Submission No 14

INQUIRY INTO USE OF CANNABIS FOR MEDICAL PURPOSES

Name: Emeritus Professor Laurence Mather

Date received: 24/01/2013

LEGISLATIVE COUNCIL
Inquiry into the use of cannabis for medical purposes

Terms of Reference

1. That General Purpose Standing Committee No. 4 inquire into and report on the use of cannabis for medical purposes, and in particular:

(a) the efficacy and safety of cannabis for medical purposes;

(b) if and how cannabis should be supplied for medical use;

(c) legal implications and issues concerning the use of cannabis for medical purposes; and

(d) any other related matters.

2. That the Committee report by 14 May 2013.

A submission by
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21 January 2013

One page outline of this submission

Preamble

(a) The present inquiry. This submission considers various issues concerning the medical uses of cannabis, and is written with the assumption that the Committee is familiar with the Report of the Working Party on the Use of Cannabis for Medical Purposes, August 2000 ("NSW Report"). Its purpose was to provide complementary and more recent evidence supporting the reintroduction of cannabis pharmacotherapy for the medical conditions indicated in that Report.

(a) My relevant professional knowledge and background. I was a member of the previous Working Party. My role was as an academic medical research scientist with a long history of research and development in the fields of anaesthesia and pain management. Since then, I have retired, but have kept an interest in the main developments in cannabis pharmacotherapy.

(c) Cannabis and cannabinoids. This section outlines some of the science underlying cannabinoid pharmacotherapy, the need to standardise doses of the chemical mixture that constitutes botanical cannabis, and outlines some of the ideological issues that impact on medical management of patients. To date, most information has been produced about the social use of cannabis and problems arising, mostly without knowledge of the chemical constitution/strength of the cannabis used, and is therefore of questionable scientific value, especially to the issue of medical use by patients.

Term of Reference 1a: "…concerning the efficacy and safety of cannabis for medical purposes"

Weak historical evidence and strong recent scientific evidence indicates the efficacy of cannabis pharmacotherapy for certain, mainly neurological, medical conditions. There is also evidence that cannabis does not cause direct toxicity, i.e., it does not risk death or serious impairment from clinically useful doses. Evidence shows that although a minority of patients may experience some side effects, these are predictable and relatively minor, especially when compared to non-treatment or other drugs used to achieve the same therapeutic goals.

Term of Reference 1b. "…if and how cannabis should be supplied for medical use"

There is enough evidence to indicate that cannabis pharmacotherapy should be re-introduced, and there are various models for this. An administration method that provides rapid feedback to the patient of the efficacy is essential. Smoked cannabis does this, but is generally unacceptable for reasons that include the inability to regulate doses as well as the health problems of smoking itself. Presently, an oromucosal dosage form (Sativex, a chemically standardised mixture of the plant cannabinoids THC and CBD) is under extensive international evaluation and, whilst it is not ideal, it is the best controlled dosage form presently available. Other forms may become available in the future.

Term of reference 1c: "…legal implications and issues concerning the use of cannabis for medical purposes"

I am not qualified to comment on these issues: legal implications and issues were dealt with in the NSW report and by others. An update will be necessary as the NSW Report did not foresee ARTG licensing by the TGA of a botanical cannabis product (i.e. Sativex).

Term of reference 1d: "…any other related matters"

Because cannabis is associated with a 'recreational' drug culture, it is adversely prejudged by sections of society. Patients who could benefit from cannabis pharmacotherapy will continue to be ignored, or have to resort to breaking the law, until there is a legally available product for them. In the decade since the 2000 Report, the commercial botanical product Sativex has already been found useful in so many trials that further local trials of its usefulness are superfluous. Synthetic cannabinoids, of which there are already many, may prove superior in the future. The important issue is that support is given for the best possible patient care that medical science can offer.

The Hon Sarah Mitchell MLC, The Nationals, Chair
The Hon Robert Borsak MLC, The Shooters and Fishers Party, Deputy Chair
Dr John Kaye MLC, The Greens
The Hon Trevor Khan MLC, The Nationals
The Hon Charlie Lynn MLC, Liberal Party
The Hon Adam Searle MLC , Australian Labor Party
The Hon Lynda Voltz MLC, Australian Labor Party

To the Members of General Purpose Standing Committee No. 4

Thank you for the invitation to make a submission to your Standing Committee concerning the use of cannabis[1] for medical purposes. At the outset, I emphasise that this submission is concerned only with the medical use of cannabis. Nonetheless, it is undeniable that the medical and recreational uses of cannabis have been inextricably linked throughout history. In this submission, I have attempted to draw together a variety of sources to provide an up-to-date commentary to assist the Committee in their deliberations, with the assumption that the Committee is to consider such evidence in any justification for the reintroduction of cannabis pharmacotherapy. Reference sources, that are more representative than exhaustive, and explanatory notes that are hopefully in reasonably clear language, are provided in the footnotes.

Preamble

Some 50 years ago, cannabis was removed from its long-standing medical use in Australia for politico-legal, rather than medical, reasons. Briefly, cannabis was removed from the domain of controlled medicines at a time when there was very little scientific knowledge about it. This was due to domestic implementation of international agreements that had been instigated on the basis of unsound and/or spurious notions about "narcotics" generated mainly in the United States several decades earlier. Cannabis thereafter passed into the domain of criminal law in Australia where it has remained. At the time of its proscription, evidence for the medical usefulness of cannabis was certainly more anecdotal than scientific, and it probably wasn't sorely missed[2].. Although one might argue that there have been so many recent pharmaceutical and medical improvements that cannabis remains an unnecessary medicine, there is also recent and cogent scientific evidence that cannabis pharmacotherapy is useful, and may be successful where conventional treatments fail, most notably in the pharmacotherapy of neurological injuries.

[1] Cannabis is also referred to as marijuana or marihuana (see later footnote on cannabinoids for further description).

[2] Also see Crowley F, Cartwright LA. A citizen's guide to marihuana in Australia. Angus and Robertson publishers, Revised edition 1981. Frank Crowley was then Professor of History, and Lorna Cartwright, a pharmacognosist, was then Principal Tutor in Pharmacy, both at The University of Sydney.

(a) The present inquiry

The purpose of the present inquiry is not entirely clear to me. The Committee will be well acquainted with the documents of the Working Party on the Use of Cannabis for Medical Purposes convened by the Premier of NSW in 1999 that made its recommendations in 2000 (hereafter referred to as the NSW Report[3]). That Working Party considered the evidence, along with the medical and legal implications, and clearly indicated these were sufficient to recommend that the Government could proceed with the implementation of legislation supporting cannabinoid pharmacotherapy for certain medical conditions.

If the purpose of the present inquiry is to again pursue the pathway to the legalisation of medical cannabis, then it seems that this was offered to previous governments by the NSW Report. This, as you know, did not occur but the reason for the ultimate demise of the Working Party's recommendations were never enunciated – it was implied to be due to federal-state legal complexities, but this position has been disputed, and it surely wasn't due to public resistance[4].

