationship, work, education) [17,31-43]
5) Effect on IQ and IQ regression [13,44-48]
6) Effect to increase numerous psychiatric and psychological disorders [49-62]
7) Effect on respiratory system [63-85]
8) Effect on reproductive system [7,86-91]
9) Effect in relation to immunity and immunosuppression [92-108]
10) Effect of now very concentrated forms of cannabis, THC and CBD which are widely available [109,110]
11) Outdated epidemiological studies which apply only to the era before cannabis became so potent and so concentrated [110].

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These issues are all well covered by a rich recent literature including reviews from such major international authorities as Dr Nora Volkow Director of NIDA at NIH [1,3,5,110-112], Professor Wayne Hall [113-117] and others [118].

Cannabinoid Therapeutics

In my view the therapeutic effects of cannabinoids have been wildly inflated by the press.

Moreover, with over 1,000 studies listed for cannabinoids on clinicaltrials.gov, the chance of a type I experimental error, or studies being falsely reported to be positive when in fact they are not, is at last 25/1,000 at the 0.05 level.

THC as dronabinol is actually a failed drug from USA which has such a high incidence of side effects that it was rarely used as superior agents are readily available for virtually all of its touted and alleged therapeutic applications. My American liaisons advise that dronabinol sales have climbed in recent times as patients use it as a ruse to avoid detection of cannabinoid use at work in states where it is not yet legal. So when I call is a failed therapeutic I mean in a traditional sense, not in the novel way it is now applied for flagrantly flouting the law.

In considering the alleged benefits of cannabis one has to be particularly mindful of cannabis addiction in which cannabinoids will alleviate the effect of drug withdrawal as they do in any other addiction. Moreover, the fact that cannabis itself is known to cause both pain and nausea, greatly complicates the interpretation of many studies.

I also have the following concerns which relate in sum to the **arteriopathy and vasculopathy** and the **genotoxicity of cannabis, tetrahydrocannabinol and likely including *cannabidiol* and various other cannabinoids**:

Cannabinoid Arteriopathy

12) Cannabis is now known to have an important arteriopathic effect and cardiovascular toxic effect [5,110,119-183]. Particularly noteworthy amongst these various reports are two reports by Dr Nora Volkow in 2014, the Director of the National Institute of Drug Abuse at NIH to the New England Journal of Medicine which together document the adverse cardiovascular and cerebrovascular effects of cannabis at the epidemiological level [5,110]; a report from our own clinic in 2016 documenting the effect of cannabis to increase cardiovascular aging to BMJ Open [183]; a series of reports showing a fivefold increase in the rate of heart attack within one hour after cannabis smoking [121-123]; several reports of cannabis related arteritis [162,163,168,170,171]; other reports of the cerebrovascular actions of cannabis [184-187]; documentation that cannabis exposure increases arterial stiffness and cardiovascular and organismal aging [183]; and a recent report showing that human endothelial vascular function – vasodilation - is substantially inhibited within just *one minute* of cannabis exposure [188].

13) It is also relevant that a synthetic cannabinoid was recently shown to directly induce both thromboxane synthase and lipoxygenase, and so be directly vasoconstrictive, prothrombotic and proinflammatory [189].

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14) Vascular aging, including both macrovascular and microvascular aging is a major pathological feature not only because most adults in western nations die from

myocardial infarction or cerebrovascular accidents, but also because local blood flow and microvascular function is a key determinant of stem cell niche activity in many stem cell beds. This has given rise to the vascular theory of aging which has been produced by some of the leading researchers at the National Health Lung and Blood Institute at NIH, amongst many others [190-192]. It can thus be said not only that "You are as old as your (macrovascular) arteries", but also that "you are as old as your (microvascular) stem cells." Hence the now compelling evidence for the little known arteriopathic complications of cannabis and cannabinoids, carry very far reaching implications indeed. This was confirmed directly in the clinical study of arterial stiffness from my clinic mentioned above [119].

