Further Information on the Medical Benefits of Cannabis

Compiled by Jeremy Acton, June 2011

Contents

Combining marijuana components enhances inhibitory effects on brain cancer

http://patients4medicalmarijuana.wordpress.com/2010/01/11/combining-marijuana-components-enhances-inhibitory-effects-on-brain-cancer-2/

New research shows that marijuana components fight an aggressive form of brain cancer. And the media says – nothing, again.

Combining the two most common cannabinoid compounds in Cannabis may boost the effectiveness of treatments to inhibit the growth of brain cancer cells and increase the number of brain cancer cells that die off. That's the finding of a new study published in the latest issue of the journal *Molecular Cancer Therapeutics*.

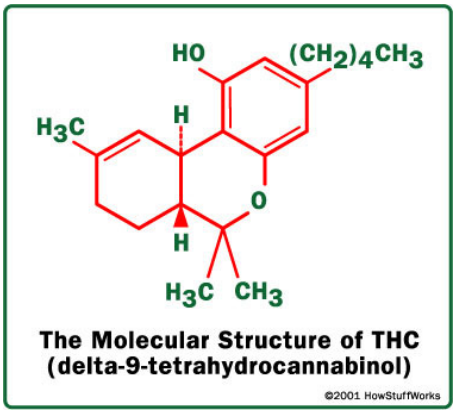
Marijuana components have been found to inhibit the growth of the most common, and aggressive form of brain tumor, a glioblastoma, according to a study published in the January 6 issue of Molecular Cancer Therapeutics. T download a PDF file of the full text go to:

http://mct.aacrjournals.org/content/early/2010/01/02/1535-7163.MCT-09-0407.abstract

The study was done at the California Pacific Medical Center by researchers who combined a non-psychoactive ingredient of marijauna, cannabidiol (**CBD**), with Δ9-tetrahyrdocannabinol (Δ9-**THC),** the primary psychoactive ingredient in Cannabis. The findings demonstrated the inhibitory effect of these two ingredients on brain cancer cells when used together.

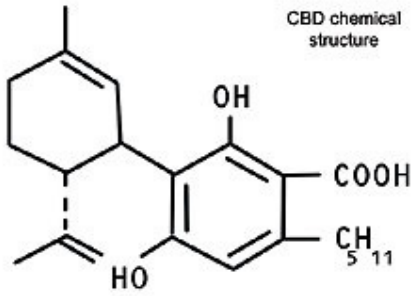
"Our study not only suggests that combining these two compounds creates a synergistic effect," says Sean McAllister, Ph.D., a scientist at CPMCRI and the lead author of the study. "but it also helps identify molecular mechanisms at work here, and that may lead to more effective treatments for glioblastoma and potentially other aggressive cancers."

"Previous studies had shown that Δ9-THC was effective in inhibiting brain cancer growth in cell cultures and in animal models and prompted a small clinical trial in Spain. There is also evidence that other compounds in Cannabis might prove effective against tumors, but limited scientific evidence is available," the report stated.



The report cites Dr. McAllister as stating:

"Compared to using Δ9-THC alone against glioblastoma cell lines, the combination therapy of Δ9-THC and CBD showed a significant improvement in activity, both in slowing down the growth of those cells and also, and perhaps more importantly, in doubling the number of cancer cells which underwent apoptosis or programmed cell death." (Source)