If legalisation in favour of the medical use of cannabis is the purpose, what can this inquiry offer that wasn't previously offered? Certainly there is new and stronger evidence about the usefulness of medical cannabis, much of it being obtained over the past decade with a standardised botanical preparation of cannabis that was in its infancy at the time of the NSW Report, and this may be more persuasive now. Moreover, it is not clear which pathway or combination of pathways for the possible re-introduction of medical cannabis the legislators would be seeking, if this is the purpose – decriminalisation of patient-sourced cannabis from self- or dealer-supported plant growing, provision to patients of a pharmaceutical proprietary cannabis product upon prescription, support of local research for development of a novel, perhaps transpulmonary or transnasal, product, or what? Such possibilities were elaborated in the NSW Report. Alternatively, if the purpose is merely to re-open the policy debate as a societal intellectual exercise, then the usual ideological divide is likely to re-surface and the public won't be served yet again.

[3] Report of the Working Party on the Use of Cannabis for Medical Purposes. Office of the Premier of NSW, 2000; Volumes 1 to 3, August 2000; Volume 4 July 2001. The 24 recommendations covered many aspects of therapeutic trial use, flexibility in TGA registration, possible user surveys, relevant pharmacological development and clinical trial research, compassionate use, legal/regulatory changes deemed necessary with provisions for lawful possession and use, and certification medical for prescribers and users/carers.

[4] See, as examples, Major C. The case for medicinal cannabis. Of Substance - the national magazine on alcohol, tobacco and other drugs 2003;1(1):14-17; Topp L. Medical cannabis lost in politics. Of Substance - the national magazine on alcohol, tobacco and other drugs 2006;4(1):12-13.

Cannabis remains a subject of common interest to the parallel ideologies of the "recreational drug users club" seeking legalisation, or at least decriminalisation, of this beneficent herb, and the "war on drugs industry" seeking preclusion of anyone's access to this life-threatening, or at least personality destroying, weed. We have become used to seeing government body statistical reports revealing that X-% of people of Y-years of age consumed illicit cannabis in some year or another, to watching images of police with seized bags of cannabis plants having "street values of Z-millions of dollars", and to reading headlines about the "newly discovered damage that cannabis causes" to the brains of our susceptible youth. Accordingly, almost everyone has an opinion about cannabis. Unfortunately, not all of these opinions are factually correct - misinformation abounds, and criminal justice or prohibitionist ideology dominates reason about legalising the medical (and the non-medical) use of cannabis. The result is that countless patients in Australia, as in many places elsewhere, still self-medicate with non-medical quality cannabis in an imprecise, possibly unsafe, and definitely illegal, manner[5].

(b) My relevant professional knowledge and background

It is difficult to know where to begin this submission but I do so by again drawing your attention to the Report of the NSW Working Party, of which I was a member. My role in that working party was that of an academic medical research scientist with over 40 years of clinical and laboratory research in anaesthesia and pain management, mainly in Australia and the United States. My interest in cannabis science goes back some four decades when I performed one of the first-ever laboratory studies at The University of Sydney demonstrating the variability in the putatively active chemical constituents of (seized) Australian grown cannabis[6]. The Committee will be well aware that cannabis, for centuries, has been administered via the lungs by smoking plant derived material. Over the past 2 decades, of specific relevance to this submission, I have convened scientific research groups to study non-invasive techniques for the medical aerosol administration of drugs into the lungs for pain management and for the control of diabetes[7].

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[5] Swift W, Gates P, Dillon P. Survey of Australians using cannabis for medical purposes. Harm Reduction Journal 2005;19:293–300.

[6] Cartwright L, Mather LE. Investigation of some samples of Australian grown cannabis. Australian Journal of Pharmaceutical Sciences 1972;1: 49-51.

[7] As examples, Ward ME, Woodhouse A, Mather LE, Farr SJ, Okikawa JK, Lloyd P, Schuster JA, Rubsamen MR. Morphine pharmacokinetics after pulmonary administration from a novel aerosol inhalation delivery system. Clinical Pharmacology & Therapeutics 1997;62: 596-609; Mather LE, Woodhouse A, Ward E, Farr SJ, Rubsamen RM, Eltherington LG. Pulmonary administration of aerosolised fentanyl: pharmacokinetic evaluation of systemic delivery. British Journal of Clinical Pharmacology 1998; 46:37-43; Farr SJ, McElduff A, Mather LE, Okikawa J, Ward ME, Gonda I, Vojtech L, Rubsamen RM. Pulmonary insulin administration using the AERx® System: Physiological and physicochemical factors influencing insulin effectiveness in healthy fasting subjects. Diabetes Technology & Treatment 2000;2:185-197.

My viewpoint at the conclusion of the NSW Working Party was acceptance of cannabinoid pharmacotherapy being re-introduced under trial protocols for certain (specified) medical conditions, for the chemical content of any cannabis medicine to be standardised, for the method of cannabis administration to be improved beyond smoking, and for rigorous scientific method being adopted in any preclinical or clinical trials or studies. All of these requirements, I then believed were, and still believe are, necessary to enable clear, ideology-free, evaluation of the outcomes, especially to identify, evaluate and describe any real cause of adverse effects rather than simply attribute them by association to the treatment – as is often uncritically done. However, as pointed out below, the need for "trials" to be conducted locally has diminished as many of the unknowns of the NSW Report period are now successful knowns.

On 20 May 2003, the Premier of NSW announced that legislation would be introduced to permit the medical use of cannabis as an "obligation to minimise human pain and distress"[8]. Many people took this announcement at face value and it gave hope to many people that they would not face criminal proceedings for using cannabis to treat their own medical conditions[9]. Advice of such an introduction was published in the Australian medical literature soon after publication of the NSW Report[10], and there was a strong sense of optimism.

In my own optimistic belief that the time was then right to initiate a program to proceed, I convened a consortium of scientists and clinicians in NSW to develop standardized botanical cannabinoids for formulation into medication, to develop an inexpensive but medically acceptable dosing delivery platform using state-of-the-art concepts and aerosol technology, and to evaluate the relevant efficacy and safety of the formulations/platform initially in patients having neurological injuries, an area where we believed the greatest immediate gains for patients could be made, and where others have since shown that our program was likely to have been successful. Such a collaborative research program, I rationalized, had important potential humanitarian and financial gains for this state, and were consistent with both governmental and societal expectations[11] and avoided legal/logistical issues involving state boundaries. However, after this program failed to attract support with either federal (NHMRC) or state (NSW

[8] Mr Bob Carr, NSW Legislative Assembly Hansard Article No 9 of 20/05/2003, Parliament of NSW.

[9] As examples, "Marijuana to be trialled as pain drug" Sydney Morning Herald 21 May, 2003 (Nick O'Malley); "Medicine pot" Cover story, The Bulletin 27 July, 2004 (Joshua Gliddon).

[10] Hall WJ, Degenhardt LD, Currow D. Allowing the medical use of cannabis. Medical Journal of Australia 2001;175:39-40.

[11] Mr Paul Pearce, Mr Bob Carr. NSW Legislative Assembly Hansard Article No.13 of 12/05/2004.

