Court File No.: T-2030-13

FEDERAL COURT

BETWEEN:

NEIL ALLARD
TANYA BEEMISH
DAVID HEBERT
SHAWN DAVEY

Plaintiffs

and

HER MAJESTY THE QUEEN IN RIGHT OF CANADA

Defendant

AFFIDAVIT OF HAROLD KALANT

I, Harold Kalant, Professor Emeritus, of the City of Toronto, in the Province of Ontario, SWEAR THAT:

1. I am a Professor Emeritus, employed by the Department of Pharmacology and Toxicology, University of Toronto, in the Province of Ontario and as such have personal knowledge of the matters hereinafter deposed to by me, except where same are stated to be based on information and belief and where so stated I verily believe them to be true.

2. I have been retained by the Attorney General of Canada in the above proceeding to provide an expert report for the Court. Attached at **Exhibit "A"** is my expert report, dated 29 Sep 2014.

3. On June 5, 2014, the Attorney General of Canada provided me with an instruction letter to complete my expert report. Attached as **Exhibit "B"** is a copy of the instruction letter.

4. Further, on June 5, 2014, I was provided with a copy of the Code of Conduct for Expert Witnesses. Attached as **Exhibit "C"** is a copy of the Code of Conduct for Expert Witnesses.

5. Attached as **Exhibit "D"** is a copy of my current Curriculum Vitae.

SWORN before me at the City of Toronto, in the Province of Ontario, this 30 day of Sept, 2014.

R Drummond

Commissioner for taking Affidavits in and for the Province of Ontario

Roselle Sheryl Drummond, Notary Public, City of Toronto, limited to the attestation of instruments and the taking of affidavits, for the University of Toronto. Expires February 20, 2017.

Harold Kalant

Dr. Harold Kalant

Court File No. T-2030-13

FEDERAL COURT

Allard et al. v. Her Majesty the Queen in Right of Canada

Expert report on Medical Use of Cannabis and Cannabinoids

Harold Kalant

Prepared by: Harold Kalant, M.D., Ph.D., F.R.S.C.
Professor Emeritus, Pharmacology & Toxicology
Faculty of Medicine
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Toronto, Ontario M5S 1A8

Date of Submission: September 29, 2014

R D Drummond

Roselle Sheryl Drummond, Notary Public, City of Toronto, limited to the attestation of instruments and the taking of affidavits, for the University of Toronto. Expires February 20, 2017.

Sept 30, 2014

This is Exhibit "A" referred to in the affidavit of Harold Kalant sworn before me at Toronto, ON this 30th day of September 20 14.

R D Drummond

Roselle Sheryl Drummond, Notary Public, City of Toronto, limited to the attestation of instruments and the taking of affidavits, for the University of Toronto. Expires February 20, 2017.

Issues to be addressed in this report:

This report will address the following matters:

(1) The nature of cannabis, marijuana and pure cannabinoids;

(2) The quality requirements for the use of any substance as a therapeutic agent;

(3) The biological mechanism of action of cannabinoids;

(4) The current scientific knowledge with respect to the beneficial therapeutic effects of marijuana and other forms of cannabis and cannabinoids;

(5) Methods of administration of cannabis and cannabinoids for medical purposes;

(6) The dosage range of marijuana for medical uses;

(7) The scientific evidence with respect to claimed selective benefits of particular strains of marijuana;

(8) The adverse effects of marijuana consumption;

(9) Contraindications to the medicinal use of marijuana; and

(10) The limitations of knowledge, and problems for medical supervision of marijuana use for medical purposes.

My qualifications on the issues to be addressed:

I received the M.D. degree in 1945, followed by a B .Sc. (Med) in 1948, and a Ph.D. in Pathological Chemistry in 1955, all from the University of Toronto. I had three years of postgraduate training in Internal Medicine, and a post-doctoral fellowship in Biochemistry at the University of Cambridge, U.K.

I was the Head of the Biochemistry Section of the Defence Research Medical Laboratories, Downsview, ON, from 1956 to 1959. From September 1959 to June 1989 I held joint appointments as Associate Professor and then Professor of Pharmacology in the Faculty of Medicine, University of Toronto, and Associate Director and then Director of Biological and Behavioral Research at the Addiction Research Foundation of Ontario. From July 1989 to the present I have been, and continue to be, Professor Emeritus in the Department of Pharmacology and

Toxicology of the University of Toronto, and Research Director Emeritus in the Centre for Addiction and Mental Health, Toronto.

I have carried out basic and clinical research on various aspects of the actions of, and addiction to, alcohol, cannabis and other psychoactive drugs for over 50 years, and have published over 385 papers in scientific and clinical journals, the great majority of which deal with alcohol, cannabis, and other psychoactive drugs. I have edited or written 24 books on the same topics. I have been a member or chairman of scientific advisory committees on alcohol, cannabis and other drugs, to the World Health Organization, the International Council on Alcoholism and Addictions, Health Canada, the Government of Ontario, The National Institute on Alcohol Abuse and Alcoholism and the National Institute on Drug Abuse (USA), and the Addiction Research Foundation of California. I have prepared letters of Expert Opinion on alcohol, cannabis and other drug matters in over 550 cases, including many in which I have been accredited as an expert witness in Courts in British Columbia, Alberta, Manitoba, Ontario, Quebec, Newfoundland, and the Federal District Court in Washington, D.C.

With particular reference to cannabis, I have written or co-edited the following books:

- H. Kalant and O.J. Kalant: *Drugs, Society and Personal Choice,* General Publishing Co., 1971, translated into French (1973) and Norwegian (1974)
- K. O'B. Fehr and H. Kalant (eds.): *Cannabis and Health Hazards: Proceedings of an ARF/WHO Scientific Meeting* (1983)
- H. Kalant, W.A. Corrigall, W. Hall and R.G. Smart (eds.), *The Health Effects of Cannabis,* Centre for Addiction and Mental Health (1999).

In addition I have published 31 research papers on various aspects of the pharmacology of cannabis and cannabinoids in scientific journals and multi-author books. I chaired a World Health Organization working party on health effects of cannabis (1994-98), and chaired two Expert Advisory Committees for Health Canada, one on Medical Marihuana Research (2004-06), and one on Information for Physicians

on Medical Marihuana (2011-13). I was an invited witness on health effects of cannabis for the House of Commons Standing Committee on Health (2014), an invited member of an advisory group to the Minister of Health on effects of cannabis on youth (2014), and an invited speaker on medical uses of cannabis to a committee of the National Academy of Sciences of the USA (2014).

Nature of Cannabis, Marijuana, and Pure Cannabinoids

Cannabis is the botanical name of the hemp plant that grows throughout temperate and tropical climates in almost any soil condition. Traditionally two main variants have been recognized and designated as *Cannabis sativa* and *Cannabis indica,* which were said to differ in appearance and in chemical composition. However, this differentiation is now being called into question because environmental growing conditions can produce such marked variation in each that both may be simply part of a wide spectrum of variants of a single species (CanniMed, 2014). *Marijuana* (marihuana) is the common name for the crude preparation of dried, chopped flowering tops and leaves of the cannabis plant. Although this material contains hundreds of different chemical compounds, those which are most distinctive of cannabis are the substances known as cannabinoids. These are found in highest concentration in the resinous material that coats the buds and upper leaves of the plant, and is known by various names including hash, hashish, charas and others.

More than 85 cannabinoids have been isolated from the cannabis plant, but the major pharmacologically active constituent responsible for its characteristic mental and behavioral effects is delta-9-tetrahydrocannabinol (Δ^9-THC, referred to as THC). Delta-8-tetrahydrocannabinol (Δ^8-THC) is equipotent to Δ^9-THC but is present only in very small amount, and cannabinol (CBN) is much less potent than THC with respect to the psychoactive effects, so that neither CBN nor Δ^8-THC is believed to make a significant contribution to the total effect of marijuana on behaviour or perception and other cognitive functions. Cannabidiol (CBD) has different pharmacological effects that may become increasingly important for therapeutic use, but has also been reported to modify the pharmacological activity of

THC when both are ingested at the same time; this will be discussed in more detail later in this report. In freshly harvested and carefully dried marijuana, at least half of the THC is present as tetrahydrocannabinolic acid (THCA), which readily degrades on heating or smoking to yield THC. Statements concerning the potency of cannabis preparations are now normally based on the combined totals of THC and THCA contained in the various preparations.

Apart from its content of volatile cannabinoids, the smoke from marijuana cigarettes is chemically similar to that from tobacco cigarettes, but contains more tar than smoke produced from the same weight of tobacco (Fehr and Kalant, 1972). Some investigators report that two potent carcinogens in tobacco smoke, benzanthracene and benzo[a]pyrene, are present in higher concentrations in marijuana smoke. Differences in the smoking techniques used by marijuana and tobacco smokers are reported to result in three-fold higher levels of tar and five-fold higher levels of carbon monoxide being retained in the lungs during the smoking of cannabis than of tobacco. This greater retention of tar and carbon monoxide from cannabis smoke, combined with the higher content of certain carcinogens in cannabis smoke, may cause a marijuana smoker to have as great or greater exposure to lung irritants than a tobacco smoker despite typically smoking fewer cigarettes per day than a tobacco smoker. Moreover, in those cannabis smokers who are also tobacco smokers (Leatherdale and Burkhalter, 2012) the cannabis smoke adds to the tobacco smoke with respect to the risk of bronchial and pulmonary irritation and damage.

The THC content of marihuana available from illicit sources has increased over the last 35 years. At the time of the LeDain commission in Canada, typical "street" samples of marihuana contained 0.5 to 1% THC. In contrast, 22% of street samples seized in Canada from April 2000 to April 2002 were of poor quality, with THC contents of 0-3%, but the remaining 78% of the samples had a mean THC content (including THCA) of about 10% (range 3-30%). Preparations marketed by licensed producers under the new regulations governing medical use of marijuana since April 1, 2014, contain as much as 23.1% THC. The range of amounts of THC in a marihuana cigarette, which also is variable in weight and is smoked with different techniques by different users, leads to a wide range of delivered dose.