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15) Whilst aging, myocardial infarction and cerebrovascular accidents are all highly significant outcomes and major public health endpoints, these effects assume added significance in the context of congenital anomalies. Some congenital defects, such as gastroschisis, are thought to be due to a failure of vascular supply of part of the anterior abdominal wall [193-198]. Hence in one recent study the unadjusted odds ratio of having a gastroschisis pregnancy amongst cannabis users (O.R.=8.03, 95%C.I. 5.63-11.46) was almost as high as that for heroin, cocaine and amphetamine users (O.R.= 9.35, 95%C.I. 6.64-13.15), and the adjusted odds ratio for any illicit drug use (of which was 84% cannabis) was O.R.=3.54 (95%C.I. 2.22-5.63) [199] and for cannabis alone was said by these Canadian authors to be O.R.=3.0 [200]. Hence cannabis related vasculopathy - arteriopathy beyond its very serious implications in adults also carries implications for paediatric and congenital disorders and may also *constitute a major teratogenic mechanism.*

Cannabinoid Genotoxicity and Teratogenesis

16) Cannabis is associated with 11 cancers (lung, throat, bladder, airways, testes, prostate, cervix, larynx) including [201,202];

17) Four congenital and thus inherited cancers (rhabdomyosarcoma, neuroblastoma, ALL, AML and AMML) [201,202];

18) Sativex product insert in many nations carries standard warning against its use by males or females who might be having a baby [203].

19) Cannabis – and likely also CBD – is known to be associated with epigenetic changes [30] some of which are believed to be inheritable for at least four generations [204];

20) Cannabis is known to interfere with tubulin synthesis [205-209] and binding and it also acts via Stathmin so that microtubule function is impeded [210]. This leads directly to micronucleus formation [113,211,212]. Cannabis has been known to test positive in the micronucleus assay for over fifty years [113,117,211]. This is a major and standard test for genotoxicity. Micronucleus formation is known to lead directly to major chromosomal toxicity including chromosomal shattering – so-called chromothripsis – and is known to be associated with cell death, cancerogenesis and major foetal abnormalities [202,213-215].

21) Cannabis has also been linked definitively with congenital heart disease is a statement by the American Heart Association and the American Academy of Pediatrics in 2007 [216], on the basis of just three epidemiological studies, all done in the days before cannabis became so concentrated. Congenital heart defects have also been linked with the father's cannabis use [217]. Indeed, one study showed that paternal cannabis use was the strongest risk factor of all for preventable congenital cardiac defects [218].

22) Cannabis has also been linked with gastroschisis in at least ***seven cohort and case control studies*** [199,219-224] some of which are summarized in a Canadian Government Report [200]. In that report the geographic incidence of most major congenital anomalies closely paralleled the use of cannabis as described in other major Canadian reports [225]. The overall adjusted odds ratio for cannabis induction of gastroschisis was quoted by these authors as 3.0 [200].

23) Moreover, outbreaks of both congenital heart disease [226] and gastroschisis in North Carolina also paralleled the local use of cannabis in that state as described by Department of Justice Reports [227]. The incidence of gastroschisis was noted to double in North Carolina 1999-2001 in the same period the cannabis trade there was rising [228]. Figures of cannabis use in pregnant women in California by age were also recently reported to JAMA [229], age group trend lines by age group which closely approximate those reported by CDC for the age incidence of gastroschisis in the USA [230] (Figure 1). Importantly much of the cannabis coming into both North Carolina and Florida is said to originate in Mexico [227,231]. An eight-fold rise in the rate of gastroschisis has been reported from Mexico [232]. Gastroschisis has also risen in Washington state [233].

24) Cannabis has also been associated with 17 other major congenital defects by major Hawaiian epidemiological study reported by Forrester in 2007 when it was used alone [221]. When considered in association with other drug use – which in many cases cannabis leads to – cannabis use was associated with a further 19 major congenital defects.

25) In addition to the effect of cannabinoids on the epigenome and microtubules, cannabinoids have been firmly linked to a reduction of the ability of the cell to produce energy from their mitochondria [78,82,91,234-249]. An extensive and robust evidence base [244] now links cellular energy generation to the maintenance and care of cellular DNA [250-253]. Moreover, as the cellular energy charge falls so too DNA maintenance collapses, and indeed, the cell can spiral where its remaining energy resources, particularly as NAD+, are routed into failing and futile DNA repair, the cell slips into pseudohypoxic metabolism like the Warburg effect well known in cancerogenesis [254], NAD+ falls below the level required for further energy generation and cellular metabolism collapses. Hence this well-established collapse of the mitochondrial energy charge and transmembrane potential forms a potent engine of continuing and accelerating genotoxicity [255].