Infrastructure) funding submissions, and with the NSW government's failure to adopt any of the recommendations of the NSW Report, despite innumerable proclamations to the Parliament and to the public, my interest in developing cannabinoid pharmacotherapy was thwarted. Since then, I have retired but have kept an interest in the cannabis research literature mainly through monthly newsletters of the International Association for Cannabinoid Medicines (IACM) [12].

(c) Cannabis and cannabinoids[13]

Apart from law enforcement, commercial/industrial cannabis/hemp fibre and cannabis seed/oil production, a number of academic disciplines have interests in cannabis research. These include physical and chemical sciences to determine the molecular structures, synthesis and metabolism of such substances; biological and neurosciences to determine how such foreign substances and their natural analogues work in the body; social and political sciences to determine drug policy and health issues associated with psychotropic/illicit drug use; and pharmaceutical/medical sciences to investigate the formulation and application of these substances to the treatment of medical conditions. International progress in the various disciplines, especially following proscription of cannabis, has been driven by each other's needs for more reliable information but, regrettably, progress in medical pharmacotherapy has remained thwarted, mainly on legal/ideological grounds until very recently.

Various aspects of cannabis have been reviewed in both the scientific and lay literature over the past decade, and these thereby complement the information provided in the NSW Report.

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[12] International Association for Cannabinoid Medicines: http://www.cannabis-med.org/index.php?tpl=page&id=18&lng=en (accessed 11 December, 2012).

[13] Cannabis is a Latin word meaning hemp and hence its long history of association with rope making. The expressions 'hemp' or 'Indian hemp' are particularly used in older documents and refer to the whole of the cannabis plant. The term 'cannabis' is used to designate portions of the Cannabis sativa L. or hemp plant species and/or its subtypes that produce a resinous exudate/secretion rich in specified natural product terpene chemicals. It is also referred to as a variety of street names such as 'dope', 'grass', 'pot', 'Mary Jane', and 'reefer', etc., and where a dose may be colloquially referred to as a 'joint' or 'spliff', etc..

The term 'cannabinoid' refers to the family of substances, regardless of their chemical structures and whether they are natural product or synthetic, that bind to the biological receptors (and thereby act as 'ligands') and produce the classical spectrum of pharmacological effects demonstrated by extracts of Cannabis sativa. Ligands are substances that bind to the atoms or molecules of interest; in this case, of naturally occurring substances that bid to the receptor proteins that cause or block the pharmacological effects of interest. This area is complex as at least 2 types of cannabinoid receptors, designated CB1 and CB2, are now known and generate differing pharmacological effects, and the selectivity and the potencies of the various ligands for these receptors also differ. This generally projects beyond the present inquiry but is relevant in that the active principals in cannabis extracts have different pharmacological effects and thus the standardisation of any such extracts is imperative to understanding the issues.

Among these, I have contributed two such reviews to the American and European anaesthesia and pain medicine scientific literature[14]; parts of this submission are extracted from those papers.

Members of the Committee will be aware that cannabis is not a single drug, and this is a crucial point. Cannabis is amongst a handful of ancient plant-drugs that, along with opium and coca as prime examples, have survived history to remain in common use today. Whereas opium and coca are refined for medical use into their purified "active ingredients", cannabis contains over 60 cannabinoids and over 400 substances in total, in variable proportions, and is used as a crude product. This makes research particularly difficult. Δ^9-Tetrahydrocannabinol (THC), the predominant natural cannabinoid, is mainly responsible for many of the psychoactive and analgesic effects of cannabis. Cannabidiol (CBD), another major constituent, is a non-psychoactive component that may have other pharmacological applications, such as in treatment of stroke, and is now believed to antagonize some of the undesirable psychoactive actions of THC. Research is continuing into the actions of other natural botanical cannabinoids, some of which may have useful effects. These plant cannabinoids have the chemical structure of 'terpenoids', i.e., the same family as the essential oils including eucalyptus and camphor, rather than the chemical structure of 'alkaloids', i.e. the family of morphine and cocaine. This makes such substances much more difficult to be purified and formulated for use than alkaloidal substances and explains, in part, why cannabis is typically used as a crude plant product.

The chemical content and proportions of ingredients in cannabis can differ markedly according to origin, the specific parts of the cannabis plant (flowers, leaves, etc), the cannabis plant strain and gender, conditions of growth (climate, soil, etc), and conditions of storage. Recreational cannabis growers have selectively bred strains for high THC content to maximise the (desired) psychogenic effects. Cannabis grown for medical use, where psychogenic effects are generally unwanted, is selectively bred for constancy of the THC and CBD content and the CBD is believed to offset the psychogenic effects of the THC.

Plant derived "complementary" and/or "herbal" medicines need to be prepared from standardized cultivars (plants having consistent chemical contents) using standardized methods of preparation. These are necessary requirements for proper scientific investigation and/or use of any such medicine, and cannabis is no exception. An often hidden casualty of neglecting this issue is that the conclusions drawn from various surveys and investigations can lack scientific

[14] Mather LE. Medicinal cannabis – hoax or hope? Regional Anesthesia and Pain Medicine 2001;26:484-487; Mather L. Cannabinoid pharmacotherapy: past, present and future. Minerva Anestesiologica 2005;71:405-412.

rigour if the active ingredient/doses used are uncertain or unknown. Nonetheless, the conclusions of such reports still can, and do, become ingrained and widely re-quoted as "facts", especially if they fit the chosen ideology.

Various synthetic cannabinoids, apart from those currently making headlines as a means of circumventing existing laws[15], have also been developed, mainly still with pharmaceutical company "house names" (such as HU-210 and CP55,940), and these have various laboratory and potential medical applications. Some authorities see these as the way of the future, and possibly they are correct, because synthetic cannabinoids can be prepared for patient use as precise doses of pure substances[16].

THC and other cannabinoids mimic the actions in the body of certain naturally occurring substances (collectively known as endocannabinoids), the best known example of which is anandamide, and these regulate a variety of body neural functions. As well, it is now emerging that other important drugs including paracetamol act through cannabinoid-like mechanisms although they have entirely different chemistry to THC-like substances.

Several synthetic cannabinoids have been available for some time, e.g., dronabinol (synthetic THC) and nabilone were introduced several decades ago for use as oral preparations (i.e., as an alternative to smoking) for the treatment of nausea and vomiting associated with cancer chemotherapy, but were not especially successful due largely to the complexities of the oral route of drug delivery (as explained in more detail below). Synthetic cannabinoids can become intellectual property and are thereby more appealing for pharmaceutical company development. Botanical cannabis *per se* is not a patentable product but novel chemical processes for extracting and preparing cannabis medicine have been patented. Moreover, cannabis is sometimes seen as a "pariah" drug – one with such societal negativity that many "respectable" pharmaceutical companies would not wish to be associated with it. Such a connotation would be unlikely for synthetic cannabinoids, or especially for cannabinoid antagonists.

