Cannabis Harms: An Overview of the Known Neurotoxicity and Thalidomide-like Genotoxicity of Cannabis.

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Along with many western countries the level of ignorance in Australia relating to the harms of cannabis is reaching dangerously high levels where the sustainability of the culture itself quickly becomes threatened. A quick survey of many ancient cultures in which drug use was allowed to run rife reads like a litany of failed experiments in the same cracked record – Phoenicia, ancient Egypt, Sumeria, Nineveh, Babylon. We don't need to drink cyanide ourselves to know that it is a lethal toxin – we learn from others' mistakes. So too should we inform ourselves about cannabis - a.k.a. "weed".

Cannabis has been linked with most major mental illnesses and drives the autism epidemic in children. It is clearly highly and severely neurotoxic at all ages and causes spiralling health care costs and impossible blowouts on welfare budgets.

Careful epidemiological studies in the fields of cancer and birth defects show that cannabis is a far more potent cause of cancer and birth defects than tobacco and alcohol combined in both large European and USA research studies published out of the University of Western Australia (UWA). Cannabis causes limblessness – no arms or legs - in Hawaii, France, Europe and USA - just like thalidomide.

Cannabis has now been linked with aging. Cannabis causes a massive 30% increase in biological age by age 30. And in case anyone thinks that is culturally sustainable the evidence suggests that this effects rises with age, and actually with the square of age so that it accelerates rapidly as people get older.

Together, cancer, birth defects and aging is the textbook "genotoxic trifecta". As Australia's most prosperous state Western Australia has more to lose than most. However as the level of ignorance of weed rises dangerously globally, Premier McGowan would be well served by assisting UWA researchers to get the word out to less well informed Australian and western politicians and communities alike internationally.

Clinical Experience:

In this country 99% of patients addicted to intravenous drugs commenced their hard drug career with cannabis. This "gateway effect" of cannabis was proven by David Fergusson in New Zealand in 2006 [1] and has since been confirmed internationally many times [2-11]. This means that virtually all drug-related deaths are downstream sequelae of cannabis use. Moreover, I would estimate that around 70% of the children of the patients that I see are neurologically not intact, with autism-, Aspergers- and ADHD- like symptoms being more common than not. Tales of repeated miscarriages, numerous birth defects, death during cardiac surgery and inherited cancer are common amongst these children. These well-grounded clinical observations form the basis not only for my firm opposition to widespread wholesale cannabis use and availability but also our research projects in this area. We wanted to know if the observations we saw in our patient group were confirmed at the broader population level.

Neurotoxicity:

As documented in our now extensive publication record in the peer reviewed literature the answer is a resounding "Yes indeed" – the above clinical experience is strongly confirmed wherever the data permits investigation. As the committee would be aware cannabis use has been linked with numerous mental health conditions. We showed that all four mental health disorders tracked across space and time in USA, including serious mental health disorders and suicidal thinking, were closely linked spatiotemporally and also at formal causal inference, with cannabis use [12]. Moreover we have also shown that this change is *heritable* with higher rates of autism-like disorders in children being tracked with cannabis [13-15] also across space and time and by formal causal inference [16]. We have also shown that this is explainable on the basis of the many neurotoxic features of cannabis including particularly its broad and heavy epigenomic footprint which implicates transgenerational transmissibility to multiple subsequent generations [17, 18].

Genotoxicity: Cancers:

Similarly, cannabis has been known to be genotoxic for over fifty years. Chromosomal breaks and translocations have long been known, and the rapid development of these features in cannabis-associated testicular cancer implies that cannabinoids are actually inducing the breakage-fusion-bridge cycle first described in 1938 [19]. The frequency of testicular cancer is 2.6 elevated by cannabis exposure [20] and the rate of testicular cancer development is 6.5 times faster than normal [21-26]. Moreover we went on to show in both USA and Europe than many cancers could be related in bivariate, multivariate, space-time and causal inferential paradigms to cannabis or cannabinoid exposure including breast cancer (the commonest cancer of all), acute lymphoid leukaemia (the commonest cancer in childhood), acute myeloid leukaemia (featuring chromosomal translocations and also due to inheritable genotoxicity) and cancers of the liver, thyroid, pancreas, chronic leukaemias, both Hodgkins and non-Hodgkins lymphomas, myeloma, bladder, prostate, kidney, testis and also ovarian dysgerminoma which is the female equivalent of non-seminomatous germ cell tumour in the male testis [27]. 24/28 cancers tracked in USA and 31/40 cancers tracked in Europe were shown to be cannabis related [24-29]. In many cases the relationship of these tumours with cannabis exposure was much stronger than that of testicular cancer. Cannabis was also shown to be driving the 50% rise in US pediatric – and therefore heritable (())(()) – cancer [30] and is similarly likely to be the driving force behind the 100% rise in US testicular cancer [21, 22, 31, 32] and which is rising even faster in many other countries [20, 33-36].

Genotoxicity: Congenital Anomalies:

When the same exercise was repeated for congenital anomalies (birth defects) 45/62 tracked longitudinally in USA and 89/95 in Europe were found to cannabis related [37, 38]. These changes persisted at multivariable adjustment, in a space time context and at formal causal inference. They also persisted when each system was analyzed separately including the cardiovascular,

neurological, gastrointestinal, uronephrological, chromosomal, orofacial, body wall, general and limb systems [18, 39-46]. The limblessness paper was recently published [47, 48]. Concerningly cannabis has been linked to 22/32 birth defects attributed to thalidomide and shares 12/13 cellular mechanisms in common with that known genotoxin [49, 50]. For these reasons cannabis-related teratogenesis can be said to be thalidomide-like. Once again epigenomic mechanisms are amazingly predictive of the diverse multisystem pattern of birth defects observed; which again implies multigenerational heritability [17, 47, 48, 51-53].