26) Moreover, the well documented decline in mitochondrial respiration induced by cannabinoids, including tetrahydrocannabinol, cannabidiol and anandamide [78,82,91,234-242,244-248] achieves particular significance in the light of the robustly documented decline in cellular energetics including NAD+ which not only occurs with age [251,256-268] but indeed, ***has now been shown to be one of the primary drivers of cellular and whole organismal aging*** [250-254,263,269-289]. This close parallel is illustrated in Figure 2. It follows therefore that *cannabinoid administration (including THC and CBD)* ***necessarily phenocopies cellular aging***. This implies of course that cannabinoid dependent patients are old at the cellular level. Indeed, normal human aging is phenocopied in the clinical syndrome of cannabinoid dependence which includes (most references are provided above):

1) Neurological deficits in:
    i) attention,
    ii) learning and
    iii) memory;
    iv) social withdrawal and disengagement and
    v) academic and
    vi) occupational underachievement
2) Psychiatric disorders including
    i) Anxiety,
    ii) Depression,
    iii) Mixed Psychosis
    iv) Bipolar Affective disorder and
    v) Schizophrenia,
3) Respiratory disorders including:
    i) Asthma
    ii) Chronic Bronchitis (increased sputum production)
    iii) Emphysema (Increased residual volume)
    iv) Probably increased carcinomas of the aerodigestive tract
4) Immune suppression which generally implies
    i) segmental immunostimulation in some parts of the immune system since
    the innate and adaptive immune systems exert profound homeostatic mechanisms in response to suppression of one of its parts;
    A Substantial literature on immunostimulation
5) Reproductive effects generally characterized by reduced
    i) Male and
    ii) Female fertility
6) Cardiovascular toxicity with elevated rates of
    i) Myocardial infarction
    ii) Cerebrovascular accident
    iii) Arteritis
    iv) Vascular age – vascular stiffness [119]
7) Genotoxicity in
    i) Respiratory epithelium and
    ii) Gonadal tissues.
8) Osteoporosis [290-300]

9) Cancers of the
    i) Head and neck
    ii) Larynx
    iii) Lung
    iv) Leukaemia
    v) Prostate
    vi) Cervix
    vii) Testes
    viii) Bladder
    ix) Childhood neuroblastoma
    x) Childhood acute lymphoblastic leukaemia
    xi) Childhood Acuter Myeloid and myelomonocytic leukaemia
    xii) Childhood rhabdomyosarcoma [201,202].

The issue here of course is that cannabinoid dependence therefore copies *without exception* all of the major disorders of old age, each of which is also faithfully phenocopied by cannabis dependence.

The most prominent disorders of older age include:

1) **Alzheimer's disease**
2) **Cardiovascular and cerebrovascular disease**
3) **Osteoporosis**
4) **Systemic inflammatory syndrome**
5) **Changes in lung volume and the mechanics of breathing**
6) **Cancers**

Hence this provides one powerful pathway by which cannabinoid exposure can replicate and phenocopy the disorders of old age.

This is not of course to suggest that this is the only such pathway. Obviously changes of the general level of immune activity, or alterations of the level of DNA repair occurring directly or indirectly associated with cannabis use can form similar such pathways: both are well documented in cannabis use and also in the aging literature as major pathways implicated in systemic aging. Nevertheless, the decline in mitochondrial energetics together with its inherent genotoxic implications does seem to be a particularly well substantiated and robustly demonstrated pathway which must give serious pause to cannabinoid advocates if the sustainability of the health and welfare systems is to be factored in together with any consideration of individual patient, advocate and industrial-complex rights.

27) The genotoxicity of THC, CBD and CBN has been noted against sperm since at least 1999 (Zimmerman and Zimmerman in Nahas "Marijuana and Medicine" 1999, Springer). This is clearly highly significant as sperm go directly into the formation of the zygote and the new human individual.

28) CB1R receptors are known to exist intracellularly on both the membranes of endoplasmic reticulum and mitochondria. In both locations they can induce organellar stress and major cell toxicity including disruption of DNA maintenance. Interestingly mitochondrial outer membrane CB1R's signal via a complex signaling chain involving the G-protein transduction machinery, protein kinase A and cyclic-AMP across the intermembrane space to the inner membrane and cristae, in a fashion replicating much of the G-protein signaling occurring at the cell membrane. This machinery is also implicated in mitonuclear signaling, and the mitonuclear DNA balance between mitochondrial DNA and nuclear DNA transcriptional control, which has long been implicated in inducing the mitochondrial unfolded protein cellular stress response cell aging, stem cell behaviour and DNA genotoxic mechanisms [248,301].