Abstract from Molecular Cancer Therapeutics:
The cannabinoid 1 (CB_1) and cannabinoid 2 (CB_2) receptor agonist Δ^9-tetrahydrocannabinol (THC) has been shown to be a broad-range inhibitor of cancer in culture and in vivo, and is currently being used in a clinical trial for the treatment of glioblastoma. It has been suggested that other plant-derived cannabinoids, which do not interact efficiently with CB_1 and CB_2 ^{9}-THC. There are conflicting reports, however, as to what extent other cannabinoids can modulate Δ^9-THC activity, and most importantly, it is not clear whether other cannabinoid compounds can either potentiate or inhibit the actions of Δ^9-THC. We therefore tested cannabidiol, the second most abundant plant-derived cannabinoid, in combination with Δ^9-THC. In the U251 and SF126 glioblastoma cell lines, Δ^9-THC and cannabidiol acted synergistically to inhibit cell proliferation. The treatment of glioblastoma cells with both compounds led to significant modulations of the cell cycle and induction of reactive oxygen species and apoptosis as well as specific modulations of extracellular signal-regulated kinase and caspase activities. These specific changes were not observed with either compound individually, indicating that the signal transduction pathways affected by the combination treatment were unique. Our results suggest that the addition of cannabidiol to Δ^9-THC may improve the overall effectiveness of Δ^9-THC in the treatment of glioblastoma in cancer patients. receptors, can modulate the actions of Δ

The next step in the research is to carry out similar studies in animal models of aggressive brain cancer. Even if the synergistic effect is not evident in those studies, the combination treatments may allow for stronger doses to be given to patients due to non-overlapping toxicities and decrease development of resistance to the activity of Δ9-THC or CBD alone.

Despite the promising findings of the study the researchers point out that they are not a recommendation for people with brain cancer to smoke marijuana. They say it is highly unlikely that effective concentrations of either Δ9-THC or CBD could be reached by smoking cannabis.

The study was funded by the National Institute of Health and the SETH group.

Outside of the lab… Rick Simpson has been healing cancer with a formulation he calls "Hemp Oil". His healing oil is created by a distillation process that extracts the cannabinoids (including THC, CBD and 78 others) from the cannabis/marijuana plant which can then be taken like a pill. Read more about that here. His home was recently raided for the second time and he remains in exile as the result of his work with cannabis.

Cannabis chemicals stop prostate cancer growth

Wednesday 19 August 2009
Cancer Research UK Press Release

ACTIVE chemicals in cannabis have been shown to halt prostate cancer cell growth according to research published in the British Journal of Cancer today. For a full text of the study go to

http://www.nature.com/bjc/journal/v101/n6/full/6605248a.html

Researchers from the University of Alcala, in Madrid tested the effects of the active chemicals in cannabis called cannabinoids on three human prostate cancer cell lines - called PC-3, DU-a45 and LNCaP.

The prostate cancer cells carry molecular 'garages'- called receptors- in which cannabinoids can 'park'. The scientists showed for the first time that if cannabinoids 'park' on a receptor called CB2, the cancer cells stop multiplying.

But Dr Lesley Walker, Cancer Research UK's director of cancer information warned patients against smoking the drug. She said: "This is interesting research which opens a new avenue to explore potential drug targets but it is at a very early stage - it absolutely isn't the case that men might be able to fight prostate cancer by smoking cannabis."

Dr Walker added: "This research suggest that prostate cancer cells might stop growing if they are treated with chemicals found in cannabis but more work needs to be done to explore the potential of the cannabinoids in treatment."

To confirm the findings the scientists switched off the CB2 receptors - or 'closed the garage doors'- on the prostate cells. When cannabinoids were then added to cells without the CB2 receptor, the prostate cancer cells carried on dividing and growing. This suggests that cannabinoids connect with the CB2 receptors on prostate cancer cells to stop cell division and spread.

Professor Ines Diaz-Laviada, study author at the University of Alcala said: "Our research shows that there are areas on prostate cancer cells which can recognise and talk to chemicals found in cannabis called cannabinoids. These chemicals can stop the division and growth of prostate cancer cells and could become a target for new research into potential drugs to treat prostate cancer."

Prostate cancer is the most common cancer in men in the UK- affecting more than 35,000 men in the UK each year. A quarter of all new cases of cancer diagnosed in men are prostate cancers.

ENDS

Notes to editors

*Inhibition of human tumour prostate PC-3 cell growth by cannabinoids R (+)-Methanandamide and JWH-015: Involvement of CB2. British Journal of Cancer.

**The cannabinoids used were called R(+)-Methanandamide (MET) and JWH-015. The research was both in mice and also on the cells separately.