Genotoxicity: Ageing:

Cellular and organismal aging is the third clinical manifestation of genotoxicity [54]. This was confirmed at the whole patient level by studying cardiovascular ageing but there are actually 12 lines of evidence for accelerated aging in long term cannabis exposure [17]. Again epigenomic mechanisms, which have been shown to be the primary regulator of the aging process [54-57] have been shown to be foundational in explaining these patterns of illness after cannabis exposure, including chromosomal aneuploidies and genetic deletions, truncations, translocations and duplications (including chromothripsis (chromosomal shattering) [21, 58-64]). It was recently demonstrated both that cannabis users experience a range of chronic health disorders (coronary artery disease, mycardial infarction and stroke, chronic pain, vomiting, injuries and visits to the emergency room, and outpatient and inpatient departments) [65] and have an epigenetic age which is advanced and displayed positive dose-response relationships with both the amount used and the recency of use [66].

Majority of the Genome:

If one adds the length of the chromosomes affected by testicular cancer (chromosomes 1, 7, 8, 11, 12, 13, 18, 21, X and Y = 1,254 megabases) [36] to those affected by acute lymphoid leukaemia (4, 9, 10 , 11, 22 = 645 megabases) [67] to those directly affected by chromosomal trisomies and monosomies (13, 18,

21, X = 388 megabases) it is observed that 1,754 megabases of the 3,000 megabases of the total human genome or 59% (excluding duplicate counting) is directly damaged by cannabis. Cells which survive can pass their damaged genetic material on to subsequent generations.

Superimposability of USA: European Analyses:

The virtually identical findings in Europe confirming earlier epidemiological findings for both cancers and birth defects from USA provide strong confirmatory evidence of these important public health observations [17, 24-29, 37, 38]. Indeed in most respects the European findings are substantially worse than those in USA as the European data collects more cancers and birth defects and has much better regional data on daily cannabis use [17, 27-29].

All Cannabinoids:

It is important to observe that all cannabinoids are implicated in these actions. This was shown as long ago as 1999 in the laboratory [68, 69] and has since been confirmed epidemiologically for Δ9THC, cannabidiol, Δ8THC, cannabinol, cannabigerol and cannabichromene for cancer and birth defects [17, 23-26, 37, 70, 71]. This wide ranging effect of cannabinoids is consistent with the laboratory finding that the genotoxic moiety is the cannabinoid nucleus of cannabinoids known as olevitol, with relativity little action ascribable to the usually diminutive side chains of the cannabinoid molecules [68, 69].

Exponentiation:

Aside from the broad and diverse range of cannabinoids implicated in genotoxic and neurotoxic activities perhaps the least reckoned with is its exponential effects. It is normal in the cannabis mutagenic literature to see exponential curves describing the dose-response relationship of cannabis [72-82].

Similar remarks apply to the mitochondrial metabolic toxicity of cannabinoids which supply both energy and small molecule substrates to the epigenomic machinery [83-88]. While it is often said that cannabis now is more potent than formerly, what many often do not appreciate is that the prevalence of cannabis use is rising, the intensity of daily use is rising and the cannabinoid potency of available strains is also rising – all at the same time and in the same populations [89-92]. This creates a triple confluence of genotoxins which effectively catapults the community relatively abruptly up into the higher dose zone where genotoxic effects are common [47, 52, 53, 89, 90, 93]. This apparent step like effect or sudden and abrupt jump explains the 60-fold elevation of limb lessness in north-eastern France in human and bovine babies where large cannabis crops are grown [94-98] (and also Germany [99]) but not in nearby Switzerland where cannabis is not allowed to enter to food chain.

Transgenerationality:

The heavy epigenomic footprint of cannabis, which is manifested in cancerogenic, teratogenic and ageing findings necessarily implies transgenerational transmission for at least three or four generations – that we know of... and perhaps more [100].

Comparison with Tobacco & Alcohol:

Detailed comparative studies show that the effects of cannabis are worse than tobacco and alcohol [101]. In many studies they are worse than tobacco and alcohol combined [101].

Decriminalization / Legalization:

Of course, it goes without saying that with legalization / decriminalization one essentially licences all day everyday smoking and use of cannabis of increasing potency by the whole community. This aggressive permission modelling and the subsequent commercializing and inevitable industrializing of this

psychotropic toxin, necessarily jet propels whole sections of the community into the egregiously amplified genotoxic / neurotoxic dose range where the severe outcomes described above become so common as to be normative. Even without formal health econometric analysis such enormous health burdens quickly and obviously become unsustainable.

Conclusion:

Hence the combined exponentiation of neurotoxicity, genotoxicity and transgenerational transmission and particularly the multigenerational epigenomic effects make cannabis legalization not only foolhardy and the height of folly in terms of public health policy but also completely and patently unsustainable and unsupportable from the point of view of responsible Government necessarily charged with the passing the best community we can on to those generations which must follow – and will manifestly and necessarily be tasked with caring for their elders.

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Further Research

1. Dalgarno Institute - Cannabis as Medicine?
2. Dalgarno Institute - Cannabis Conundrum
3. Genotoxicity of Cannabis Info Sheet

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