29) You are no doubt aware that human sperm are structured like express outboard motors behind DNA packets with layers of mitochondria densely coiled around the rotating flagellum which powers their progress in the female reproductive tract (Figure 3). These mitochondria also carry CB1R's and are significantly inhibited even at 100 nanomolar THC. The acrosome reaction is also inhibited [239].

30) A similar arrangement is shown in Figure 4, where mitochondria are shown in green surrounding the mitotic spindle (pink, with the chromosomes shown in blue), which is the cellular machinery and apparatus of cell division. Mitosis and meiosis, the classical processes of cell division, are highly energy dependent and mitochondria are clearly positioned strategically to supply the required energy for this process, just as they are positioned in proximity to the root of the sperm flagellum rotor in that situation.

31) Cannabidiol is known to act via the PPARγ system [101,302-308]. PPARγ is known to have a major effect on gene expression, reproductive and embryonic and zygote function during development [309-332] so that significant genotoxic and / or teratogenic effects seem inevitable via this route. Drugs which act in this class, known as the thiazolidinediones, are classed as category B3 in pregnancy and caution is indicated in their use in pregnancy and lactation.

32) The Report of the Reproductive and Cancer Hazard Assessment Branch of the Office of Environmental Health Hazard Assessment of the Health Department of California was mentioned above in connection with the carcinogenicity of marijuana smoke [333]. ***Since virtually <u>all mutagens are also teratogens</u>*** it follows therefore from the basic tenets of mutagenesis that if cannabis is unsafe as a known carcinogen it must also be at the very least a putative teratogen.

33) CBD has also been noted to be a genotoxic in other studies [334-336].

34) All of which points to major teratogenic activity for both THC and CBD.

Some of the quotations from Professor James Graham's classical book on the effects of THC in hamsters and white rabbits, the best animal models for human genotoxicity, bear repeating [337] :

a) "The concentration of THC was relatively low and the **malignancy severe**."
b) "40-100µg resin/ml there occurred **marked inhibition of cell division.**
c) "large total dose, Hamsters, 25-300mg/kg ..."oedema, **phocomelia**, **omphalocoele**, **spina bifida, exencephaly**, multiple malformations and **myelocoele**. **This is a formidable list**."
d) "It is to this **anti-mitotic action** that the authors attribute the **embryotoxic** action of cannabis."
e) "By such criteria resin or extract of cannabis would be **forbidden to women** during the first three months of **pregnancy**." [337]

Indeed, even from the other side of the world I have heard many exceedingly adverse reports from US states in which cannabis has been legalized including Colorado, Washington, Oregon, Florida and California [231,233,338-342]. Taken together the above evidence suggests that these negative reports stem directly from the now known actions of cannabis and cannabinoids, and are by no means incidental epiphenomena somehow related to social constructs surrounding cannabis use or the product forms, dosages, or routes of administration involved [343].

Cannabis that contains increasingly high levels of THC is now widely available, particularly in the jurisdictions where the use of cannabis has been legalized. This means that another major genotoxin, akin to Thalidomide, is being unleashed on the USA and the world. This is clearly a very grave, and. indeed, an entirely preventable occurrence.

Dr Frances Kelsey of FDA is said to have the public servant based at FDA who saved American from the thalidomide scandal which devastated so many other English-speaking nations including my own [344]. This occurred because the genotoxicity section of the file application with FDA was blank. It was blank because thalidomide tested positive in various white rabbit and guinea pig assays. ***It is these same tests which cannabis is known to have failed*** [88,337,345,346]. Dr Kelsey's photograph has been published in the medical press with President Kennedy for her service to the nation (Figure 5) [344]. The challenge to FDA at this time seems whether Science can triumph over agenda driven populism, its primary vehicle, the mass media, and its primary proximate driver the burgeoning cannabis industry. Since FDA is the Federal agency par excellence where Health Science is weighed, commissioned and thoughtfully considered the challenge in our time would appear to be no less.