Many synthetic cannabinoids have been produced, and a number of these apart from synthetic THC have pharmacological activities that are not identical to those of THC. Among these active compounds are ajulemic acid and dexanabinol, which do not have the psychoactive effects of THC but are being investigated for possible therapeutic effects, described later in this report.

Neither cannabis plant material nor crude extracts prepared from it are approved by Health Canada as drugs for therapeutic use in Canada. However, dronabinol (pure synthetic THC which is identical in all respects to the THC isolated from the plant) is an approved drug, marketed in Canada until recently under the trade name of Marinol®. Nabilone, a synthetic keto derivative of THC that is not found in the plant material but retains virtually all the pharmacological actions of THC, is marketed under the trade name of Cesamet®. Both dronabinol and nabilone are taken by mouth, and were approved in Canada for prescription use in the treatment of nausea and vomiting, and for the stimulation of appetite in patients suffering severe wasting caused by cancer or AIDS. Nabiximols (a standardized liquid extract of cannabis, containing THC and CBD in equal concentrations, and marketed as Sativex®) has been approved in Canada for treatment of neuropathic pain. It is used in a dose-metered "puffer" to deliver a pre-set amount of spray into the mouth or under the tongue, and is not smokeable. A liquid preparation of CBD (Epidiolex®) has received "orphan drug" status in the United States for clinical trial in the treatment of a severe and rare form of epilepsy in infants, but it is not yet available in Canada.

Quality Requirements for Use of a Substance as a Therapeutic Agent

To be approved for use as a medication in Canada, a substance must meet all of the following requirements:

- exact known chemical composition, including the identities and reproducible amounts of all active components
- standardized testing of safety and efficacy, first in preclinical studies and then in large, well designed, double-blind, placebo-controlled and statistically valid clinical studies

• production under strict supervision to ensure purity, quality and consistency.

To date, marijuana has not met any of these requirements, even that which has been authorized under the former Marihuana Medical Access Regulations, or under the new Marihuana for Medical Purposes Regulations that went into effect on April 1, 2014. In contrast, the pure cannabinoids and standardized extracts mentioned in the previous section have met these requirements, as have all other medications approved for sale on prescription in Canada. The safety requirement normally involves a balancing of the degree of tolerated risk against the therapeutic importance of the drug in question. A higher degree of risk of serious adverse events is tolerable if the drug is used in treatment of a life-threatening disease and no safer alternative is available. In contrast, cannabis is not the drug of first choice for the treatment of any of the disorders described below on pp. 8-15, as more selective and potent drugs of known composition and standardized dosage are available, but it can be useful as an alternative or complementary agent (see, for example, Soderpalm et al., 2001; Machado Rocha et al., 2008; Sofia et al., 1975; Karst & Wipperman, 2009; Elikottil et al., 2009; Teasell et al., 2010)). Therefore a high risk of serious adverse effects would not normally be acceptable if it were undergoing screening for approval by Health Canada.

Biological Mechanisms of Action of Cannabinoids

The pharmacologically active cannabinoids produce their effects by acting on the *endocannabinoid system,* a complex network of endocannabinoids (specialized chemical substances produced in the body, different from the plant cannabinoids but with generally similar effects), the enzymes which produce the endocannabinoids and break them down, receptors (specific protein structures to which they attach themselves and through which they produce their effects), and regulatory substances that modulate the degree of activity of the various enzymes and endocannabinoid receptors (Mechoulam & Parker, 2013; Kalant, 2013). The components of this system are widely distributed throughout most tissues and organs of the body, and serve to regulate the degree of activity of the cells in which they are located.

The plant cannabinoids act by attaching to the endocannabinoid receptors and

producing similar *but not identical* effects. The endocannabinoids are produced on demand, act rapidly but briefly, and are then broken down, so that they serve for fine-tuning the normal level of activity of the cells in which they are located. In contrast, when the plant cannabinoids attach to those receptors they remain attached for a longer time and therefore produce more intense and longer-lasting effects than those of the endocannabinoids. This stronger and more sustained action of the exogenous cannabinoids is responsible for both the therapeutic and the adverse effects of cannabis, but in general the therapeutic effects are obtained with lower doses than the adverse effects. A number of studies have found that progressive increase in dose at first increases the therapeutic effect, but further increases lead to loss of therapeutic effect and its replacement by adverse effects (Kalant, 2013).

Much recent evidence has demonstrated that plant cannabinoids do not bind only to endocannabinoid receptors, but also to a number of receptors of types involved in the initiation and maintenance of inflammatory reactions. This is of growing interest in relation to additional possible therapeutic actions of cannabinoids, described below.

Current Scientific Knowledge with Respect to Beneficial Therapeutic Effects

In keeping with the widespread presence of the endocannabinoid system throughout the body, there are many different claimed therapeutic effects of cannabis in a variety of different organs and systems. The major therapeutic uses have been reviewed by many authors (Kalant, 1972; Kalant, 2001; Leung, 2011; Russo, 2007; Robson, 2014), and a very comprehensive and valuable source of information is the Health Canada publication authored by Abramovici (2013). However, the claims differ widely in terms of the amount of scientific evidence supporting them. It is therefore convenient to group them into those which are well supported by both basic research and clinical experience, those for which there is promising evidence from basic research but not yet from sufficient clinical experience, those for which there is little or no scientific support, and those which are clearly rejected on clinical grounds. The great preponderance of scientific evidence concerning therapeutic effects has

been obtained in studies using pure cannabinoids, and relatively little with cannabis itself, whether smoked or eaten.

(a) Therapeutic uses with good scientific support

(i) Pain Both smoked cannabis and oral cannabinoids have been shown to provide moderately good relief of chronic musculoskeletal and neuropathic pain. Sativex® is also approved in Canada for neuropathic pain. In contrast, they give little or no benefit in acute pain associated with injuries, or post-surgery. Thus, cannabis is a more limited and less potent analgesic than opioids, but combining smaller doses of cannabis (or cannabinoid) and an opioid may give good pain relief with fewer side effects than a larger dose of either drug alone.

(ii) **Nausea and vomiting** Cannabis, or pure THC, provides good relief of nausea and vomiting induced by chemotherapy or radiotherapy of cancer, or by drugs used to treat HIV/AIDS. Cannabis or THC is less potent for this purpose than newer antiemetics such as ondansetron or its derivatives, but may be a useful back-up in patients who do not respond to the superior drugs. If given 1-2 hours before the chemotherapy or radiotherapy, oral THC can be used to prevent nausea and vomiting. However, if nausea or vomiting has already begun, smoked cannabis has the advantage of a very rapid onset of action, and can be used by patients who could not swallow or keep down a tablet or capsule.

(iii) **Stimulation of appetite** Both cannabis and pure THC-like cannabinoids can stimulate food intake in patients with severe weight loss and tissue wasting due to cancer or HIV/AIDS. However, they increase primarily the intake of carbohydrate and fat, which provide energy, but not the intake of protein needed for tissue restoration. Therefore they are less useful for this purpose than the anabolic steroids that increase tissue mass.

(b) Promising but not yet fully validated therapeutic uses

(i) Seizure control In animal experiments, both THC and CBD have shown antiseizure activity comparable to that of conventional antiepileptic drugs, and many epileptics report using cannabis to help control their seizures (Gross et al., 2004). But

there is so far little scientific evidence in humans. One rather small study found that, in patients whose seizures were not well controlled by conventional drugs, addition of CBD together with the conventional drugs significantly improved the seizure control, but there were some flaws in the design of the experiment (Devinsky et al., 2014). A liquid preparation of CBD, marketed as Epidiolex®, is now available in the United States as an investigational drug for the treatment of a severe form of epilepsy occurring in early childhood. Since it contains no THC, it is free of unwanted psychoactivity. A very recent critical review by the American Academy of Neurology concluded that there is insufficient evidence to permit any conclusion about the value of cannabis or cannabinoid therapy in seizure disorders.

(ii) **Sedation and anti-anxiety effect** Cannabis extracts were widely used for treatment of insomnia and anxiety during the late 19th and early 20th centuries, and both THC and CBD in small doses were shown to have these effects in animal studies. However, THC in higher doses produces mental changes in humans, such as a sense of unreality that can actually produce anxiety or precipitate acute panic. CBD, which does not have psychoactivity, has recently been shown to partially block receptors for THC. Therefore CBD does not produce anxiety, and can prevent or reduce the anxiety caused by THC when the ratio of CBD to THC is 1:1 or higher. Therefore pure CBD may have greater clinical value as a sedative and anxiolytic agent, but has not yet had sufficient clinical trial to establish its utility.

(iii) **Relief of spasticity** Many claims have been made for the ability of cannabis to relieve spasticity (intense, uncontrollable, painful contraction) in skeletal muscles and in the urinary bladder, in patients with multiple sclerosis (MS). Numerous studies have shown that it relieves the pain or discomfort in patients with spasticity, but most studies found no objective evidence that the spasticity itself was actually reduced (Zajicek & Apostu, 2011). However, a recent Canadian study found that smoked cannabis reduced both the subjective discomfort and the objectively measured muscle spasticity in MS patients (Corey-Bloom et al., 2012). Additional well-designed and large-scale clinical trials are still needed to resolve the difference between the different study outcomes and determine the therapeutic value of cannabis in this condition.

(iv) Anti-inflammatory action As mentioned earlier in this report, some of the plant cannabinoids (e.g., CBD) and their synthetic analogs act to block the action of factors such as interleukins and prostaglandin derivatives that initiate inflammatory reactions. Preclinical studies and a few clinical trials suggest that this action may be helpful in various types of inflammation such as arthritis, fibromyalgia, skin eruptions and Crohn's disease (Blake et al., 2006; Lahat et al., 2012; Naftali et al., 2011). However, there has not yet been sufficient clinical trial to demonstrate the utility of cannabis or cannabinoids as a first-line anti-inflammatory medication.