Anticancer activity of cannabinoids

Journal of the National Cancer Institute,
Vol. 55, No. 3, September 1975, pp.597-602

By A.E. Munson, L.S. Harris, M.A. Friedman, W.L. Dewey, and R.A. Carchman

Department of Pharmacology and the MCV/VCU Cancer Center, Medical College of Virginia, Virginia Commonwealth University. Richmond, Va. 23298

Supported by Public Health Service grant DA00490 from the National Institute on Drug Abuse, Health Services & Mental Health Administration; by a grant from the Alexander and Margaret Stewart Trust Fund; and by an institutional grant from the American Cancer Society.

Summary --- Lewis lung adenocarcinoma growth was retarded by the oral administration of delta-9-tetrahydrocannabinol, delta-8-tetrahydrocannabinol, and cannabinol (CBN), but not cannabidiol (CBD). Animals treated for 10 consecutive days with delta-9-THC, beginning the day after tumor implantation, demonstrated a dose-dependent action of retarded tumor growth. Mice treated for 20 consecutive days with delta-8-THC and CBN had reduced primary tumor size. CBD showed no inhibitory effect on tumor growth at 14, 21, or 28 days. Delta-9-THC, delta-8-THC, and CBN increased the mean survival time (36% at 100 mg/kg, 25% at 200 mg/kg, and 27% at 50 mg/kg;, respectively), whereas CBD did not. Delta-9-THC administered orally daily until death in doses of 50, 100, or 200 mg/kg did not increase the life-spans of (C57BL/6 X DBA/2) F (BDF) mice hosting the L1210 murine leukemia. However, delta-9-THC administered daily for 10 days significantly inhibited Friend leukemia virus-induced splenomegaly by 71% at 200 mg/kg as compared to 90.2% for actinomycin D. Experiments with bone marrow and isolated Lewis lung cells incubated in vitro with delta-8-THC and delta-9-THC showed a dose-dependent (10 -4 10 -7) inhibition (80-20%, respectively) of tritiated thymidine and 14C -uridine uptake into these cells. CBD was active only in high concentrations (10 -4). ----J Natl Cancer Inst 55: 597-602, 1975.

Investigations into the physiologic processes affected by the psychoactive constitutuents of marihuana [delta-9-tetrahydrocannabinol (delta-9-THC) and delta-8-tetrahydrocannabinol (delta-8-THC)] purified from Cannabis sativa are extensive (1). However, only recently have attempts been made to elucidate the biochemical basis for their cytotoxic or cytostatic activity. Leuchtenberger et al. (2) demonstrated that human lung cultures exposed to marihuana smoke showed alterations in DNA synthesis, with the appearance of anaphase bridges. Zimmerman and McClean (3), studying macromolecular synthesis in Tetrahymena, indicated that very low concentrations of delta-9-THC inhibited RNA, DNA, and protein synthesis and produced cytolysis. Stenchever et al. (4) showed an

increase in the number of damaged or broken chromosomes in chronic users of marihuana. Delta-9-THC administered iv inhibited bone marrow leukopoieses (5), and Kolodny et al. (6) reported that marihuana ;may impair testosterone secretion and spermatogenesis. Furthermore, Nahas et al. (7) showed that in chronic marihuana users there is a decreased lymphocyte reactivity to mitogens as measured by thymidine uptake. These and other (8) observations suggest that marihuana (delta-9-THC) interferes with vital cell biochemical processes, though no definite mechanism has yet been established. A preliminary report from this laboratory (9) indicated that the ability of delta-9-THC to interfere with normal cell functions might prove efficacious against neoplasms. This report represents an effort to test various cannabinoids in several in vivo and in vitro tumor systems to determine the kinds of tumors that are sensitive to these compounds and reveal their possible biochemical sites of action(s).

MATERIALS AND METHODS

The tumor systems used were the Lewis lung adenocarcinoma, leukemia L1210, and B-tropic Friend leukemia.