Evidence to date does not suggest that major congenital malformations are as common after prenatal cannabis exposure as they are after prenatal thalidomide exposure. Nevertheless the qualitative similarities remain and indeed are prominent. It is yet to be seen whether the rate of congenital anomalies after cannabis are quantitatively as common: epidemiological studies in a high potency era have not been undertaken; and even the birth defects rates from most birth defects registers in western nations including that held by CDC, Atlanta appear to be seriously out of date at the time of writing. Moreover the non-linear dose response curve in

many cannabis genotoxicity studies which includes a sharp knee bend upwards beyond a certain threshold level which suggests that we could well be in for a very unpleasant quantitative surprise. At the time of writing this remains to be formally determined.

Dr Bertha Madras, Professor of Addiction Psychiatry at Harvard Medical School has recently argued against re-scheduling of cannabis. Her comments include the following:

> *"Why do nations schedule drugs? ..... Nations schedule psychoactive drugs because we revere this three-pound organ (of our brain) differently than any other part of our body. It is the repository of our humanity. It is the place that enables us to write poetry and to do theater, to conjure up calculus and send rockets to Pluto three billion miles away, and to create I Phones and 3 D computer printing. And that is the magnificence of the human brain. Drugs can influence (the brain) adversely. So, this is not a war on drugs. This is a defense of our brains, the ultimate source of our humanity"* [347].

I look forward to seeing the comments that you post concerning the reasons why the classification for marijuana should not be changed and that, indeed, the public should be alerted to the very harmful effects of marijuana with THC, especially in light of the wide range of marijuana's harmful effects and the high potency of THC in today's marijuana and in light of the idiosyncratic effects of marijuana of even low doses of THC and owing to the certain risk of harm to progeny and babies born to users of marijuana.

Please feel free to call on me if you would like further information concerning the research to which I have referred herein.

Yours sincerely,

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Figure Captions

Figure 1: Cannabis Use Rates in Pregnancy in California and Gastroschisis Rates USA, by Age Groups

Figure 2: Close Parallel between the Collapse of Mitochondrial NAD+ Dependent Respiration in Complexes I, II and IV and the Decline of NAD+ with Physiological Aging.

Figure 3: Sperm swimming demonstrating how mitochondria are wrapped around the central axel of the flagellum to provide local energy where it is needed.

Figure 4: Mitochondria (green) surrounding the mitotic spindle (made of microtubuiles shown in pink) which carry the chromsomes (blue) at the time of cell division. Photo taken from NIH laboratories (http://https//visualsonline.cancer.gov/details.cfm?imageid=10708).

Figure 5: Presentation of Dr Frances Kelsey of FDA to President John F Kennedy.

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Cannabis Use in Pregnancy, California & Gastroschisis Rates, USA by Age Groups

Figure 2.

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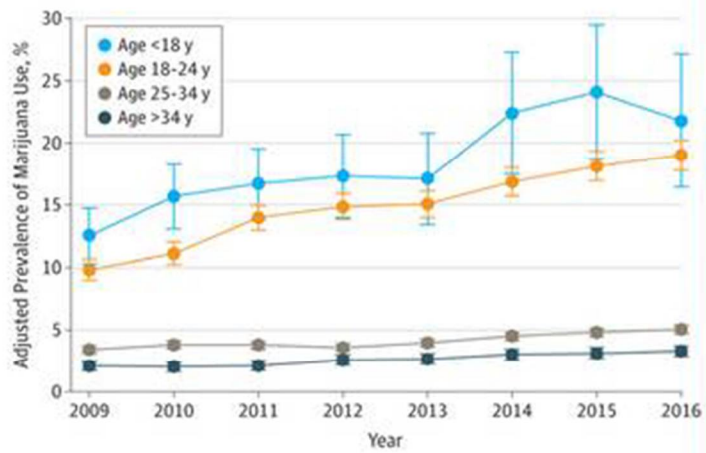

Adjusted Prevalence of Marijuana Use Among 279 457 Pregnant Females in KPNC by Age, 2009-2016

December 26, 2017

Trends in Self-reported and Biochemically Tested Marijuana Use Among Pregnant Females in California From 2009-2016

Kelly C. Young-Wolff, PhD, MPH[1]; Lue-Yen Tucker, BA[1]; Stacey Alexeeff, PhD[1]; Mary Anne Armstrong, MA[1]; Amy Conway, MPH[2]; Constance Weisner, DrPH[3]; Nancy Goler, MD[4]