Substances that block or reverse the actions of these endogenous or exogenous agonists on the same sets of receptors are known as antagonists. Whereas cannabis is used to promote appetite when this is a required effect, synthetic cannabinoid antagonists have been produced, e.g.,

[15] Report of Proceedings before Legal Affairs Committee Inquiry into Law Reform Issues Regarding Synthetic Drugs. NSW Parliament. 22 October 2012.

[16] Caswell A. Marijuana as medicine. Medical Journal of Australia 1992;156:497-498.

rimonabant, taranabant and surinabant, for use as antiobesity drugs by producing a reduction in appetite[17]. Rimonabant, however, was suspended in 2008 because of its anxiogenic and depressogenic side effects - side effects of blocking the actions of the endocannabinoid system.

There are many parallels between cannabinoids and the opioids[18], the most important class of potent pain relieving drugs that include the natural plant derived substances morphine and codeine, the morphine derivative heroin (which remains legally prescribed and used in many countries including the UK), and the totally synthetic substances pethidine, methadone and fentanyl. Indeed, the present rate of scientific discovery and publication on cannabinoid pharmacology resembles that on opioid pharmacology some 3-4 decades ago, when the discovery of opioid receptors and their endogenous or naturally-occurring ligands opened the way to pharmacotherapy unimagined by the previous generation of researchers, medical therapists and patients.

As with opioid analgesics used for pain management, it is crucial that the medical and non-medical uses of cannabinoids be divorced, but that the connection be respected. Regrettably, this distinction is often not made. Medically, with opioids, there was a need for overcoming misguided philosophical objections related to addiction, whilst the perceived risk of side effects often led to under-prescribing and insufficient doses to control pain. Concerted research with opioids showed that there is no "one dose fits all"[19] – patients usually know best what is too little – or too much! Improved opioid pharmacotherapy eventually came through research and education, and by using techniques such as the patient-controlled analgesia paradigm that was

[17] Christopoulou FD, Kiortsis DN. An overview of the metabolic effects of rimonabant in randomized controlled trials: potential for other cannabinoid 1 receptor blockers in obesity. Journal of Clinical Pharmacy & Therapeutics 2011;36(1):10-18.

[18] 'Opioid' and 'opioid receptor' have similar connotations as in the footnote on cannabinoids. Such drugs were formerly referred to, medically, as 'narcotics' but this is an obsolete and misleading term that lingers on from politico-law enforcement language as a catch-all for most illicit drugs that usually includes such diverse substances as opioids, amphetamines and cannabis.

The prototype of these drugs is morphine, the principal active component in opium, but many natural product and synthetic chemical substances bind to opioid receptors and reproduce the pharmacological spectrum demonstrated by morphine. This, too, becomes a complex issue as a number of opioid receptors have been described and these are associated with differing pharmacological effect spectra. As with cannabinoids, the selectivity of the opioid ligands for the various receptors also differs. As this discussion quickly becomes complex and is not particularly germane to the present inquiry, it is not developed further. However, an important connection should not be overlooked. The body produces various naturally occurring cannabinoids and opioids that have natural function in regulating normal physiology and mood. The body did not evolve to have these various plant drugs administered to it, but to use the naturally-occurring ligands. By-and-large, the administered drugs mimic these, and perform similar actions.

[19] Mather LE. Individual responder analyses for pain: does one dose fit all? Trends in Pharmacological Sciences 2005;26: 544-545.

explicated in Australia during the 1970s and 80s, and is now included in international best practice[20]. Clinical research over the past decade suggests that a similar paradigm should also be successful with cannabinoids with comparably high patient acceptability, but this could also require a major mind-set change for many people -- as it did for the introduction of patient controlled analgesia some 25 years ago.

Cannabis is often mentioned in the context of recreational and other non-medical drugs, including alcohol and tobacco, mainly in literature to counter their use and/or problems of their use[21]. Consequently, ideological reactions to such drug use are often promoted amid catch-phrases such as "war on drugs", "soft on drugs", "drug-free society" and "gate-ways to hard drug use", etc.,. Moreover, even the possibilities for medical use of cannabis become outweighed by the prominence accorded such local bodies as our National Cannabis Prevention and Information Centre (NCPIC) whose mission is "to prevent and reduce the use of, and problems related to, cannabis in Australia" where the focus is mainly on issues of drug dependence and harm reduction[22]. However, such bodies also produce the headline grabbing press releases, typically of the adverse effects of the drugs on the users and/or society[23]. Furthermore, much of the matter reported is by user surveys where the drug composition and/or doses, the circumstances and/or conditions of the recipients are largely unknown, if not unknowable. This commentary is not intended to denigrate the work of such organizations but to make the point that they are reflecting the societal legacy of the "war on drugs" ideology that directly influences, but has little to do with, the medical management of patients.

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[20] As examples, Mather LE, Owen H. The scientific basis of patient controlled analgesia. Anaesthesia and Intensive Care 1988;16:427-436; Owen H, Mather LE, Rowley K. Development and clinical use of patient controlled analgesia. Anaesthesia and Intensive Care 1988;16:437-447.

[21] As examples, through the Australian Government National Drugs Campaign http://www.nationaldrugstrategy.gov.au/internet/drugstrategy/publishing.nsf/Content/home (accessed 28 December, 2012); Australian Institute of Health and Welfare Drugs in Australia 2010: tobacco, alcohol and other drugs. http://www.aihw.gov.au/publication-detail/?id=10737420497 (accessed 16 January, 2013).

[22] National Drug & Alcohol Research Centre (NDARC). The National Cannabis Prevention and Information Centre (NCPIC) http://ndarc.med.unsw.edu.au/group/ncpic (accessed 6 December, 2012). It is noted that the NCPIC website states that "…prevention and treatment goals will be achieved by providing the community, in particular young people, with high quality, evidence-based information on cannabis use, and by building the capacity of the treatment providers to respond to cannabis users and their families. The Centre was officially opened in 2008 and is funded by the Australian Government Department of Health and Ageing...".

[23] See, as examples, "The trouble with cannabis" Sydney Morning Herald 24 May, 2012 (Amy Corderoy); "Prolonged cannabis use leads to drop in IQ, study shows" Sydney Morning Herald 28 August, 2012 (Nicky Phillips).

Term of Reference 1a: "…concerning the efficacy and safety of cannabis for medical purposes"

(a) Concerning the efficacy of cannabis for medical purposes

The NSW Working Party had the benefit of two major inquiries on the medical usefulness of cannabis that only briefly preceded it: The British House of Lords Session 1997-98; Science and Technology - Ninth Report (UK)[24] and the American Institute of Medicine[25]. With most of its deliberations being based on the same primary information, it is not surprising that the NSW Working Party reached most of the same conclusions[26]. Insufficient rigorous scientific evidence was found to support the unequivocal re-introduction of cannabinoids in clinical practice, but the history and less-rigorous evidence both indicated that there was efficacy, particularly when more conventional treatments had failed. Recommendations for further research were made before definitive conclusions could be made. The principles haven't changed significantly since those recommendations, except that the peer-reviewed medical and scientific literature on cannabinoids has expanded enormously and a much stronger evidence base, mainly with standardization of cannabinoid preparations, is now accruing[27].