In vivo systems.---Lewis lung tumor: For the maintenance of the Lewis lung carcinoma, approximately 1-mm3 pieces of tumor were transplanted into C57BL/6 mice with a 15-gauge trocar. In experiments involving chemotherapy, 14- to 18-day-old tumors were excised, cleared of debris and necrotic tissue, and cut into small fragments (=1mm3). Tumor tissue was then placed in 0.25% trypsin in Dulbecco's medium with 100 U Penicillin/ml and 100 mcg streptomycin/ml. After 90 minutes' incubation at 22 Degrees C, trypsin action was stopped by the addition of complete medium containing heat-inactivated fetal calf serum (final concentration, 20%). Cells were washed two times in complete medium, enumerated in a Coulter counter (Model ZB1) or on a hemocytometer, and suspended in serum-free medium at a concentration of 5 X 10 6 cells / ml. Next 1 X 10 6 cells were injected into the right hind gluteur muscle, and drugs administered as described in "Results." Standard regimens provided for 10 consecutive daily doses beginning 24 hours after tumor inoculation. Body weights were recorded before tumor inoculation and weekly for 2 weeks. Tumor size was measured weekly for the duration of the experiment and converted to mg tumor weight, as described by Mayo (10).

Friend leukemia: B-tropic Friend leukemia virus (FLV) was maintained in BALB / c mice, and drug evaluation performed in the same animals. Pools of virus were prepared from the plasma of mice given FLV and stored at -70 Degrees C. In experiments with FLV, 0.2 ml of a 1/20 dilution of plasma (derived from FLV-infected mice) in medium was inoculated ip into BALB / c mice. Cannabinoids were administered orally daily for 10 consecutive days beginning 24 hours after virus inoculation. Twenty-four hours after the last drug administration, the mice were killed by cervical dislocation, and the spleens removed and weighed. Mice not given FLV were treated as described above, to evaluate possible drug-induced splenomegaly.

L1210 leukemia: The murine leukemia L1210 was maintained in DBA/2 mice by weekly transfers of 10 (to the fifth power) cells derived from the peritoneal cavity. In these experiments, 10 (fifth power) leukemia cells were inoculated ip into (C57BL/6 X DBA/2) F 1 (BDF 1) mice, and the mice were treated daily for 10 consecutive days beginning 24 hours after tumor cell inoculation. Mean survival time was used as an index of drug activity.

In vitro cell systems. ---Lewis lung tumor: We obtained isolated Lewis lung tumor cells by subjecting 1-mm (third power) sections of tumor to 0.25% trypsin at 22 degrees C and stirring for 60-90 minutes. After trypsinization, the cells were centrifuged (1,000 rpm for 10 min) and washed twice in Dulbecco's medium containing 20% heat-inactivated fetal calf serum. They were then reconstituted to 10 7 cells/ml of 200 mm glutamine, 5,000 U penicillin, and 5,000 mcg streptomycin.

Tumor cells (3-6 ml) were dispensed into 25-ml Erlenmeyer flasks and preincubated with eithe the drug or the drug vehicle for 15 minutes in a Dubnoff metabolic shaker at 37 degrees C in an atmosphere of 5% CO2--95%)2. After preincubation, 10 ucl tritiated thymidine (3H-TDR) (10 uCi, 57 Ci/mmole; New England Nuclear Corp., Boston, Mas.) was added to each flask and incubated for various times, after which 1-ml aliquots were removed and placed in 10 X 75-mm test tubes containing 1 ml 10% trichloroacetic acid (TCA) at 4 degrees C. The TCA-precipated samples were then filtered on 0.45-u Millipore filters and washed twice with 5 ml of 10% TCA at 4 degrees C. The filters were transferred to liquid scintillation vials and counted in a toluene cocktail containing Liquifluor (New England Nuclear Corp.) (4 liters toluene to 160 ml Liquifluor). Samples were then counted in a liquid scintillator.