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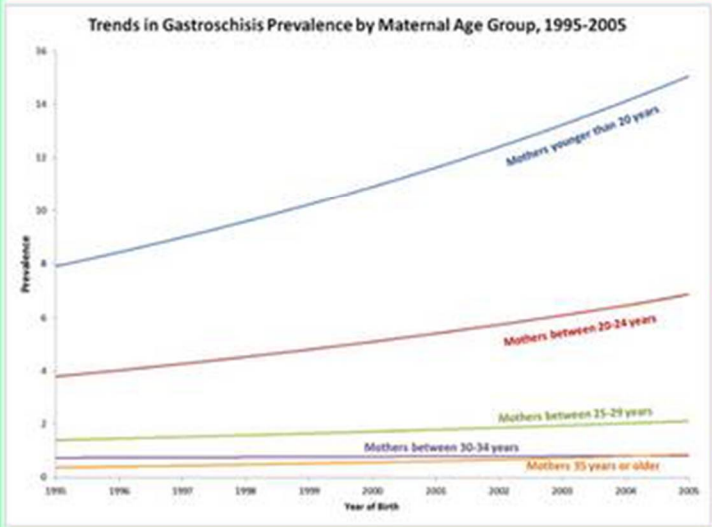
JAMA. 2017;318(24):2490-2491. doi:10.1001/jama.2017.17225



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Decline in NAD+ from Cannabinoids Mimics those Occurring with Age

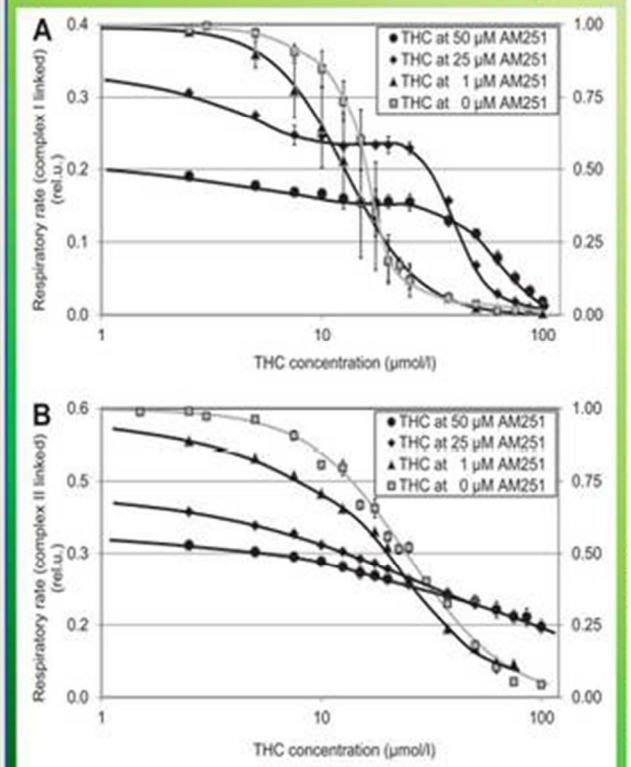

Fig. 3. THC-induced inhibition of the respiratory rate in pig brain mitochondria incubated in substrates of electron supply through (**A**) complex I or (**B**) complex II.

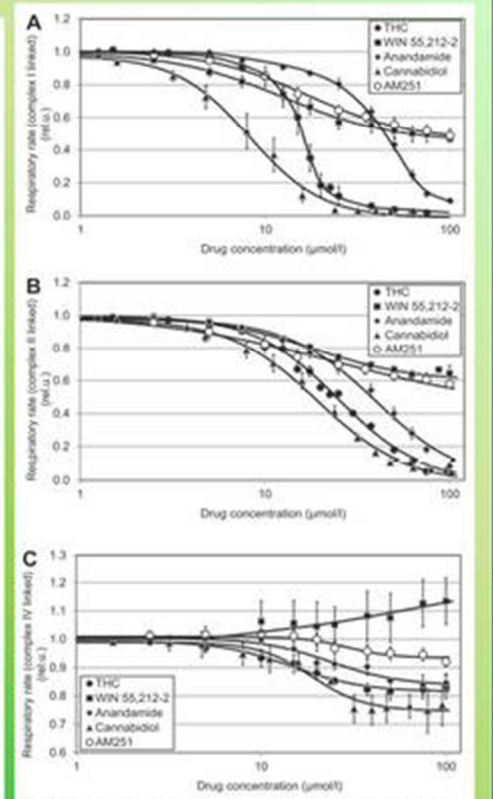

Fig. 2. Cannabinoid-induced inhibition of the respiratory rate in pig brain mitochondria incubated in substrates of electron supply through (**A**) complex I, (**B**) complex II, and (**C**) complex IV. Dose-response curves are displayed as plots of

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Cannabinoid-induced changes in respiration of brain mitochondria.