The NSW Report, like the UK and US reports before it, supported cannabis pharmacotherapy for the conditions shown in Table 1 and this has been further supported by more up-to-date reviews that give a balanced account of the uses and side effects of cannabis[28]. As mentioned above, much of the recent evidence about cannabis pharmacotherapy comes from research trial use of a commercially developed oromucosal[29] spray product based upon an extract of cannabis, with a

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[24] Select Committee on Science and Technology Second Report (2001) (UK). http://www.parliament.the-stationery-office.co.uk/pa/ld200001/ldselect/ldsctech/50/5002.htm#a2 (accessed 4 December, 2012).

[25] Joy J, Watson S, Benson J. (Eds.) Marijuana and Medicine: Assessing the Science Base. Institute of Medicine, Washington: National Academy Press, 1999. http://www.nap.edu/readingroom/books/marimed/ (accessed 4 December, 2012).

[26] Degenhardt L, Hall W. Medical marijuana initiatives: are they justified? How successful are they likely to be? CNS Drugs 2003;17(10):689-697.

[27] The medicalization of cannabis. The transcript of a Witness Seminar held by the Wellcome Trust Centre for the History of Medicine at UCL, London, on 24 March 2009. Edited by SM Crowther, IA Reynolds and EM Tansey. http://eprints.ucl.ac.uk/20363/1/20363.pdf (accessed 12 December, 2012).

[28] As examples, Russo EB. Cannabinoids in the management of difficult to treat pain. Therapeutics and Clinical Risk Management 2008;4(1):245-259; Bostwick JM. Blurred boundaries: the therapeutics and politics of medical marijuana. Mayo Clinic Proceedings 2012;87(2):172-186.

[29] A small volume of drug-containing solution is sprayed under the tongue and onto the mucous membranes of the inside of the mouth. In some literature, this method is also referred to as 'sublingual' – literally under the tongue. Ideally, the drug solute is then absorbed efficiently and rapidly into the blood circulation, and this is generally what happens with a solid dose form placed under the tongue. However, a drug solution is, in fact, much more difficult to control so that variable portions of the drug become mixed with saliva, absorbed from other parts of the mouth,

standardised THC+CBD content now known as nabiximols[30] (Sativex, GW Pharmaceutical plc, UK, see below). This product was in early stage development at the time of the NSW Report and has since been the main form of cannabis used for evaluation of efficacy and safety.

Table 1. Generally agreed potential uses of cannabinoid pharmacotherapy

- control of nausea/vomiting (e.g. from cancer chemotherapy)
- appetite stimulation (e.g. in patients with HIV-related wasting syndrome)
- control of muscle spasticity (e.g. from multiple sclerosis and spinal cord injury)
- pain management (e.g. for neuropathic pain, and possibly anti-inflammatory treatment)
- anti-convulsant effects (e.g. from epilepsy)
- bronchodilation (asthma treatment)

However, the preferred medication(s) and dose(s) for pharmacotherapy of the various medical conditions are still being determined as cannabis pharmacotherapy is becoming more widely accepted, but methodological issues in trial design and treatment delivery are, at last, being addressed so that appropriate comparisons of drug, drug strength, drug delivery method, patient symptom/treatment responder, and favourable/unfavourable outcomes, can be made[31]. For example, it is sometimes claimed that THC alone is not pharmacologically equivalent to the mixture of cannabinoids found in cannabis extract, even when dose-matched for THC content, but the evidence about this belief is still conflicting. Contemporary research is indicating that some patients respond better to THC alone, while some respond better to cannabis plant extracts[32]. Therefore, the efficacy of other ingredients in cannabis plant extracts is also being evaluated. Whether the outcomes are related to the condition being treated, the method of cannabis administration, or the individual's genetic, pathological, etc., profile, remain for future research to determine. Until recently, quality clinical research has lagged behind empirical self-treatment research conducted by patients based on home grown or illicit cannabis, all of which has been hindered by variability in the chemical composition, ways of cannabis storage/preparation, methods of administration (smoked, oral "cookies, "tea", etc.).

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and/or become swallowed, and this makes the drug absorption less efficacious and more variable. The company has since changed the descriptor to 'oromucosal' to reflect the true situation.

[30] http://en.wikipedia.org/wiki/Nabiximols (accessed 6 December, 2012).

[31] As examples, Zajicek JP, Apostu VI. Role of cannabinoids in multiple sclerosis. CNS Drugs 2011;25(3):187-201. Lynch ME, Campbell F. Cannabinoids for treatment of chronic non-cancer pain; a systematic review of randomized trials. British Journal of Clinical Pharmacology 2011:72(5):735-744.

[32] Russo EB, Guy GW, Robson PJ. Cannabis, pain, and sleep: lessons from therapeutic clinical trials of Sativex, a cannabis-based medicine. Chemistry & Biodiversity 2007;4(8):1729-1743.

(*b) Concerning the safety of cannabis for medical purposes*

It hardly needs stating that no drug can be considered absolutely "safe" or even "free from risks". Science, in general, is more concerned with probabilities than absolutes. Medical science, in this case of competing treatments or of no treatment, is more concerned with relative benefits and risks.

The safety evidence derived from cannabis-nabiximols was recently reviewed[33]. This goes a long way to answering questions raised in the NSW Report about side effect safety and drug dependence potential under more-or-less controlled conditions of chronic use by patients. Clearly, nabiximols is not free from side effects but only some 10% of the patients chose to discontinue their treatment. Notably, a greater incidence than for placebo treatment was found for disorientation (4% vs. 0.5%), disturbance in attention (3.7% vs. 0.1%), feeling drunk (2.9% vs. 0.4%), euphoric mood (2.2% vs. 0.9%), depression (1.9% vs. 0.8%), memory impairment (1.4% vs. 0.1%) and dissociation (1.7% vs. 0.1%). Tolerance did not develop, and the author concluded that abuse or dependence "is likely to occur in only a very small proportion of recipients". Cannabis would not be expected to be free from such side effects. It is known to be a "mind-altering drug" but patients do not use it to become "high" or "stoned" – such effects that are sought-after with recreational use are eschewed with medical use.

Similarly, cannabis would not be expected to be free from involvement in other adverse effects[34], for example, involvement in road accidents, or if combined with other drugs including alcohol, as is known among recreational drug users[35]. This is a separate issue. However, whilst there is circumstantial and retrospective evidence of cannabis use (composition/doses unknown) involvement with psychotic symptoms with prolonged recreational use in certain individuals[36],

[33] Robson P. Abuse potential and psychoactive effects of d-9-tetrahydrocannabinol and cannabidiol oromucosal spray (Sativex), a new cannabinoid medicine. Expert Opinions on Drug Safety 2011;10(5):675-685.

[34] Hall W. The adverse health effects of cannabis use: What are they, and what are their implications for policy? International Journal of Drug Policy 2009;20:458–466.