Bone marrow: Bone marrow cells were derived from the tibias and fibulas of BDF 1 mice. One ml Dulbecco's medium containing 1 U heparin/ml was forced through each bone by a 1-ml syringe with a 26-gauge needle. The cells were washed three times, nucleated cells were enumerated on a hemocytometer, and cell viability was ascertained by trypan blue exclusion. Cell number was adjusted to 10 (seventh) cells/ml with heparin-free Dulbecco's medium and incubated at 4 degrees C for 15 minutes. Bone marrow cells were then dispensed (3-5 ml) into a25-ml Erlenmeyer flasks containing the test drug or the drug vehicle. This preincubation period was followed by the addition of 10 ul 3H-TDR and the procedures done as outlined for the isolated Lewis lung cells.

L1210: L1210 cells were derived from DBA/2 mice as described above. They were obtained from DBA/2 mice and inoculated 7 days before the experiment by the peritoneal cavity being flushed with 10 ml Dulbecco's medium containing heparin (5 u/ml). The cells were washed three times in medium, and the final medium wash did not contain heparin. The cells were resuspended at 10 (seventh) cells/ml and treated as described above. Cells were routinely counted with a hemocytometer for the determination of cell viability with trypan blue; for Lewis lung tumor and L1210 cells, a Coulter apparatus (Mode ZB1) was also used.

All other reagents were of the highest quality grade available. Actinomycin D, 5-fluorouracil (5-FU), and cytosine arabinoside (ara-C) were provided by the Drug Development Branch, National Cancer Institute (NCI).

Cannabinoids. ---The structures of the four compounds are shown in text-figure 1. All occur naturally in marihuana and were chemically synthesized. These drugs were provided by the National Institute on Drug Abuse or the Sheehan Institute for Research, Cambridge, Massachusetts. In the preparation of the drugs, the cannabinoids were complexed to albumin or solubilized in Emulphor-alcohol. Both preparations produced similar antitumor activity. With albumin, the cannabinoids were prepared in the following manner: A stock solution of 150 mg cannabinoid per ml absolute ethanol was made. Six ml of this solution was placed in a 200-ml flask. The ethanol was evaporated off under a stream of nitrogen and 2,100 mg lyophilized bovine serum albumin (BSA) added. After the addition of 20 ml distilled water, the substances were stirred with a glass rod in a sonicator until a good suspension was achieved. Sufficient distilled water was the aldded to make the desired dilution. Concentrations were routinely checked with a gas chromatograph. When Emulphor-alcohol was used as the vehicle, the desired amount of cannabinoid was sonicated in a solution of equal volumes by absolute ethanol and Emulphor (El-620; GAF Corp., New York, N.Y.) and then diluted with 0.15 N NaCL for a final ratio of 1: 1: 4 (ethanol: Emulphor: NaCL).

RESULTS

Effects of Cannabinoids on Murine Tumors

Delta-9-THC, delta-8-THC, and cannabinol (CBN) all inhibited primary Lewis lung tumor growth, whereas cannabidiol (CBD) enhanced tumor growth. Oral administration of 25, 50, or 100 mg delta-9-THC/kg inhibited primary tumor growth by 48, 72, and 75% respectively, when measured 12 days post tumor inoculation (table 1). On day 19, mice given delta-9-THC had a 34% reduction in primary tumor size. On day 30, primary tumor size was 76% that of controls and only those given 100 mg delta-9-THC/kg had a significant increase in survival time (36%).

Mice treated with a delta-9-THC showed a slight weight loss over the 2-week period (average loss, 0.3 g at 50 mg/kg and 0.1 g at 100 mg/kg). This can be compared to cyclo-ohosphamide, which caused weight loss approaching 20% (table 2).

Delta-8-THC activity was similar to that of delta-9-THC when administered orally daily until death (table 2). However, as with delta-9-THC, primary tumor growth approached control values after 3 weeks. When measured 12 days post tumor inoculation, all doses (50-400 mg/kg) of delta-8-THC inhibited primary tumor growth between 40 and 60%. Significant inhibition was also seen on day 21, which was comparable to cyclophosphamide-treated mice. Although this was not the optimum regim;en for cyclophosphamide, it was the positive control protocol provided by the NCI (11). All mice given delta-8-THC survived significantly longer than controls, except those treated with 100 mg/kg. Mice given 50, 200, and 400 mg/kg delta-8-THC had an increased life-span of 22.6, 24.6, and 27.2%, respectively, as compared to 33% for mice treated with 20 mg cyclophosphamide/kg. Pyran copolymer, an immunopotentiator (12) when administered at 50 mg/kg, also significantly increased the survival time of the animals (39.3%).