Fišar Z[1], Singh N[2], Hroudová J[3].

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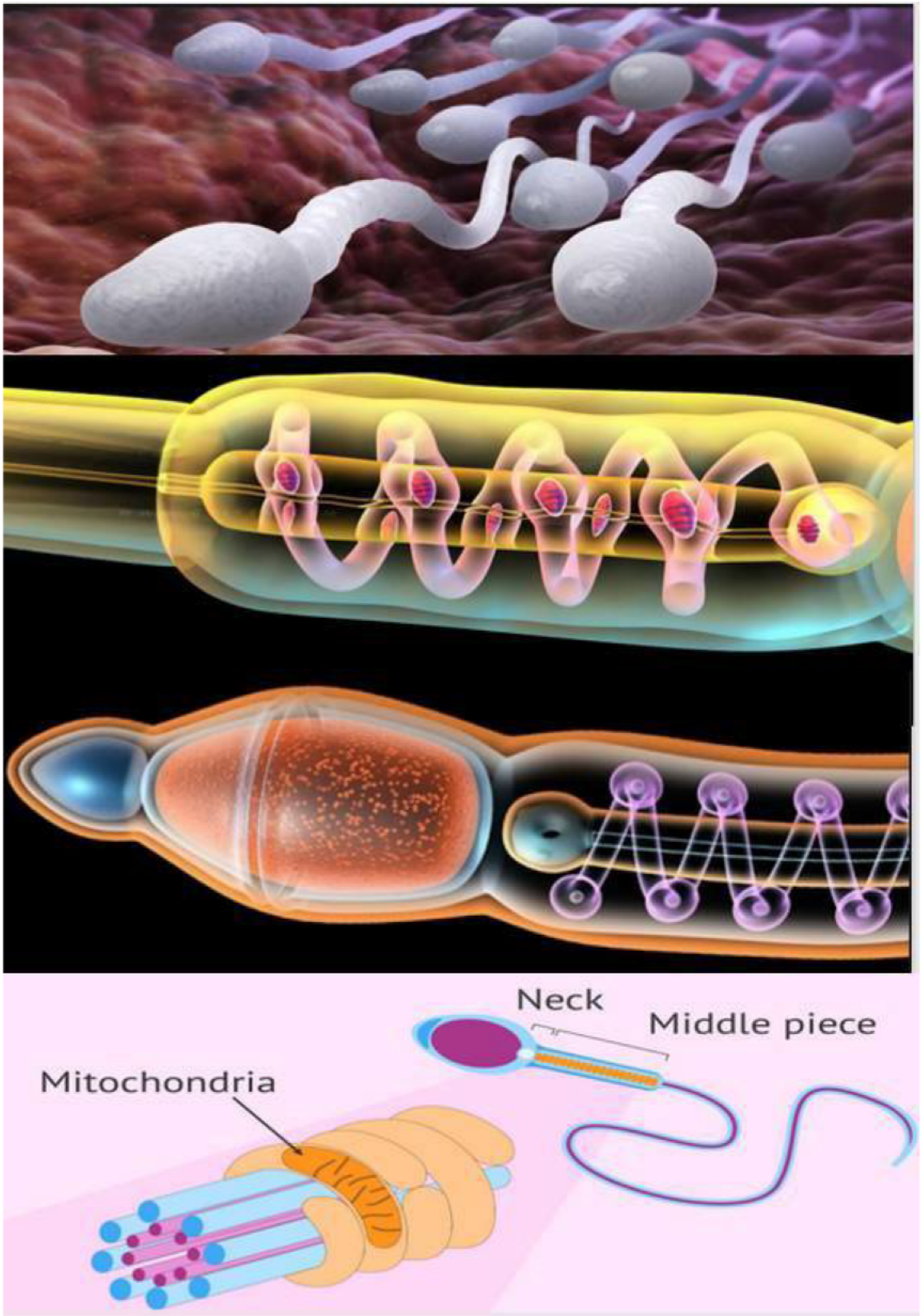