[35] For example, Drummer OH, Kourtis I, Beyer J, Tayler P, Boorman M, Gerostamoulos D. The prevalence of drugs in injured drivers. Forensic Science International 2012;215(1-3):14-17 found that The presence of drugs was investigated in 1714 injured drivers taken to hospital by researchers of Monash University, Victoria. Alcohol above 0.01 per cent was present in 29% of drivers. The prevalence of THC was 9.8%, of which 70% had a blood concentration of 10 ng/ml or higher. Antidepressants were present in 9.3%, benzodiazepines in 8.9%.

[36] For example, Moore THM, Zammit S, Lingford-Hughes A, Barnes TRE, Jones PB, Burke M, Lewis G. Cannabis use and risk of psychotic or affective mental health outcomes: a systematic review. Lancet 2007;370:319-328.

cannabis causes no acute direct life-threatening side effects, even in excessive doses [37]. Cannabis is generally believed to have a higher margin-of-safety than for most other classes of potent pharmacological agents, having a side effect profile that is probably milder than many other medications such as opioid analgesics or antidepressants, that might be used to achieve the same pharmacotherapeutic outcomes or, for that matter, of the effects of symptoms left untreated.

Term of Reference 1b. "…if and how cannabis should be supplied for medical use"

(a) <u>If</u> cannabis should be supplied for medical use

Needy patients should have ready access to medication – denial of a right to all beneficial treatments is a violation of basic human rights[38]. Based on the medical-scientific literature reviewed, I believe that there is already sufficient evidence for the re-introduction of cannabinoid pharmacotherapy for the medical conditions listed in Table 1.

From my perspective as a pharmacologist, cannabis pharmacotherapy should be based upon prescribed, regulated and reliable doses, and it would be appropriate for any such preparation to be reviewed by the Therapeutic Goods Administration as normally practised for drugs to be used in human patients.

(b) <u>How</u> cannabis should be supplied for medical use

As with opioid pharmacotherapy of pain, patients are not required to grow their own opium poppies but are supplied by prescription for a controlled product in a dosage form appropriate to their needs. A patient who is prescribed opioid analgesics for the treatment of pain can be sure of reliable doses and controlled chemical purity of the prescribed drug - a vast quality control regime ensures this.

Clearly, there needs to be a legal supplier of any cannabinoid medication, as for any other supplier of potent drugs. As pointed out in the NSW Report and elsewhere[39], neither patients nor

[37] For example, Ashton CH. Adverse effects of cannabis and cannabinoids. British Journal of Anaesthesia 1999;83:637-649.

[38] Cousins MJ, Brennan F, Carr DB. Editorial. Pain relief: a universal human right. Pain 2004;112:1-4; Clark PA, Capuzzi K, Fick C. Medical marijuana: medical necessity versus political agenda. Medical Science Monitor 2011;17(12):249-261.

[39] As examples, McDonald D, Moore R, Norberry J, Wardlaw G, Ballenden N. Legislative Options For Cannabis Use In Australia. Commonwealth of Australia 1994; Monograph No. 26. http://www.health.gov.au/internet/main/publishing.nsf/Content/64170211F1F2224BCA256F180057486A/$File/ndsp7_7.pdf (accessed 27 December, 2012); Bogdanoski T. Accommodating the medical use of marijuana: surveying the differing legal approaches in Australia, the United States and Canada. Journal of Law & Medicine 2010;17(4):508-31.

their carers should risk legal action over their need to obtain and/or use a cannabis medication or to grow their own cannabis plants. Moreover, I believe that patients or their carers should not be required to grow their own cannabis plants, as is suggested in some decriminalisation models (also see footnote: Hall, Degenhardt and Currow); nor should they have to source their supply from an irregular dealer.

In contemporary thinking, pain, spasm and spasticity are among the main symptoms considered for cannabinoid pharmacotherapy. As with opioid pharmacotherapy, the necessity for a patient to titrate their dose to the individually desired level of effect depends on a mode of administration allowing rapid feedback to the patient of the effects of each dose – this is the patient controlled analgesia (PCA) paradigm devised 25 years ago. It allows patients to decide what is sufficient or to trade off the desirable effects against any side effects, and this is exactly what is achieved with PCA. It would be ideal also with cannabis pharmacotherapy, and this has much to do with the method of administration.

Most of the anecdotal literature and some of the scientific literature is based upon transpulmonary[40] cannabinoid administration, usually from smoking and, more recently, from a vaporizer. It is suffice here to say, that "smoking a joint" or in a water pipe (a "bong") are the traditional routes for non-medical use. Whilst perhaps convenient to some patients and moderately efficacious[41], smoking is medically and pharmacologically unacceptable as a manner of drug delivery. Systemic absorption of cannabinoids by this route is rapid but systemic bioavailability[42] of THC with smoking is low (average 18%) and variable, even when a standard smoking protocol and standardized THC content cigarettes are used.[43] A low bioavailability means that doses have to be up-scaled so that sufficient of the administered dose is actually attained for the required effect. This can lead to side effects, possibly due to the effects of the other components in the mixture, or their breakdown products. In the case of cannabis, there does not appear to be research one way or the other. However, smoking, itself, is problematic

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[40] That is, across the lung membranes and into the blood (or systemic) circulation for distribution into the various parts of the body, including those parts ('receptors') that cause the required effects (and side effects).

[41] As examples, Wilsey B, Marcotte T, Tsodikov A, Millman J, Bentley H, Gouaux B, Fishman S. A randomized, placebo-controlled, crossover trial of cannabis cigarettes in neuropathic pain. The Journal of Pain 2008;9(6):506-521; Ware MA, Wang T, Shapiro S, Robinson A, Ducruet T, Huynh T, Gamsa A, Bennett GJ, Collet J-P. Smoked cannabis for chronic neuropathic pain: a randomized controlled trial. Canadian Medical Association Journal 2010;182(14):E694-E701.

[42] The fraction of the dose that gets into the blood circulation, compared to that that would be supplied by an intravenous dose where there is no absorption involved, is commonly referred to as the drug's 'bioavailability'.

[43] Grotenhermen F. Pharmacokinetics and pharmacodynamics of cannabinoids. Clinical Pharmacokinetics 2003;42:327-60.

for a variety of health reasons, and the doses of required and other substances, and their by-products, are unregulated and uncontrollable due to the heating-burning process. However, expedience also needs to be considered, particularly if the anticipated time course is reasonably brief; hence legal and other provisions need to be made for such "compassionate" use, as recommended in the NSW Report.

Vaporization changes substances into their gaseous forms without combustion by heating under controlled conditions. Vaporization of cannabis has been shown to produce a similar rapid absorption of the THC component from the lungs as from smoking[44] but without the same issues of chemical contamination. This is because the lungs have the ideal circumstances of large surface area and high blood flow to allow the absorption of most materials, as long as they are introduced with particular characteristics. Vaporizers have been part of the recreational cannabis scene for some time (and can be purchased over the internet), and more recently medical grade vaporization devices have been produced[45]. Transpulmonary vaporised cannabis appears to provide the appropriate level of precision with rapidity of control[46], and it would be expected that further support for even newer versions of this method will be forthcoming.