CBN, administered by gavage daily until death, demonstrated antitumor activity against the Lewis lung carcinoma when evaluated on day 14 post tumor inoculation (table 3). Primary tumor growth was inhibited by 77%, at doses of 100 mg/kg on day 14 but only by 11% on day 24. At 50 mg/kg on day 14 but only by 11% on day 24. At 50 mg/kg, CBN inhibited primary tumor growth by only 32% when measured on day 14, and no inhibition was observed on day 24; however, these animals did survive 27% longer. CBD, administered at 25 or 200 mg/kg daily until death, showed no tumor-inhibitory properties as measured by primary Lewis lung tumor size or survival time (table 4). In this experiment, CBD-treated mice showed enhanced primary tumor growth. However, the control tumor growth rate in this experiment was decreased as compared to the previous studies. Survival time of BDF 1 mice hosting L1210 leukemia was not prolonged by delta-9-THC treatment (table 5). Mice treated with delta-9-THC at doses of 50, 100, and 200 mg/kg administered orally daily until death, survived 8.5, 7.8, and 8.6 days, respectively, as compared to 8.6 days for mice treated with the diluent. However, delta-9-THC inhigited FLV-induced splenomegaly by 71% at 200 mg/kg as compared to 90.2% for the positive control actinomycin D (0.25 mg/kg). Although there was a dose-related inhibition, only the high dose was statistically significant (table 6).

Effect of Cannabinoids on Isolated Cells In Vitro

Isolated cells incubated in vitro represent a simple, reliable, and, hopefully, predictive method for the monitoring of the effects of agents on several biochemical parameters at the same time. The incorporation of 3H-TDR into TCA-precipitable counts in isolated Lewis lung cells is shown in text-figure 2. Similar types of curves were seen for bone marrow and L1210 cells. In all instances, for 15-45 minutes there was a linear increase in 3H-TDR uptake into the TCA-precipitable fraction. Qualitatively, similar data (not shown) were seen after a pulse with 14C-uridine. Actinomycin D (1 mcg/ml) preferentially inhibited 14C-uridine incorporation after uridine uptake had decreased to less than 30% that of control (data not shown). This is indirect evidence that we were measuring RNA synthesis. Experiments (data not shown) done with 5-FU (10 -4 M) indicated that, in isolated bone marrow cells, both thymidine uptake with time by delta-9-THC (10 -5 M) on Lewis lung cells is depicted in text-figure 2. In this experiment, delta-9-THC caused a nonlinear uptake of 3H-TDR. At

30 minutes, uptake of 3H-TDR into the acid-precipitable fraction was about 50% that of control Longer incubations (i.e., 60 min) did not significantly change the uptake pattern for control and de;ta-9-THC treated tumor cells.

The effect of several cannabinoids on the uptake of 3H-TDR into cells incubated in vitro indicated that delta-9-THC, delta-8-THC, and CBN produced a dose-dependent inhibition of radiolabel uptake in the three cell types (table 7). These results, presented as percent inhibition of radiolabel uptake as compared to control, represented an effectof cannabinoids on one aspect of macromolecular synthesis. CBD was the least active of the cannabinoids, but showed its greatest activity in the L1210 leukemia cells. Other data (not shown) indicate that these compounds similarly effect the uptake of 14C-uridine into the acid-precipitable fraction. Ara-C markedly inhibited 3H-TDR uptake more dramatically than did the cannabinoids (table 7). Note that delta-9-THC exhibited inhibitory properties in the isolated Lewis lung tumor and L1210 cells at concentrations that did not interfere with thymidine uptake into bone marrow cells. At certain concentrations of CBD (2,5 X 10 -6 and 2.5 X 10 -7M), radiolabel uptake was consistently stimulated in bone marrow cells and in several experiments with the isolated Lewis lung cells.