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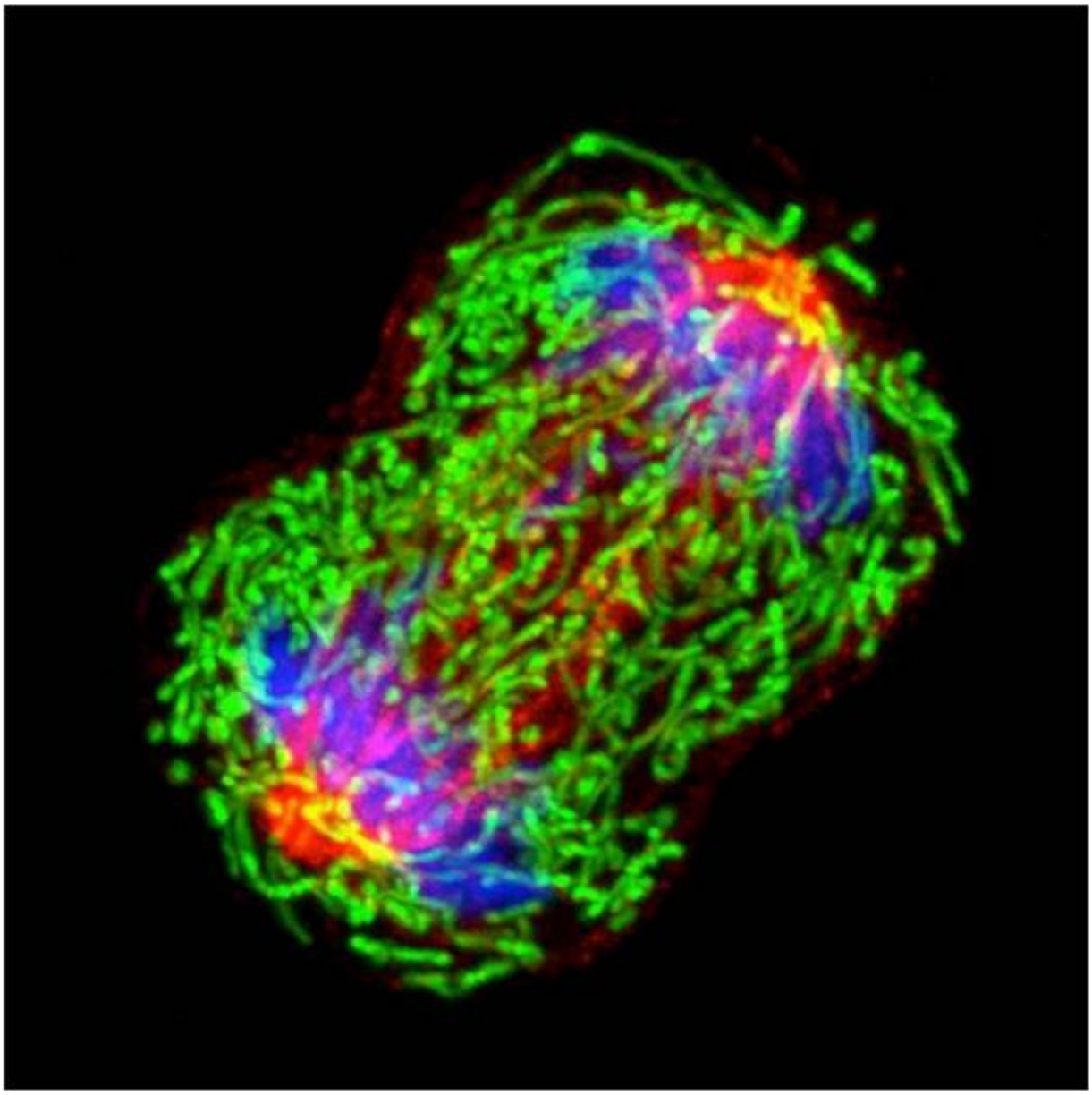
Cell Dividing



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Dr Frances Kelsey @ FDA
Saved USA from Thalidomide

Figure 2. Dr Frances Kelsey is awarded the President's Award for Distinguished Federal Civilian Service from President John F. Kennedy in 1962.

Therapeutic Advances in Hematology — *Review*

The rise, fall and subsequent triumph of thalidomide: lessons learned in drug development

Waqas Rehman, Lisa M. Arfons and Hillard M. Lazarus