Experience with transpulmonary aerosol opioid analgesics[47] suggests that this method also would be suitable, and this delivery method was proposed for development by the NSW research consortium mentioned in the preamble. This technology requires exquisite control over particle size and speed of particle movement, but would require further development for a botanical cannabis product. There is also new evidence that a transnasal inhalation may provide a more of a direct route of drug administration to the brain, thereby minimising the total body dose required[48] but such technology is, as far as is known from the scientific research literature, still

[44] Gieringer D, St Laurent J, Goodrich S. Cannabis vaporizer combines efficient delivery of THC with effective suppression of pyrolytic compounds. Journal of Cannabis Therapeutics 2004;4(1):7-27; DI Abrams DI, Vizoso HP, Shade SB, Jay C, Kelly ME, Benowitz NL. Vaporization as a smokeless cannabis delivery system: a pilot study. Clinical Pharmacology and Therapeutics 2007;82(5):572–578.

[45] For example, Alexza Pharmaceuticals. http://www.alexza.com/ (accessed 2 January, 2013).

[46] Wilsey B, Marcotte T, Deutsch R, Gouaux B, Sakai S, Donaghe H. Low-Dose vaporized cannabis significantly improves neuropathic pain. The Journal of Pain 2013 (in press) Available online 11 December, 2012.

[47] Farr SJ, Otulana BA. Pulmonary delivery of opioids as pain therapeutics. Advanced Drug Delivery Reviews 2006;58(9-10):1076-1088.

[48] Substances inhaled as a nasal spray can, depending on the particle size, can simply act locally in the nose and/or become absorbed across the nasal mucosa and into the nasal blood vessels and into the systemic circulation to cause systemic effects, i.e., away from the nose, or can pass into the back of throat and be swallowed. More recent evidence indicates that substances may also track along nerve pathways into the base of the brain and produce a direct effect without being transported by the blood. Accordingly, research is proceeding to attempt to direct drugs

being explored as to its mechanisms and potential, and has never been applied to cannabis. Both transpulmonary aerosol and transnasal developments would likely require the use of solubilising agents because the main plant cannabinoids are water insoluble. Research into such novel drug delivery systems is proceeding for other applications, albeit slowly with small development companies or academic researchers leading the way. In the (unsuccessful) cannabis research program, mentioned above, a small development company in Sydney[49] that had developed technology for transpulmonary and transnasal drug administration, was one of the named research consortium partners.

Over the past decade, there have been many reports clearly demonstrating the pharmacotherapeutic potential of cannabis-nabiximols (Sativex as supplied by GW Pharmaceuticals plc)[50]. This company has invested very heavily into the production of standardised cultivars, then blending the extracts to produce a standardised product (something like wine making).

As noted above, Sativex is supplied as an oromucosal dosing form whereby a standardised dose of nabiximols is sprayed for absorption under the tongue and into the cheek pouch[51]. This form of treatment has been found effective in treating chronic non-cancer and cancer pain[52], not generally like conventional opioid pharmacotherapy, but notably in many cases when conventional treatments have failed. This form of drug delivery does not provide the rapid absorption of the cannabinoids as first expected (and believed at the time of the NSW Working Party). Indeed, recent research has shown that it is not particularly faster than administration by mouth, strongly suggesting that some portion of the absorption does come from swallowed drug[53]. However, as the psychogenic effects (cannabis "highs") are probably associated with

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into the brain to produce an effect from a very small dose. See, for example, Landis MS, Boyden T, Pegg S. Nasal-to-CNS drug delivery: where are we now and where are we heading? An industrial perspective. Therapeutic Delivery 2012 3(2):195-208.

[49] The Sheiman Ultrasonic Research Foundation Pty Ltd.

[50] http://www.gwpharm.com/default.aspx (accessed 6 December, 2012).

[51] Russo EB, Guy GW, Robson PJ. Cannabis, pain, and sleep: lessons from therapeutic clinical trials of Sativex, a cannabis-based medicine. Chemistry & Biodiversity 2007;4:1729-1743.

[52] As examples, Notcutt W, Price M, Miller R, Newport S, Phillips C, Simmons S, Sansom C. Initial experiences with medicinal extracts of cannabis for chronic pain: results from 34 'N of 1' studies. Anaesthesia 2004;59(5):440-452; Portenoy RK, Ganae-Motan ED, Allende S, Yanagihara R, Shaiova L, Weinstein S, McQuade R, Wright S, Fallon MT. Nabiximols for opioid-treated cancer patients with poorly-controlled chronic pain: a randomized, placebo-controlled, graded-dose trial. Journal of Pain 2012; 13(5):438-449.

[53] Karschner EL, Darwin WD, Goodwin RS, Wright S, Huestis MA. Plasma cannabinoid pharmacokinetics following controlled oral Δ9-tetrahydrocannabinol and oromucosal cannabis extract administration. Clinical

rapid absorption such as after smoking, and as the "highs" are usually an unwanted side effect of medical cannabis, the oromucosal absorption method is probably quite a reasonable method for routine patient use.

Most of the remaining literature is based upon oral cannabinoid administration, with or without a standardised THC content (using regulated forms such as capsules and unregulated forms such as 'cannabis cookies', 'cannabis tea', and the like). Oral dosage forms of pure THC for control of chemotherapy-induced nausea and vomiting were developed to correct the problem of smoked cannabis. Regrettably, these have generally lacked marked success because of the inability to accurately match the dose to the required effect because oral THC has low and variable bioavailability and a slow systemic absorption[54], thereby precluding easy titration of dose to the required effect. Nevertheless, the possibilities for a simple standardised cannabis "tea" bag or equivalent preparation, are appealing from a consumer's perspective and deserve quality research to evaluate how this could be best achieved.

Term of reference 1c: legal implications and issues concerning the use of cannabis for medical purposes

I am not qualified to make legal commentary. Legal implications and issues regarding medical use of cannabis were dealt with in the NSW Report. Many others have dealt with legal implications of the use of cannabis in Australia since then, and some of these are cited in the footnotes. In particular, the Dutch model is commended to the Committee for further consideration. My knowledge of this model relates to the first iteration of a policy to supply medical grade cannabis to patients and to make appropriate preparations (e.g. cannabis "tea") for home consumption[55]. Interim reports, before the establishment of and recommendations from controlled clinical trials, of the application of the Dutch model for supply, regulation and distribution by prescription indicate that cannabis is useful in the adjunctive management of

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Chemistry 2011; 57(1): 66-75; Stott CG, White L, Wright S, Wilbraham D, Guy GW. A phase I study to assess the effect of food on the single dose bioavailability of the THC/CBD oromucosal spray. European Journal of Clinical Pharmacology 2012; DOI 10.1007/s00228-012-1393-4; Stott CG, White L, Wright S, Wilbraham D, Guy GW. A phase I study to assess the effect of food on the single dose bioavailability of the THC/CBD oromucosal spray. in European Journal of Clinical Pharmacology 2012; DOI 10.1007/s00228-012-1441-0.