(v) Neuroprotective action A considerable amount of preclinical research has demonstrated that a number of plant cannabinoids and synthetic analogs, including THC, CBD, dexanabinol and ajulemic acid, are able to reduce or prevent death of brain cells caused by injury, inflammation, circulatory obstruction, reactive oxygen, or excessive activation of the nerve cells by excitatory neurotransmitters. No studies have so far been carried out with crude cannabis preparations. The fact that CBD shares these effects indicates that various receptors apart from the endocannabinoid receptors are involved, and that the psychoactive effects of THC are not required for the neuroprotection.

It is also noteworthy that the neuroprotective effect of CBD and other cannabinoids is obtained with relatively low doses; at first the effect increases with increasing dose up to a maximum effect, but further increases in dose actually reduce the protective effect. High doses of THC can actually damage neurons rather than protect them. Virtually all the literature on neuroprotective actions of cannabinoids relates to animal experiments. To date, only two clinical trials have been reported, using dexanabinol rather than cannabinoids from plant material. A phase II trial reported promising results with lowering of intracranial pressure, but a later large-scale international phase III trial demonstrated that dexanabinol was safe, but did not produce any improvement in outcome at six months after the injury (Kalant, 2013).

Another area in which neuroprotective effect has been sought is multiple sclerosis (MS). A recent large-scale multicentre study in the United Kingdom found that dronabinol (synthetic THC) had no beneficial effect on the rate of deterioration in patients with progressive MS. Many studies have shown beneficial effects on the

subjective symptoms of MS, especially spasticity and pain, as noted above, but no beneficial effect has so far been found on the disease process itself.

(c) Claimed therapeutic effects with little or no scientific evidence to date

(i) Movement disorders Malfunction of parts of the central nervous system can give rise to disorders of muscle control in the face, limbs and trunk. The best known examples are Parkinson's disease, Huntington's disease, amyotrophic lateral sclerosis (ALS, or Lou Gehrig disease) and Tourette syndrome. Anecdotal claims have been made for a beneficial effect of cannabis in these conditions. However, there is little or no scientific basis for expecting benefits in Huntington's disease or ALS, or for encouraging long and expensive clinical trials.

Many patients with ***Parkinson's disease*** have reported trying cannabis and obtaining some improvement in tremor or rigidity of the limb muscles. However, the one small clinical trial reported to date found no improvement of tremor after smoking marijuana. CBD has been found to produce changes in the basal ganglia (the brain structures where Parkinson's disease arises) that are conceivably related to its neuroprotective actions, and which might therefore suggest an ability to prevent or retard progression of the disease. However, much more basic research is required before clinical trials can be considered.

Tourette syndrome is characterized by uncontrollable motor and vocal tics. Four published case reports have described apparent improvement after smoking cannabis, but it is not clear whether the improvement was due to improvement in the underlying neurological disorder, or due merely to sedation. However, a recent small but well designed placebo-controlled clinical trial found a reduction in tics by THC, that was proportional to the THC dose given. No comparable trial with smoked cannabis has been reported. Further trials, of longer duration, are needed to find whether the benefit is sustained and clinically useful.

In summary, the available evidence does not indicate any significant beneficial effect of cannabis or cannabinoid therapy in the motor disorders mentioned here, apart from any improvement that may be secondary to relief of pain and, questionably, of spasticity.

(ii) Anticancer therapy A substantial body of literature describes the ability of THC and other cannabinoids to inhibit the genesis and growth of several types of cancer cells in cell cultures, or of induced or implanted cancers in experimental animals, and to stimulate apoptosis (genetically programmed cell death) in experimental cancer cells (Alexander et al., 2009; Freimuth et al., 2010; Bowles et al., 2012). Cannabinoids have also been reported to inhibit the growth of blood vessels (angiogenesis) that supply enlarging cancers, and the ability of cancer cells to detach from a primary tumor and be carried in the blood to secondary sites (metastasis). However, these effects, which in theory might become therapeutically useful, have so far been found only at concentrations very much higher than those measured in the blood of heavy users of cannabis (Kalant and Porath-Waller, 2012). Only one small clinical trial of THC therapy has been carried out in nine patients with recurrent brain cancers as soon as the recurrence was detected. THC was injected directly into the cancers, and at first relieved the patients' symptoms, but did not prevent the re-growth of the cancer or prolong the patients' survival time (Guzman et al., 2006).

(iii) Psychosis Claims have also been made for cannabis as a possible therapeutic agent in the treatment of psychosis. In view of the evidence concerning precipitation of psychosis by cannabis and by THC, this proposal lacks credibility. CBD, or specially developed strains or extracts of cannabis with low THC and high CBD content, are perhaps worthy of investigation in this regard, but so far there is little or no evidence to permit judgment about their efficacy and safety (Devinsky et al., 2014).

(d) Claimed therapeutic uses which have been rejected on clinical grounds

(i) Glaucoma In glaucoma, elevated fluid pressure within the eyeball results in damage that can result in blindness. THC and cannabis have been shown to reduce the intraocular pressure, but the effect of a tolerated dose is limited to a few hours. To prevent damage to the eye, it is necessary to reduce the pressure continuously throughout the day and night (Green, 1998). Therefore, for the effect of cannabis to be clinically useful it would be necessary to smoke it every few hours,

day and night. This is obviously impractical, and has been rejected by the ophthalmological societies of Canada and other countries.

(ii) Bronchial asthma In asthma, constriction of the bronchi impedes movement of air into and out of the lungs. Smoked cannabis and THC by aerosol inhalation (Hartley et al., 1978; Tetrault et al., 2007) have both been reported to relax the constricted bronchial muscles and facilitate the air movement for up to two hours. However, frequent smoking of cannabis gives rise to bronchial irritation (see below under Adverse Effects), which tends to offset the initial beneficial effects and render it no longer useful for the treatment of asthma. Pure cannabinoids, administered by methods not involving smoking, may possibly have a future place in the therapy of asthma, but there is insufficient evidence to support their use at present (Davies et al., 1975).

(iii) Hypertension Cannabis and THC have a relaxant effect on the muscle of the walls of small arteries and arterioles, which could theoretically be useful in the treatment of hypertension (high blood pressure). This effect is manifested in the phenomenon of orthostatic hypertension, which is a sudden fall in blood pressure, and a consequent feeling of faintness, on changing from a sitting to a standing position by those who have just smoked cannabis. This is a temporary response which is quickly corrected by normal physiological adjustment. The treatment of hypertension, however, requires sustained and controllable reduction of pressure, which is not attained with cannabis use. No clinical trials have demonstrated any utility of cannabis or cannabinoids as treatment for hypertension.

(iv) Depression Claims have been made for the use of cannabis as an antidepressant, presumably on the basis of the mood-elevating effect in normal subjects. Similar improvement in mood has been observed in patients being treated with cannabis or cannabinoids for chronic pain (Ware et al., 2010). There is good evidence that disturbance of the endocannabinoid system is involved in the expression of depression (Gorzalka & Hill, 2011). However, several studies have shown an increased risk of depression in chronic smokers of cannabis, especially in those who began use early in adolescence (Degenhardt et al., 2003; Harder et al., 2006, 2008). There are no adequately designed studies showing a sustained,

clinically useful antidepressant action of either smoked cannabis or oral cannabinoids in primary depression or bipolar disorder.

Methods of Administration of Cannabis and Cannabinoids for Medical Purposes

Cannabis and various cannabinoids have been administered by several different routes, which affect the speed of onset, intensity and duration of their effects.

Smoking is used primarily for cannabis itself, but has also been used experimentally for administering pure THC added to cannabis material from which all the originally present cannabinoids have been extracted (a way of standardizing the THC content), or added to tobacco. As noted, the heat of combustion of cannabis converts the THCA to free THC, volatilizes much of the THC, and delivers the volatilized cannabinoid to the lungs. The cannabinoids are very highly soluble in fatty substances, and this enables them to diffuse very rapidly across cell membranes, so that in the lung they pass rapidly across into the blood. However, they have very little solubility in water, and therefore must bind reversibly to proteins in the blood to be carried throughout the body to the various tissues in which they act. They then separate from the protein carrier and pass rapidly into the tissues.

Vaporization avoids the production of smoke from the herbal cannabis material by heating it at a temperature a little below the point of combustion, but high enough to convert THCA to THC and volatilize the THC, which can then be inhaled in the same manner as cannabis smoke. However, it has not yet been studied enough to demonstrate whether the high temperature of the vapor can also irritate the airways.

For experimental purposes, ***intravenous injection*** can be used, provided that the cannabinoid has been mixed with an appropriate non-toxic carrier such as serum albumin. However, this is too difficult a technique to permit its therapeutic use. Smoking, vaporization and intravenous injection all deliver a very rapid onset of action, a high initial maximum concentration in the blood that falls rapidly as the cannabinoid redistributes into the tissues, and a relatively short duration of action

(typically 3-4 hours at ordinary doses) as the bulk of the cannabinoid is converted into inactive and more water-soluble metabolic derivatives that are excreted in the bile and the urine. However, because of the high solubility of the cannabinoids in fatty tissues the last traces of cannabinoid take a long time to be extracted from the tissues. The half-life for elimination ranges from 29 to 52 hours in different individuals, and screening tests for the metabolites in urine may remain positive for several days after a single use, or for up to several weeks after discontinuation of chronic use.