DISCUSSION

We investigated four cannabinoids for antineoplastic activity against three animal tumor models in vivo and for cytotoxic or cystostatic activity in two tumor cell lines and bone marrow cells in vitro. The cannabinoids (delta-9-THC, delta-8-THC, and CBN) active in vivo against the Lewis lung tumor cells are also active in the in vitro systems. The differential sensitivity of delta-9-THC against Lewis lung cells versus bone marrow cells is unique in that delta-8-THC and CBN are equally active in these systems. Johnson and Wiersma (5) reported that delta-9-THC administered iv caused a reduction in bone marrow metamyelocytes and an increase in lymphocytes. It is unclear from the data whether this is a depression of myelopoiesis or if it represents a lymphocyte infiltration into the bone marrow. The use of isolated bone marrow cells, which represent a nonneoplastic rapidly proliferating tissue, enables the rapid evaluation and assessment of drug sensititity and specificity, and thereby may predict toxicity related to bone marrow suppression. CBD showed noninhibitory activity either against the Lewis lung cells in vivo or Lewis lung and bone marrow cells in vitro at 10 -5M an 10 -6M, respectively. Indeed, the tumor growth rate in mice treated with CBD was significantly increased over controls. This may, in part, be the consequence of the observation made in vitro (i.e., 10 -7M CBD stimulated thymidine uptake), which may be reflected by an increased rate of tumor growth.

One problem related to the use of cannabinoids is the development of tolerance to many of its behavioral effects (13). It also appears that tolerance functions in the chemotherapy of neoplsms in that the growth of the Lewis lung tumor is initially markedly inhibited but, by 3 weeks, approaches that of vehicle-treated mice (tables 1, 3). This, in part, may reflect drug regimens, doses used, increased drug metabolism, or conversion to metabolites with antagonistic actions to delta-9-THC. It may also represent some tumor cell modifications rendering the cell insensitive to these drugs. Of further interest was the lack of activity of delta-9-THC against the L1210 in vivo, whereas the invitro L1210 studies indicated that delta-9-THC could effectively inhibit thymidine uptake. The apparent reason for this discrepancy may be related to the high growth fraction and the short doubling time of this tumor. The in vitro data do not indicate that the cannabinids possess that degree of activity; e.g., ara-C, which "cures"L1210 mice, is several orders of magnitude more potent on a molar basis than delta-9-THC in vitro.

Inhibition of tumor growth and increased animal survival after treatment with delta-9-THC may, in part, be due to the ability of the drug to inhibit nucleic acid synthesis. Preliminary data with Lewis lung cells grown in tissue culture indicate that 10 -5M delta-9-THC inhibits by 50% the uptake of

3H-TDR into acid-precipitable counts over a 4-hour incubation period. Simultaneous determination of acid-soluble fractions did not show any inhibitory effects on radiolabeled uptake. Therefore, delta-9-THC may be acting at site(s) distal to the uptake of precursor. We are currently evaluating the acid-soluble pool to see if phosphorylation of precursor is involved in the action of delta-9-THC.

These results lend further support to increasing evidence that, in addition to the well-known behavioral effects of delta-9-THC, this agent modifies other cell responses that may have greater biologic significance in that they have antineoplastic activity. The high doses of delta-9-THC (i.e., 200 mg/kg) are not tolerable in humans. On a body-surface basis, this would be about 17 mg/m(2) for mice. Extrapolation to a 60-kg man would require 1,020 mg for comparable dosage. The highest doses administered to man have been 250-300 mg (14). Whether only cannabinoids active in the central nervous system (CNS) exhibit this antineoplastic property is not the question, since CBN, which lacks marihuana-like psychoactivity, is quite active in our systems (15). With structure-activity investigations, more active agents may be designed and synthesized which are devoid of or have reduced CNS activity. That these compounds readily cross the blood-brain barrier and do not possess many of the toxic manifestations of presently used cytotoxic agents, makes them an appealing group of drugs to study.