[54] Drugs administered into the gut become absorbed into the 'portal' blood that drains into the liver and where they are subjected to metabolic degradation. The metabolites (biochemical breakdown products) produced are largely fed back into the blood circulation where they may produce a pharmacological effect that can augment or oppose the required effects, or have no effect at all. This is so for all manner of drugs and chemicals and foodstuffs.

[55] Personal communication: Willem K. Scholten, Head of the Office of Medicinal Cannabis, Department of Pharmaceutical Affairs, Ministry of Health. Welfare and Sport, The Hague, The Netherlands. See also: Scholten WK. Dutch measures to control medical grade marijuana: facilitating clinical trials. Drug Information Journal 2001;35:481-484.

patients with cancer but, importantly, the authors stated that there was not a problem of diversion of medical cannabis to recreational use[56].

Term of reference 1d: any other related matters.

By way of closing, I would like the Committee to remember that much effort is spent on "discovering" new drugs. I believe that many old drugs and sometimes rejected drugs need objective re-evaluation with today's methodology, and that many old drugs are removed from use for the wrong reasons. Some drugs may fall into disuse because their method of administration is lacking. Cannabis tincture was the last form of this drug used in Australia. It was not standardised as to the cannabinoid content because methods were not available at the time for this to occur. It was administered by mouth and the discussion above points out that this is a poor method for cannabis pharmacotherapy. The conditions for which it was used, and the patients for which it was prescribed, also were probably ill-chosen. Cannabis tincture, probably, was not sorely missed except maybe by a small number of patients for whom it was particularly beneficial. This preparation predates my professional life.

Because cannabis is associated with an illicit 'recreational' drug culture, it is adversely prejudged by sections of society and this, no doubt, makes reform-minded politicians nervous[57]. For over two decades, cannabis has received considerable press attention, especially by patients and their advocate groups who await law changes to make their medical supply-lines legal, by those who see medical cannabis as the "thin end of the wedge" to breach or avoid issues of the legality and/or criminality of recreational cannabis, and by those who see the side effects as too big a risk for any use[58]. All of these positions are expressed in the Submissions to the NSW Report. If medical cannabis is to be re-introduced – how should this be done?

For now, my opinion is that working with the natural product botanical cannabinoids, in strictly standardised concentrations, and addressing the issue of improving their mode of delivery, would seem to have the most favourable cost-benefit ratio for further research and immediate

[56] de Jong FA, Engels FK, Mathijssen RHJ, van Zuylen L, Verweij J, Peters RPH, Sparreboom A. Medicinal cannabis in oncology practice: Still a bridge too far? Journal of Clinical Oncology 2005; 23:2886-2991; Correspondence: Scholten WK. Journal of Clinical Oncology 2005:23:7755-7756; de Jong FA, Engels FK, Mathijssen RHJ, van Zuylen L, Verweij J, Peters RPH, Sparreboom A. Journal of Clinical Oncology 2005; 23:7756.

[57] "Why changing drug laws is a political problem, not a scientific one." Sydney Morning Herald 23 May, 2012 (Don Weatherburn); "Two-thirds opposed to easing of drug laws." Sydney Morning Herald 21 May, 2012 (Mark Metherell, Lisa Davies); "After 33 years, I can no longer ignore the evidence on drugs." Sydney Morning Herald 7 June, 2012 (Mick Palmer).

[58] See, for example, "Going to pot. The momentum to legalise marijuana in America is growing, as is the number of smokers. Will the US war on drugs soon be over?" Sydney Morning Herald 15 June, 2012 (Peter Foster).

pharmacotherapy needs. Since the NSW Report, much of this work has been done overseas. Due to the more unified enlightenment pervading the United Kingdom, early governmental acquiescence towards cannabinoid pharmacotherapy facilitated the development of a commercially sound botanical cannabis based medication project (see footnote: The Medicalization of Cannabis). From this, marketing agreements between GW Pharmaceuticals plc and other companies for Sativex have now been formed, allowing many trials in many countries, and also Governmental approvals for medical use, e.g., in Canada. Such a product, probably in the form of Sativex, for which there is evidence of effectiveness and a scientific basis of use would offer the most rapid pathway to patient use in NSW.

On 11 April 2011, GW Pharmaceuticals announced that it has entered into an exclusive licence agreement for the multinational pharmaceutical company Novartis Pharma (Australia) to commercialise the cannabis extract Sativex in Australia and New Zealand, among other countries[59]. Novartis has now filed with the Therapeutic Goods Association with a start date of November 26, 2012[60] and the Sativex product is expected to be available in the second half of 2013. This was not seen as a probable outcome in the NSW Report, but ought to simplify the ultimate pathway to patient use.

The NSW Working Party advocated local trials of cannabis pharmacotherapy, and this was a sensible position a decade ago. I believe that there now are sufficient trials of the pharmacotherapy, mainly using Sativex, for this form of cannabis to be introduced under controlled conditions with data collection by an appropriate regulation agency but without a major trial protocol being imposed as per the NSW Report.

Looking at the future, the effectiveness of vaporized cannabis suggests that this may be a more efficacious form overall, but still requires a greater research effort to confirm this opinion. Other transpulmonary aerosol or transnasal forms would require much longer development paths and it is not clear whether sufficient expertise exists locally to develop them, despite the technology for their application originating in Sydney. It is unclear whether any grant structure could be applied to such local development, or even whether such local development is still possible.

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[59] IACM-Bulletin of 24 April 2011; also see GW Pharmaceuticals website: http://www.gwpharm.com/Sativex.aspx (accessed 17 January, 2013).

[60] TGA Summary for ARTG Entry: 181978 Sativex Oromucosal Spray, nabiximols 80 mg/mL pump actuated metered dose aerosol. https://www.ebs.tga.gov.au/servlet/xmlmillr6?dbid=ebs%2FPublicHTML%2FpdfStore.nsf&docid=80AE3C9BF0BDD408CA257AC2003CB6EF&agid=(PrintDetailsPublic)&actionid=1 (accessed 17 January, 2013).

When cannabis was removed from medical use, and even industrial use, in Australia some 50 years ago, it was in reality removed because it was being used by many people around the world as a recreational substance prohibited by international treaties. Although the medical and non-medical uses get confused in many peoples' minds, the problems of the latter are not really related to the potential benefits of the former. Besides, making cannabis an illegal substance did not preclude its recreational use, anyway, in Australia or elsewhere.

Reintroducing a readily affordable cannabis product for legal medical use, albeit with more efficacious methods of administration than when it was last a legal preparation, would be a valiant move. It is bound to be resisted by certain conservative ideologues on the basis of its association with drug cultures, by certain members of the medical and paramedical professions on the basis of association with possible mental health and/or other side effects, and by others on the basis of natural resistance to change.

On the other hand, reintroduction of cannabis pharmacotherapy may change the quality of peoples' lives, especially for medical conditions that are presently poorly treated. Hence, the Committee's announcement should be welcomed, hopefully as another new start in determining whether the ancient cannabis plant can again be used for the good of suffering humankind. Synthetic cannabinoids, of which there are already many, may prove superior in the future, but the important issue for now is that support is given for the best possible patient care that medical science can presently offer.

End of submission