Oral administration with intestinal absorption can be used for crude cannabis preparations, and was the normal method in traditional Indian medicine. It is also used with edible cannabis preparations such as baked goods and oils, and is the common method of administering pure cannabinoids. Absorption from the intestine is slower than from the lung, so that the onset of effects usually takes up to two hours, but it has the advantage of being gradual and prolonged, without a very high initial effect. As a result, for therapeutic use it has the advantages of requiring less frequent doses, and producing relatively less psychoactivity for a given degree of therapeutic effect. Since the absorbed cannabinoid passes first to the liver before entering the general circulation, a higher proportion of the dose is converted to the 11-hydroxy metabolite than occurs after smoking. However, this does not affect the therapeutic utility of the drug, because that metabolite is also pharmacologically active.

Oral spray is the method used for administration of the standardized liquid extract of cannabis known as Sativex®. It is sprayed under the tongue or on the lining membrane of the cheek, but not swallowed. Absorption occurs through the oral lining, and the absorbed material passes directly into the circulating blood without going first to the liver. The speed of onset and duration of action by this method are intermediate between those associated with smoking and those found after conventional oral administration.

Juicing is another form of oral administration employed by some users who prefer fresh (undried) to dried plant material. The fresh material is subjected to pressure that yields a small amount of liquid which the user ingests. The reason for

this preference is unclear. If an analogy is drawn with a preference for undried versus dried fruits or vegetables, it is indeed conceivable that fresh cannabis juice contains some substance or substances that add to the flavour or nutritional value, but are lost during drying. However, the present action concerns the use of cannabis not as a food but as a medication, and I have been unable to find a single scientific study comparing the therapeutic effects of undried versus dried cannabis. Any claims for a special medicinal value of the undried material so far are anecdotal and based purely on conjecture or on the well-known placebo effect.

Percutaneous absorption (absorption through the intact skin) has been demonstrated in test-tube experiments and in living animals, and has been described anecdotally by humans who have applied oily extracts of cannabis to themselves for relief of localized muscular or skeletal pain. However, the permeability of human skin to the cannabinoids is very low, so that blood concentrations of cannabinoid achieved by this method are also very low, and no scientific studies of its efficacy for medical purposes have so far been published.

Dosage Range of Marijuana for Medical Uses

The recommended therapeutic dosage range of any medication depends upon its potency and dose-response curve for the desired effect, the time course of its metabolic inactivation in the body, and the dose-response curves for its various undesired or toxic effects. In view of the variability of composition and potency of different preparations of cannabis, there is so far insufficient evidence on which to base scientifically reasoned dosage ranges for different medical uses. However, some information is available from clinical experience about the effective and tolerated doses used in clinical trials. The average dose used by 5,540 users of medically prescribed cannabis in The Netherlands was 0.68 g/day, ranging from 0.82 g/day in those under 20 years of age to 0.66 g/day in those aged 41-60 years (Hazekamp and Heerdink, 2013). An addendum to Health Canada's publication on medical marihuana information for physicians (Abramovici, 2013) indicates that the average daily amount of dried cannabis used by patients in the medical marijuana program in Israel in 2011-12 was 1.5 grams. A number of other studies have found similar

effective dose ranges in other countries.

A Canadian study of 30 patients receiving cannabis under the MMAR for relief of pain used amounts ranging from less than 1 to 5 g/day, taken by smoking or by oral consumption, and maintained for a mean treatment period of 2 years (Lynch et al., 2006). Ware et al. (2010) found a significant reduction of neuropathic pain with the remarkably small daily dose of 75 mg of dried cannabis with a THC content of 9.4%, which also improved sleep and decreased anxiety. There is thus a high degree of agreement concerning effective dose ranges for a variety of medical purposes in different populations.

The endocannabinoid system exhibits a phenomenon that has been referred to as "receptor overload" (Lichtman et al., 2010). If the dose of cannabis or cannabinoid is increased beyond a certain point, further increases no longer produce a greater effect but actually decrease or abolish it because of desensitization of the receptors, so that the therapeutic effect disappears or is even replaced by adverse effects (Kalant, 2013). It seems reasonable, therefore, to infer that use of much higher daily dosages than those described above for therapeutic purposes represents either very inefficient use of the drug, or use for non-medical purposes.

Scientific Evidence with Respect to Claimed Selectivity of Therapeutic Value of Different Strains of Cannabis

Frequent claims have been made by cannabis users or advocates of medical use of cannabis that different strains of cannabis, presumably containing different proportions of various cannabinoids, have differential effectiveness in the treatment of different diseases. This claim is at present impossible to substantiate, for two reasons. The first is that it is not at all clear that the large number of so-called strains advertised on the internet are in fact distinct strains as defined botanically. The second is that there is very little scientific evidence derived from properly designed clinical trials to show that different strains have different therapeutic advantages for treating different diseases or symptoms.

For cannabis, the definition of "strain" is essentially the same as that of "cultivar" as set out in the international code of nomenclature for cultivated plants,

i.e., "an assemblage of plants that (a) has been selected for a particular character or combination of characters, (b) is distinct, uniform, and stable in these characters, and (c) when propagated by appropriate means, retains those characters" (Dr. E. Small, Agriculture Canada, personal communication). The selected characters may include the physical appearance of the plant, as well its chemical composition. The growers licensed under the new Marihuana for Medical Purposes Regulations do provide information on the cannabinoid contents of their cannabis preparations, which probably do meet the criteria to be defined as strains. However, the very numerous fancifully named "strains" of cannabis advertised on the internet are not accompanied by any evidence that they meet these criteria, or that they have even been analysed chemically for their contents of various cannabinoids. The claims of differential therapeutic selectivity of such preparations are based either on subjective anecdotal reports, or promotional advertising by the producers. Indeed, a study of 5,540 Dutch users of medically prescribed cannabis dispensed by pharmacies found no consistent relation between the medical diagnosis and the preferred strain of cannabis (Hazekamp & Heerdink, 2013).

The only scientific basis so far available for the existence of differential therapeutic value of different cannabis strains is the ability of CBD, noted above, to produce certain therapeutic effects by acting on receptors other than the CB1 and CB2 receptors through which THC acts. CBD in high concentrations relative to THC also acts as a partial blocker of THC binding to CB1 cannabis receptors in the nervous system, as described earlier in this report. The selection of different strains of cannabis by illicit producers in recent years, however, has been mainly directed toward increasing the concentration of THC rather than of CBD, in order to increase the potency in production of the psychoactive effects sought by non-medical users. It is probable that many of these preparations have some degree of variation in the THC:CBD ratio, though all would have much more THC than CBD. To date, there have been no published scientific studies comparing different preparations of cannabis of this type with each other and with pure cannabinoids, with respect to their efficacy and potency for the various therapeutic effects mentioned above.

Adverse Effects of Marijuana Consumption

Studies of therapeutic effects of cannabis or cannabinoids have mainly been of relatively short duration, and have employed relatively lower doses than are used by many non-medical users. Therefore they have reported only on short-term ("acute") adverse effects, and have generally found them to be mild and fairly well tolerated. The major such effects have been drowsiness, dry mouth, nausea, dizziness and difficulty in concentration. In contrast, serious chronic adverse effects have been studied almost entirely in non-medical users (Kalant, 2004; Hall and Degenhardt, 2009). There is a genuine need for studies of adverse effects in long-term medical users. Therefore it should be recognized that the following descriptions of acute and chronic adverse effects are derived from two different populations.

(a) Acute adverse effects

Intoxication Acute intoxication with cannabis is characterized by psychoactive effects (also known as the "high") that are the main reason for non-medical use, but that usually constitute undesired effects when it is used for medical reasons, or when the user is engaged in driving or other activities that require vigilance, skill and rapid responses. The "high" includes euphoria, talkativeness and laughter, increased physical and emotional sensitivity and empathy, followed by lethargy and drowsiness. These effects may in themselves reduce anxiety and thus augment the pharmacologically based anti-anxiety effect that provides relief of fear or anxiety in many patients. On the other hand, feelings of unreality can disturb patients unused to cannabis effects, and result in drop-out from treatment. These psychoactive effects have been observed even at the relatively low doses of cannabinoids recommended for clinical use for the treatment of pain (Issa et al., 2014).

The "high" is also accompanied by distortion in the sense of time, deficits in short-term memory and learning, difficulty in focusing attention on tasks at hand, and decreases in psychomotor functions such as hand steadiness, tracking tasks, divided attention tasks and reaction speed. These effects result in impaired performance in

driving or flying simulators and in test driving, that may still be found up to 24 hours after smoking marijuana. The effect is proportional to the peak serum concentration of THC and its active metabolites. Early reviews of cannabis and driving tended to find no evidence of a role of cannabis in driving accidents and fatalities (e.g., Bates and Blakely, 1999). However, more recent studies have found fairly strong evidence. US national data for traffic fatalities in 2010 showed that of drug-impaired drivers killed in accidents, the largest group with illicit drugs had cannabis, about half and half without alcohol as well (Wilson et al., 2014). Since the "commercialization" of medical marijuana in Colorado in 2009 involvement of drivers impaired by cannabis in fatal motor vehicle accidents increased sharply while the involvement of alcohol remained unchanged (Salomonsen-Sautel et al., 2014).

Epidemiologic studies in Canada and other countries have yielded strong evidence of an association between use of cannabis and involvement in driving accidents, injuries and fatalities, especially among those who use alcohol and cannabis simultaneously (Terry-McElrath et al., 2014), and even among cyclists (Asbridge et al., 2014). Some culpability studies have indicated a direct relationship between the driver's blood level of THC and the driver's responsibility for causing the accident, though there is not unanimous agreement on this finding (Kalant, 2004). Such effects are especially worrying in adolescents, because studies in Ontario and the Atlantic provinces (Adlaf et al., 2003; Asbridge et al., 2005) have shown that 15-20% or more of 15-18 year olds had driven within an hour of using marijuana, and many of these had been involved in accidents.

Mood disorders and psychosis High doses of smoked or orally ingested cannabis can cause a variety of mood disturbances, including anxiety, paranoia, panic and depression, usually in inexperienced subjects. Perceptual disturbances such as illusions or hallucinations have also been reported. These reactions usually disappear spontaneously within hours after the use of cannabis, especially with reassurance and support, but in some cases after unusually high doses there may be an acute toxic psychosis, usually of somewhat longer duration (days rather than hours). Population studies have found that up to 15% of those who have ever used cannabis have experienced psychosis-like symptoms at some time, either early during their history

of use, or later after an unexpectedly high dose or unusually potent preparation.

A more serious effect is the precipitation of schizophrenia in individuals with a genetic predisposition but who had not previously displayed psychotic symptoms, and the triggering of clinical relapse in schizophrenic patients who had been in remission prior to the use of cannabis (Kalant, 2004, Hall & Degenhardt, 2009). Patients with overt clinical pictures of schizophrenia have a poorer response to treatment if they use cannabis (van Dijk et al., 2012). Population studies have shown that early use of cannabis is a predictor of increased risk of schizophrenia as well as of depression and bipolar disorder. In contrast early depression does not predict later use of cannabis. Early display of schizophrenic symptoms does predict later use of cannabis, as it does of a variety of other drugs, apparently as a form of self-medication, but therapeutic results with antipsychotic medication are poorer in patients who use cannabis.

Cardiovascular system The major acute effects of cannabis on the cardiovascular system are an increase in heart rate, and a decrease of sympathetic nervous system control of the smaller branches of the arterial tree. The latter effect results in poorer compensation for the effects of gravity when the user changes from sitting or lying to a standing position. The small arterioles do not constrict quickly enough to maintain the arterial blood pressure, resulting in insufficient blood supply to the brain ("orthostatic hypotension") and consequent faintness. This is not a serious problem, and tolerance to this effect probably develops in regular users. In contrast, increase in heart rate increases the work load, and therefore increases the oxygen requirement of the heart muscle. Several case reports have described heart attacks (myocardial infarction) or serious disturbances of heart rhythm precipitated by the smoking of marijuana in middle-aged men with some evidence of pre-existing narrowing of the coronary arteries which prevented a compensatory increase in coronary blood flow (Kalant, 2004).

(b) Adverse effects of chronic use

Respiratory system Prolonged regular smoking of cannabis has long been known to give rise to chronic inflammatory changes in the walls of the bronchi, with chronic cough, wheezing, and increased production of phlegm (Kalant, 2004; Tetrault

et al., 2007)). An appreciable percentage of cannabis users are also tobacco users (Leatherdale and Burkhalter, 2012), and the effects of the two substances are at least additive. Histological and biochemical analyses of biopsy samples of bronchial mucous membrane from long-term cannabis smokers have revealed typical precancerous changes. Cannabis smoke condensates have been found capable of inducing cancer when applied to the skin of experimental animals. A number of epidemiological studies have found a significantly increased risk of airways cancer in chronic smokers of cannabis, with the increase of risk being proportional to the duration and intensity of cannabis exposure. The effect of cannabis remained significant even after statistical correction for the effect of concurrent use of tobacco. However, at least one large and well designed population study found no significant increase in risk among long-term cannabis users. The reason for the disagreement is not yet clear, so that no definitive statement about cannabis smoking and cancer risk is yet possible.

A similar uncertainty is shown in the literature concerning the role of cannabis smoking in the production of chronic obstructive pulmonary disease (Kalant, 2004; Tetrault et al., 2007). One study found an apparent causal link, whereas another equally large and well executed study failed to find such a link. A third longitudinal study (Taylor et al., 2002) found only a marginally significant adverse effect of cannabis alone on lung function, but a significant interaction with tobacco smoking. No firm conclusion is yet possible.

Circulatory system A rare but serious problem attributed to cannabis use is peripheral vasculitis, an inflammation of the walls of blood vessels in the leg that can obstruct blood flow and lead to gangrene of the foot.

Psychiatric and cognitive disturbances A number of large population studies of adolescents and young adults in North America, Europe, Australia and New Zealand have demonstrated a significantly increased risk of schizophrenia, depression, anxiety and panic, and poor psychosocial adjustment (poor school and work performance, drop-out, antisocial behavior, police encounters) in those who took up marijuana use early in adolescence and continued using it (Crean et al., 2011; Homel et al., 2014). Young adults who were regular smokers of marijuana, tested

after 28 days of abstinence, showed reductions in overall intelligence and in a variety of specific cognitive functions that were proportional to their average rates of cannabis use (Bolla et al., 2002). The time relationships and dose-dependence strongly suggest that cannabis was a precipitating or causal factor in these problems rather than a response to them. However, cross-sectional studies can not rule out the possibility that both the early marijuana use and the later psychiatric, cognitive and personality problems were due to other unidentified factors of either genetic or family environmental nature.

The best evidence for a causal link is provided by a recent analysis of the findings of a remarkable prospective study known as the Dunedin Study. This is a study of a birth cohort of 1,037 children born in Dunedin, New Zealand, in a one-year period spanning 1972-73, comprising 91% of all children born during that period (McGee et al., 2000; Meier et al., 2012). They were examined every few years from birth to 38 years of age. Detailed neuropsychological testing was performed at age 13 years before the start of cannabis use and again at subsequent examinations at ages up to 38 years. Those who did not become cannabis users showed a small gain in intelligence from age 13 to age 38, whereas those who became regular cannabis users showed losses in intellectual functions that were greater the more they had used and the earlier they had started using it. The losses were found in at least five different areas of mental function, and were shown not to be due to residual cannabis still in the body, to fewer years of schooling or to pre-existing mental problems before they started cannabis use. Those who began using it at later ages and then stopped using it recovered their mental functioning completely, but those who began at the youngest ages and later stopped using it did not recover fully.

These findings are consistent with other evidence that cannabis use inhibits maturation of brain cell pathways involved in executive functions (working memory, judgment, problem solving, etc.) that occurs during adolescence (Kalant, 2013). If cannabis is used throughout this period, maturation can not occur even if use is discontinued later. This failure of maturation has been proposed as a possible mechanism of the precipitation of psychosis by cannabis (Bossong & Niesink, 2010). The effects in the Dunedin study resulted in more school drop-out, poorer social

adjustment, and greater risk of depression later (Fergusson & Boden, 2008).

The brain also undergoes rapid development during growth of the fetus during pregnancy. Two ongoing studies, one in Ottawa and a later one in Pittsburgh, have shown that offspring of mothers who smoked cannabis during pregnancy have similar effects on memory and other executive functions of the brain when examined during early school years, adolescence, and young adulthood (Fried, 2011). Functional MRI studies of some of the Ottawa subjects who have reached adulthood have shown ted alterations in those brain regions that carry out executive functions (Smith et al., 2010).

Dependence (addiction) Studies in many countries have confirmed that about 8-10% of chronic users of cannabis for non-medical purposes become addicted, as defined by great difficulty or inability to stop using it even when serious drug-related problems make it necessary to do so (Jones et al., 1976; Hall & Solowij, 1998; Wagner & Anthony, 2002; Kalant, 2004; Budney et al., 2004; Lichtman & Martin, 2005). The picture includes physical dependence as shown by a withdrawal syndrome on temporary cessation of use. The withdrawal reaction includes restlessness, irritability, insomnia, sleep disturbance, nausea and cramps, and can be severe enough to contribute to relapse in those who are attempting to stop use. Those who begin using in early adolescence have a significantly higher risk (about 16%) of addiction (Wagner & Anthony, 2002).

Contraindications to the Medicinal Use of Marijuana

For obvious reasons, based on the review above, four groups of potential patients should not be treated with cannabis or psychoactive cannabinoids. These groups are: (1) pregnant women, (2) children and adolescents, (3) persons with a personal or family history of schizophrenia, and (4) those with previous histories of abuse or dependence on alcohol, tobacco, cannabis or other drugs acting on the central nervous system.

Limitations of Knowledge, and Problems for Medical Supervision of Marijuana Use for Medical Purposes

Tolerance Repeated administration of cannabis or of THC has been shown to produce a significant degree of tolerance to many of the physiological and behavioral effects, after relatively short periods of use, in both experimental animals and humans (Hart et al., 2010; Iversen, 2003; Kalant & LeBlanc, 1974; Kirk & de Wit, 1999; Loflin & Earleywine, 2014). The increase in tolerance is lost quickly when use of the drug is stopped. Most of the research dealing with tolerance has focused on non-medical use of fairly high doses, and tolerance to the side effects of therapeutic doses. It has been reported that no tolerance developed to the beneficial effects of Sativex® on pain and sleep in studies lasting up to four years (Russo et al., 2007) but this was based on patient reports. To date, there have been no studies with actual measurement to see whether tolerance develops to the therapeutic effects during long-term use of lower doses for medical purposes.

Age of user Early clinical studies of the use of cannabinoids or cannabis in the treatment of pain or nausea and vomiting in cancer patients, who typically are of older age than the great majority of non-medical users of cannabis, found fairly numerous dropouts because of adverse effects such as drowsiness, confusion, and feelings of unreality. These complaints are seldom reported by young non-medical users. The question arises as to whether this represents an age-related difference in the effects of cannabis and cannabinoids. To date, no objective evidence has been found of such a difference. Therefore it is more likely that older patients at the time of those studies had not had any previous experience with cannabis, and that the same effects that young users seek in non-medical use (the "high") were unpleasant for the older patients mainly because of unfamiliarity with those effects.

Interactions with other drugs Since much of the claimed medical use of cannabis occurs without medical supervision, and many of the users also employ other drugs, whether licit or illicit, there are many opportunities for drug interactions. Because of the very wide range of actions of cannabinoids, interactions can occur with many different types of drug. These may be either metabolic or functional interactions, and may either increase or decrease the action of one or other, or both, of the interacting drugs. A valuable review of the different known interactions is contained in the Health Canada publication (Abramovici, 2013). Much of the

literature on drug interactions with cannabis or cannabinoids is based on animal experiments, and the metabolic interactions are not necessarily applicable to humans, since there are significant interspecies differences in metabolic pathways for drugs.

However, there are numerous clinical studies and case reports of interactions in humans. In general, the depressant effects of cannabis are at least additive with those of alcohol, opiates, benzodiazepines and muscle relaxants. On the other hand, cannabis can increase the risk of manic episodes and delirium in patients treated with certain types of antidepressant medication or with disulfiram (Antabuse), and can increase heart rate, blood pressure, and risk of heart attacks when used together with anticholinergics and adrenalin-like drugs. The suppressant effect of cannabis on the immune system, though not strong by itself, can become a problem when it is used together with corticosteroids, which are also immunosuppressant. An interaction of much concern recently is that between cannabis and "ecstasy" used together, but there is insufficient evidence to permit any conclusion as to its risks.

In contrast to these adverse consequences of drug interaction, it must also be noted that interactions can be therapeutically useful in some cases. For example, as noted above, the combination of low doses of opioid and cannabis can give good relief of pain with fewer side effects than are produced by a higher dose of either drug alone. Similar benefit could be produced by combining low doses of cannabis and benzodiazepine for the relief of anxiety or insomnia. The use of such combinations, however, requires careful medical supervision of the dosage.

Who are the users of cannabis for claimed medical purposes ?

Health Canada authorized about 40,000 Canadians to possess and use cannabis for medical reasons certified by physicians under the previous Medical Marihuana Access Regulations. Population surveys, however, have found well over a million Canadians who say they use cannabis for medical reasons, but who have not applied for or received authorization from Health Canada. Studies in California found that the largest group of applicants for cannabis therapy were young males aged 18 to 34 years, complaining of chronic back or neck pain, sleep difficulty, or emotional disorders (Nunberg et al., 2011). Since these are not typically complaints of young males, they suggest that many of these do not really have medical reasons for use, but

claim medical reasons as a pretext for non-medical use. Therefore one of the risks of medical marijuana programs is the possibility of diversion of cannabis from the intended medical uses to non-medical use, with its increased probability of adverse effects. Recent evidence tends to support the reality of this risk. Comparison of U.S. states that enacted medical marijuana laws (MML) with states that did not do so revealed that the MML states had significantly higher rates of marijuana use and lower perceptions of its risk by adolescents (Wall et al., 2011), and higher rates of adult use, abuse and addiction (Cerdá et al., 2011). Canadian physicians have expressed their fears of contributing to such outcomes if they are required to actually prescribe cannabis under the new Marihuana for Medical Purposes Regulations.

Inadequate Knowledge by Physicians Surveys of Canadian physicians by Health Canada, the Canadian Medical Association and the Canadian College of Family Practice have indicated that the majority of physicians are highly reluctant to accept responsibility for prescribing cannabis for medical purposes because of the following concerns:

- it has never been approved by Health Canada for efficacy and safety in clinical use as is required for other medications;
- there are no truly standardized preparations of cannabis available;
- they feel that they lack knowledge of its valid indications for use and its proper dosage for such uses;
- they are worried about the risk that bogus patients with bogus complaints will put pressure on them to obtain cannabis for what is really non-medical use;
- they are worried about their legal responsibility in the event of adverse effects on patients.

The same concerns would obviously impede their ability to supervise patients using cannabis for medical purposes. Health Canada is making efforts to supply knowledge and recommendations to physicians to alleviate these concerns, but the program is not yet in full operation.

SUMMARY

Cannabis and cannabinoids exist in many different forms, with different composition of active agents, different potencies, different routes of administration, and different durations and intensities of effect. Except for the approved extracts and pure cannabinoids, none of these are standardized, and none have received official Health Canada approval for safety and efficacy as medications.

Good evidence exists for the therapeutic utility of cannabis or cannabinoids for relief of chronic musculoskeletal or nerve pain, for relief of nausea and vomiting due to chemotherapy, and for stimulation of appetite in patients with severe wasting of body tissues. Promising laboratory evidence exists for use in control of epileptic seizures, anxiety, insomnia, muscle spasticity, inflammation, and brain damage due to injury or stroke, but there is not yet sufficient clinical evidence of benefit in human patients with these disturbances. There is very little evidence yet to support use in treatment of movement disorders or cancer. Finally, there are strong clinical reasons ***against*** claimed use for glaucoma, bronchial asthma, high blood pressure, schizophrenia or depression.

Different routes of administration result in different speeds, intensities and durations of action. Both cannabis smoking and inhalation of vaporized cannabis produce rapid and intense but relatively short-lasting effects, while oral use gives slower, less intense but more prolonged effects which are better suited for most therapeutic uses. In addition, smoking itself causes irritation of the airways which limits its clinical usefulness. Vaporization does not produce smoke, but it has not yet been studied sufficiently to demonstrate its freedom from adverse pulmonary effects.

Cannabis and various cannabinoids act by combining with the receptors for the endocannabinoid system, as well as with other types of receptor involved in immune and inflammatory responses. Therefore they have a very wide range of actions in different body organs and tissues, and the potential therapeutic uses are correspondingly numerous and varied. These include relief of pain, nausea and vomiting; stimulation of appetite; sedation and relief of anxiety; relief of muscle spasticity and of inflammation; and protection of brain cells against the effects of head injury or stroke. However, only the first three of these have so far been

validated by good clinical evidence; the others still require adequate clinical trials. Other claims of therapeutic effects against movement disorders, and against certain types of cancer, have very little scientific backing, and others, such as treatment of glaucoma, depression, asthma and high blood pressure, have been rejected by clinicians as impractical, ineffective or harmful.

While cannabis is usually smoked for non-medical purposes because of its rapid onset of action and high peak effect, there are very few situations in which these features are needed for medical use. Oral administration is usually better in providing an even and more prolonged effect, and pure cannabinoids are used almost exclusively by mouth. Other routes of administration are so far only experimental. The duration, intensity, and tolerability of effect are also influenced by tolerance (in regular heavy users), by the age and experience of the user, and by interaction with other drugs used concurrently with cannabis. Some drug interactions can be medically useful, whereas others are harmful. Therefore the possibility of drug interactions must be considered carefully when cannabis drugs are used therapeutically.

While the appropriate dosage ranges for different medical purposes has not yet been fully defined, there is sufficient knowledge to demonstrate that it lies in the range of less than 1 to at most 4 or 5 grams of dried cannabis a day. Larger amounts decrease or abolish the therapeutic effect because of receptor desensitization, and there is no evident medical reason for prescribing larger amounts.

There is no scientific evidence to support claims of differential therapeutic effects of different so-called strains of cannabis, other than the fact that strains with high ratio of THC to CBD have strong psychoactivity (which underlies many of the adverse effects with respect to medical use), whereas strains with high ratio of CBD to THC retain many of the desired effects such as analgesic, anti-inflammatory, antiseizure and neuroprotective actions, with very much less psychoactivity.

Information about adverse effects of cannabis has been obtained mainly from studies of non-medical users, and there has been little systematic study of adverse effects arising during medicinal use, especially during long-term use for chronic conditions. Acute adverse effects of cannabis use arise mainly from its impairment of

mental and motor skills involved in driving and other complex and attention-demanding tasks, and from its ability to precipitate acute psychotic episodes, especially in those with a family history of schizophrenia. Acute effects on the heart and circulation can be serious but are only rarely so.

Adverse effects of chronic use are chiefly on the respiratory system (chronic bronchitis, and a still uncertain link to cancer), on mental functions (memory, judgment, motivation) and mood disturbances that interfere with school and work performance and social adjustment, and the development of addiction (dependence) that is more common than originally realized, especially in young users. An important effect on those who begin use early in adolescence and continue into their adult years is interference with maturation of brain structures involved in the development of executive functions (working memory, reasoning, judgment, problem solving) that can not be recovered even after discontinuation of use in those who begin use at the youngest ages and use most heavily during the developmental period. Similar though less marked changes have been found in children of mothers who used cannabis regularly during pregnancy. Therefore children and adolescents, pregnant women, and those with a history of abuse of other drugs should not be considered for therapy with cannabis or cannabinoids.

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June 4, 2014

By Email to

Dr. Harold Kalant, Professor Emeritus
University of Toronto
Department of Pharmacology & Toxicology
Room 4221, Medical Sciences Building
1 King's College Circle
Toronto, Ontario, M5S 1A8
Phone: 416-978-2730
FAX: 416-978-6395
Email: harold.kalant@utoronto.ca

Harold Kalant

R Drummond

Roselle Sheryl Drummond, Notary Public, City of Toronto, limited to the attestation of instruments and the taking of affidavits, for the University of Toronto. Expires February 20, 2017.

Sept 30, 2014

This is Exhibit "B" referred to in the affidavit of Harold Kalant sworn before me at Toronto, ON this 30th day of September 20 14.

R Drummond

Dear Dr. Kalant:

Re: *Allard et al. v. Her Majesty the Queen in Right of Canada*
Instruction Letter for Expert Report

Thank you for agreeing to provide the Attorney General of Canada ("AGC") with an expert report in the matter of *Allard et al. v. Her Majesty the Queen in Right of Canada*. As discussed, this Federal Court litigation involves a constitutional challenge to the *Marihuana for Medical Purposes Regulations* (the "MMPR").

Background Information

The plaintiffs in this litigation, all of whom are medical marihuana users, are challenging the constitutionality of the MMPR on the basis that they cause several unjustified violations of their rights to liberty and security of the person under the Canadian *Charter of Rights and Freedoms*.

The plaintiffs' constitutional challenge in *Allard* focuses on four aspects of the MMPR that differ from the old medical marihuana regime: (1) the elimination of personal cultivation of marihuana in favour of requiring approved individuals to purchase from licensed producers; (2) the restriction that licensed producers may not cultivate marihuana in dwelling places or outdoor areas; (3) the limit on possession of marihuana to either 150g or 30 times the amount prescribed for daily consumption by the individual's medical practitioner, whichever is less; and (4) the failure of the MMPR to permit the production and possession of non-dried marihuana such as cannabis oils, salves, tinctures and edibles.

The plaintiffs have obtained an injunction from the Court that permits them to continue personal production of medical marihuana until the constitutionality of the MMPR is decided by the Court.

Roselle Sheryl Drummond, Notary Public, City of Toronto, limited to the attestation of instruments and the taking of affidavits, for the University of Toronto. Expires February 20, 2017.

The AGC is the defendant and it is the AGC's position that the current medical marihuana regime is constitutionally sound, a position that will be defended by legal counsel

Facts and Assumptions

The facts alleged by the plaintiffs are outlined in the Amended Notice of Civil Claim which is enclosed.

Questions for Your Expert Report

Please address the following matters in your expert report:

(1) The nature of cannabis, marijuana and pure cannabinoids;

(2) The quality requirements for the use of any substance as a therapeutic agent;

(3) The mechanism of action of cannabinoids;

(4) The scientific knowledge with respect to the beneficial therapeutic effects of marijuana;

(5) Methods of administration in respect of medical marijuana;

(6) The dosage range of marijuana for medical uses;

(7) The scientific evidence with respect to the selective therapeutic benefits of particular strains of marijuana;

(8) The adverse effects of marijuana consumption;

(9) Any contraindications to the medicinal use of marijuana; and

(10) The limitations of knowledge and problems for medical supervision of marijuana for medical purposes.

Format of Your Expert Report

Your report must be prepared in accordance with the Federal Courts Rules. As such, we ask that you do the following in the body of your report:

1. Set out the issues to be addressed in the report;
2. Describe your qualifications on the issues to be addressed;
3. Attach your current curriculum vitae as a schedule to the report;
4. Attach this letter of instruction as a schedule to the report;
5. Provide a summary of your opinions on the issues addressed in the report;
6. Set out the reasons for each opinion that is expressed in the report;

7. Attach any publications or other materials specifically relied on in support of the opinions;
8. If applicable, provide a summary of the methodology used in the report;
9. Set out any caveats or qualifications necessary to render the report complete and accurate, including those relating to any insufficiency of data or research and an indication of any matters that fall outside of your field of expertise; and,
10. Particulars of any aspect of your relationship with a party to the proceeding or the subject matter of your report that might affect your duty to the Court.

Please number each paragraph of your report as this will aid us in referring to your report in Court.

Please sign and date your report.

Duty to the Court

As an expert witness, you have a duty to the Court which is set out in the attached Code of Conduct for Expert Witnesses. Please carefully review this Code of Conduct and, after doing so, sign the attached Certificate and send it back to us.

Due Dates and Procedural Matters

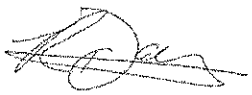
We are required to file our expert reports on or before November 1, 2014. The trial has been set for three weeks commencing February 23, 2015. You may be required to attend the trial for cross-examination and, if so, we will attempt to accommodate your schedule to the extent possible.

Please keep all correspondence pertaining to this assignment in a separate "Expert Witness Report" folder.

We look forward to receiving a draft of your report the **first week of September, 2013**.

Please do not hesitate to contact me by telephone at 604-666-4031 if you require further information or have questions regarding the foregoing.

Yours truly,



Robert Danay
Counsel

Enclosures: Certificate for Expert Witnesses; Code of Conduct for Expert Witnesses; Amended Notice of Civil Claim

SCHEDULE
(Rule 52.2)

CODE OF CONDUCT FOR EXPERT WITNESSES

GENERAL DUTY TO THE COURT

1. An expert witness named to provide a report for use as evidence, or to testify in a proceeding, has an overriding duty to assist the Court impartially on matters relevant to his or her area of expertise.

2. This duty overrides any duty to a party to the proceeding, including the person retaining the expert witness. An expert is to be independent and objective. An expert is not an advocate for a party.

EXPERTS' REPORTS

3. An expert's report submitted as an affidavit or statement referred to in rule 52.2 of the *Federal Courts Rules* shall include

(*a*) a statement of the issues addressed in the report;

(*b*) a description of the qualifications of the expert on the issues addressed in the report;

(*c*) the expert's current *curriculum vitae* attached to the report as a schedule;

(*d*) the facts and assumptions on which the opinions in the report are based; in that regard, a letter of instructions, if any, may be attached to the report as a schedule;

(*e*) a summary of the opinions expressed;

(*f*) in the case of a report that is provided in response to another expert's report, an indication of the points of agreement and of disagreement with the other expert's opinions;

(*g*) the reasons for each opinion expressed;

(*h*) any literature or other materials specifically relied on in support of the opinions;

(*i*) a summary of the methodology used, including any examinations, tests or other investigations on which the expert has relied, including details of the qualifications of the person who carried them out, and whether a representative of any other party was present;

(*j*) any caveats or qualifications necessary to render the report complete and accurate, including those relating to any insufficiency of data or research and an indication of any matters that fall outside the expert's field of expertise; and

(*k*) particulars of any aspect of the expert's relationship with a party to the proceeding or the subject matter of his or her proposed evidence that might affect his or her duty to the Court.

4. An expert witness must report without delay to persons in receipt of the report any material changes affecting the expert's qualifications or the opinions expressed or the data contained in the report.

ANNEXE
(règle 52.2)

CODE DE DÉONTOLOGIE RÉGISSANT LES TÉMOINS EXPERTS

DEVOIR GÉNÉRAL ENVERS LA COUR

1. Le témoin expert désigné pour produire un rapport qui sera présenté en preuve ou pour témoigner dans une instance a l'obligation primordiale d'aider la Cour avec impartialité quant aux questions qui relèvent de son domaine de compétence.

2. Cette obligation l'emporte sur toute autre qu'il a envers une partie à l'instance notamment envers la personne qui retient ses services. Le témoin expert se doit d'être indépendant et objectif. Il ne doit pas plaider le point de vue d'une partie.

LES RAPPORTS D'EXPERT

3. Le rapport d'expert, déposé sous forme d'un affidavit ou d'une déclaration visé à la règle 52.2 des *Règles des Cours fédérales*, comprend :

a) un énoncé des questions traitées;

b) une description des compétences de l'expert quant aux questions traitées;

c) un *curriculum vitae* récent du témoin expert en annexe;

d) les faits et les hypothèses sur lesquels les opinions sont fondées et à cet égard, une lettre d'instruction peut être annexée;

e) un résumé des opinions exprimées;

f) dans le cas du rapport qui est produit en réponse au rapport d'un autre expert, une mention des points sur lesquels les deux experts sont en accord et en désaccord;

g) les motifs de chacune des opinions exprimées;

h) les ouvrages ou les documents expressément invoqués à l'appui des opinions;

i) un résumé de la méthode utilisée, notamment des examens, des vérifications ou autres enquêtes sur lesquels l'expert se fonde, des détails sur les qualifications de la personne qui les a effectués et une mention quant à savoir si un représentant des autres parties était présent;

j) les mises en garde ou réserves nécessaires pour rendre le rapport complet et précis, notamment celles qui ont trait à une insuffisance de données ou de recherches et la mention des questions qui ne relèvent pas du domaine de compétence de l'expert;

k) tout élément portant sur la relation de l'expert avec les parties à l'instance ou le domaine de son expertise qui pourrait influencer sur son devoir envers la Cour.

4. Le témoin expert doit signaler immédiatement aux personnes qui ont reçu le rapport tout changement important ayant une incidence sur ses qualifications et les opinions exprimées ou sur les données figurant dans le rapport.

R Drummond

Sept 30, 2014

Harold Kalant

This is Exhibit "C" referred to in the affidavit of Harold Kalant sworn before me at Toronto, ON this 30th day of September 2014.

R Drummond

EXPERT CONFERENCES

5. An expert witness who is ordered by the Court to confer with another expert witness

(*a*) must exercise independent, impartial and objective judgment on the issues addressed; and

(*b*) must endeavour to clarify with the other expert witness the points on which they agree and the points on which their views differ.

SOR/2010-176, s. 13

CONFÉRENCES D'EXPERT

5. Le témoin expert à qui la Cour ordonne de s'entretenir avec un autre témoin expert doit, à la fois :

a) faire preuve d'un jugement indépendant, impartial et objectif quant aux questions traitées;

b) s'efforcer de clarifier avec les autres témoins experts les points sur lesquels ils sont en accord et ceux sur lesquels ils ont une divergence d'opinions.

DORS/2010-176, art. 13

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CURRICULUM VITAE

May 30, 2014

Name: Harold KALANT
Date of Birth: November 15, 1923
Birthplace: Toronto, Canada
Citizenship: Canadian

R Drummond
Roselle Sheryl Drummond, Notary Public, City of Toronto, limited to the attestation of instruments and the taking of affidavits, for the University of Toronto. Expires February 20, 2017.
Sept 30, 2014
Harold Kalant

Academic Degrees:

M.D., University of Toronto	(1945)
B.Sc. (Med.), Toronto	(1948)
Ph.D., Pathological Chemistry, Toronto	(1955)

Post-Doctoral Fellowship:

Biochemistry, University of Cambridge, England (1955-56)

Military Service:

Royal Canadian Army Medical Corps (1943-47)

This is Exhibit "D" referred to in the affidavit of Harold Kalant
sworn before me at Toronto, ON
this 30th day of September 20 14.
R Drummond

Post-Graduate Medical Training:

Internal Medicine, 3 years residency at:

Saskatoon Veterans' Hospital	(6 months)
Toronto General Hospital	(1 year)
Hospital del Salvador, Santiago, Chile	(1.5 years)

Roselle Sheryl Drummond, Notary Public, City of Toronto, limited to the attestation of instruments and the taking of affidavits, for the University of Toronto. Expires February 20, 2017.

Other Clinical Experience:

Part-time attending physician, Bell Clinic for Alcohol Problems, Toronto	(1952-55)
Locum tenens (summers), general practice, Matachewan ON	(1951, 1952)

H. Kalant - Curriculum Vitae

Current Positions: Professor Emeritus (Pharmacology & Toxicology), University of Toronto

Director Emeritus (Biobehavioral Research), Addiction Research Foundation, now incorporated into Centre for Addiction and Mental Health

Positions Held: (Previous)

1956-59 -	Biochemistry Section Head, Defence Research Medical Laboratories, Toronto
1959-64 -	Associate Professor, Department of Pharmacology, University of Toronto
-	Assistant Research Director, Alcoholism and Drug Addiction Research Foundation of Ontario, Toronto
1964-89 -	Professor, Department of Pharmacology, University of Toronto
1964-79 -	Associate Research Director (Biological Studies), Addiction Research Foundation of Ontario, Toronto
1979-89 -	Director, Biobehavioral Research (4 sections), Addiction Research Foundation of Ontario, Toronto

Honours:

Alpha Omega Alpha Honorary Medical Society	(1942)
Cody Silver Medal, Medicine	(1945)
Starr Medal for Research, University of Toronto	(1955)
Jellinek Memorial Award for Research on Alcoholism (jointly with R.E. Popham), Amsterdam	(1972)
Raleigh Hills Foundation International Gold Medal Award for excellence in research on alcoholism	(1981)
Fellowship in the Royal Society of Canada	(1981)
4th Annual Research Award, Research Society on Alcoholism, U.S.A.	(1983)
Upjohn Award, Pharmacological Society of Canada	(1985)
Nathan B. Eddy Award, College on Problems of Drug Dependence	(1986)
President-Elect, International Society for Biomedical Research on Alcoholism	(1989)

Honours (continued)

First Honorary Fellow, Society for the Study of Addiction (U.K.)	(1994)
Distinguished Scientist Award, American Society of Addiction Medicine	(1995)
Mark Keller Memorial Lecturer, NIH (USA)	(2001)
Isaacson Memorial Award for Research on Addiction (USA)	(2004)
Member, Order of Canada	(2012)

Membership in Scientific Societies:

Biochemical Society (U.K.)	(1956-78)
Pharmacological Society of Canada	(1965-2008)
Canadian Society for Pharmacology and Therapeutics	(2008-)
American Association for the Advancement of Science	(1968-93)
College on Problems of Drug Dependence, U.S.A.	(1978-)
International Society for Biomedical Research on Alcoholism (member of founding committee)	(1981-)
President	(1990-94)
Immediate Past President	(1994-98)
Foreign Corresponding Member, Société de Biologie, France	(1993-98)

Membership in Advisory Bodies:

Scientific Advisory Board, North American Association of Alcoholism Programs	(1961-1970)
Scientific Advisory Board, International Council on Alcoholism and Addiction (Lausanne)	(1972-1975)
Expert Panel on Drugs of Dependence, World Health Organization (Geneva)	(1978-1984)
Grants Review Committee, Non-Medical Use of Drugs Directorate (Ottawa)	(1970-1972)
Grants Review Committee, National Institute on Alcoholism and Alcohol Abuse, U.S.A.	(1970-1974)
Scientific Advisory Board, Addiction Research Foundation, Palo Alto, California - member	(1974-1977)
- chairman	(1977-1982)
Banting Research Foundation	(1976-1980)
Comité des Centres de Recherche, Fonds F.C.A.C., Québec	(1983-1984)
Chairman, Board of Scientific Counselors, NIAAA	(1983-1988)

Extramural Advisory Board, NIAAA (USA)	(2006-2008)
Canadian Centre on Substance Abuse, Ottawa - appointed to first Board of Directors by Governor-General in Council	(1989-1993)
Member, Emeritus Board	(2012-)
Extramural Research Advisory Board, N.I.D.A. (USA)	(1990-1992)
Chairman, WHO Working Group on Cannabis and Health	(1994-1998)
Health Canada, Scientific Advisory Committee on Medical Marijuana Research – Chair	(2004-2006)
Health Canada, Expert Advisory Committee on Information for Physicians on Medical Marihuana – Chair	(2011- 2013)
Invited witness on cannabis and health, committees of Senate and House of Commons, Canada	(various)
ISBRA Council of Past Presidents	(2008-)

Editorial Functions:

Associate Editor - Canadian Journal of Physiology and Pharmacology	(1975-1981)
Pharmacology Field Editor - Journal of Studies on Alcohol	(1983-1992)
Member, Editorial Boards of:	
- Alcohol	
- Alcoholism: Clinical and Experimental Research	
- Biochemical Pharmacology	(1968-1999)
- Drug and Alcohol Dependence	(1975-1995)
- Electroencephalography & Clinical Neurophysiology	(1977-1984)
- Journal of Studies on Alcohol	(1992-2004)
- Medical Biology	(1974-1984)
- Neuroscience and Biobehavioral Reviews	(1977-1988)
- Pharmacology, Biochemistry and Behavior	
- Progress in Neuro-Psychopharmacology	
- Psychopharmacology	(1974-1999)
- Research Advances in Alcohol and Drug Problems	(1974-1990)

Theses Supervised:

1965	R.A. Hickie: "Influence of divalent cations on some membrane properties of normal and malignant cells"	Ph.D.
	Y. Israel: "Studies on the biochemical effects of ethanol"	Ph.D.
1966	W. Grose: "Neurotropic drugs and cerebral acetylcholine"	M.Sc.
	I. Ockenden: "The inhibition of cephalosporin β-lactamase by cloxacillin, with special reference to the development of an assay system for cloxacillin"	M.Sc.
	K.J. Ryan: "A method for determining the electrical properties of synaptic vesicles"	M.Sc.
1968	A.E. LeBlanc: "Methodological studies on the measurement of ethanol intoxication and acquired tolerance in rats"	M.Sc.
1969	K.J. Ryan: "Electrophoretic properties of subcellular particles involved in synaptic transmission"	Ph.D.
1970	G. Bustos: "Studies on the production of fatty liver induced by ethanol"	Ph.D.
	K.L. Hepburn: "Effects of ethanol on discrimination behaviours in rats"	M.Sc.
1971	R.G. Perrin: "Effects of ethanol, tetrahydrocannabinol, and procaine on electrical activity of the brain in the intact cat"	M.Sc.
	M.D. Willinsky: "Pharmacological studies on Δ^1-trans-tetrahydrocannabinol in the rat"	Ph.D.
1972	K.A. O'Brien Fehr: "Studies on methods of administration of Δ^1-trans-tetrahydrocannabinol in the rat"	M.Sc.

Theses Supervised: (cont'd)

1972	A.E. LeBlanc: "Behavioral and pharmacological variables in the development of ethanol tolerance"	Ph.D.
1973	F. Finkelberg: "Pituitary mechanisms in ethanol self-selection"	Ph.D.
	D.W. Haist: "Isolation and characterization of rat liver alcohol dehydrogenase"	M.Sc.
	A.J. Siemens: "Acute and chronic metabolic interactions of delta^1-tetrahydrocannabinol and other drugs"	Ph.D.
1974	J.W. Clark: "Ethanol tolerance and release of cerebral cortical acetylcholine in vitro"	M.Sc.
1977	K.A. O'Brien Fehr: "The behavioral toxicity of cannabis in the rat"	Ph.D.
1978	N. Rangaraj: "Effects of alcohol, amphetamine and stress on rat brain (Na^+ + K^+)-ATPase"	M.Sc.
1979	G.I. Sunahara: "Effect of ethanol on stimulated acetylcholine release in vitro from rat cortical and hippocampal tissue"	M.Sc.
1980	R.F. Mucha: "Behavioral factors in tolerance to morphine in the intact organism"	Ph.D.
1983	A. Stiglick: "Residual effects of chronic cannabis administration on behavior in the rat"	Ph.D.
	D.D. Walczak: "Biochemical correlates of alcohol tolerance: role of cerebral protein synthesis"	Ph.D.
1985	G.M. Spinosa: "An investigation of the role of Angiotensin II in voluntary ethanol intake"	M.Sc.
	W.D. Hutchison: "Effects of chronic ethanol treatment on levels of immunoreactive-β-endorphin in rat brain regions"	M.Sc.

Theses supervised (cont'd):

1986	M.B. Speisky: "Effects of vasopressin on alcohol tolerance: sites of action and neurochemical correlates"	Ph.D.
1987	S.J. Mihic: "Methodological issues in the measurement of (Na^+ + K^+)-ATPase"	M.Sc.
1988	M.J.K. Walker: "Motivational properties of spontaneous withdrawal"	M.Sc.
1989	M. Singh: "Role of pharmacokinetic factors in Pavlovian conditioned tolerance/cross-tolerance to various hypothermic agents"	M.Sc.
1992	S. J. Mihic: "Comparative studies of sedative action and tolerance on $GABA_A$ receptor-mediated chloride influx in brain"	Ph.D.
1993	M.J.K. Walker: "Naloxone-induced antinociception: Characteristics and mechanism of a non-opioid form of stress-induced antinociception"	Ph.D.

H. Kalant - Curriculum Vitae

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Court File No. T-2030-13

FEDERAL COURT

BETWEEN:

NEIL ALLARD
TANYA BEEMISH
DAVID HEBERT
SHAWN DAVEY

PLAINTIFFS

and

HER MAJESTY THE QUEEN IN RIGHT OF CANADA

DEFENDANT

Certificate Concerning Code of Conduct for Expert Witnesses

I, Harold Kalant, having been named as an expert witness by the Defendant, Her Majesty the Queen in Right of Canada, certify that I have read the Code of Conduct for Expert Witnesses set out in the schedule to the *Federal Courts Rules* and agree to be bound by it.

Date: June 6, 2014

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