REFERENCES

1. Singer AJ: Marihuana: Chemistry, pharmacology and patterns of social use. Ann NY Acad Sci 191: 3-261, 1971

2. Leuchtenberger C, Leuchtenberger R, Schneider A: Effects of marijuana and tobacco smoke on human lung physiology. Nature 241: 137-139,1973

3. Zimmerman AM, McClean DK: Action of narcotic and hallucinogenic agents on the cell cycle. In Drugs and the Cell Cycle (Zimmerman AM, Padilla GM. Cameron IL, eds.). New York, Academic Press, 1973, pp.67-94

4. Stenchever MA, Kunysz TJ, Allen MA: Chromosome breakage in users of marihuana. Am J Obstet Gynecol 118: 105-113, 1974

5. JohnsonRT, Wiersema V: Repression of bone marrow leukopoieses by delta-9-THC . Res Commun Chem Pathol Pharmacol 7: 613-616, 1974

6. Kolodny RC, Masters WH, Kolodner RM, et al: Depression of plasma testosterone levels after chronic intensive marijuana use. N Engl J Med 290: 872-874, 1974

7. Nahas GG, Suchu-Foca N, Armand JP, et al: Inhibition of cellular immunity in marihuana smokers. Science 183: 419-420, 1974

8. Levy JA, Munson AE, Haris LS, et al: Effect of delta-8 and delta-9-tetrahydrocannabinol on the immunre response in mice. The Pharmacologist 16: 259, 1974

9. Harris LS, Munson AE, Friedman MA, et al: Retardation of tumor growth by delta-9-tetradydrocannabinol. The Pharmacologist 16: 259, 1974

10. Mayo JG: Biologic characterization of the subcutaneously implanted Lewis lung tumor. Cancer Chemother Rep 3: 325-330, 1972

11. Geran RI, Greenberg NH, MacDonald MM, et al: Protocols for screening chemical agents and natural products against animal tumors and other biological systems. Cancer Chemother Rep 3: 13, 1972

12. Munson AE, Regelson W, Lawrence W: The biphasic response of the reticuloendothelial system (RES) produced by pyran copolymer and its relationship to immunologic response. J Reticuloendothel Soc 7: 375-385, 1970

13. McMillan DE, Dewey WL, Turk RF, et al: Blood levels of 3H-delta-9-tetrahydrocannabinol and its metabolites in tolerant and non-tolerant pigeons. Biochem Pharmacol 22: 383-397, 1973

14. Jones RT: The 30-day trip-clinical studies of cannabis tolerance and dependence. Proceedings of the International Conference on the Pharmacology of Cannabis. Savanah, Georgia, 1974, p.29

15. Hollister LE: Structure-activity relationships in man of cannabis constituents and homologs and metabolites of delta-9-tetrahydrocannabinol. Pharmacology 11: 3-11, 1974

Marijuana Health Effects

For access to all these reports, go to

http://www.mpp.org/library/marijuana-health-effects.html

MPP handouts, reports, briefing papers, etc.

- Marijuana: Myths vs. Reality
- Common Questions About Marijuana
- Treatment for Marijuana Problems - Separating Fact From Fiction

Outside reports, studies, etc.

- Treating Depression With Cannabinoids - Prohibitionists sometimes claim marijuana causes depression and scoff at marijuana as a treatment for depression. Here a Viennese doctor describes repeated clinical successes using oral THC to treat depression.
- Understanding the Association Between Adolescent Marijuana Use and Later Serious Drug Use: Gateway Effect or Developmental Trajectory? - This rather complicated study looks at the "gateway theory" through data collected from 510 pairs of twins who participated in a very large, long-term health study -- and the gateway theory doesn't emerge with much backing.
- Toxicology of Cannabis and Cannabis Prohibition - This review describes short and long term negative effects of marijuana use from a cost-benefit perspective.
- Testing Hypotheses About the Relationship Between Cannabis Use and Psychosis - The relationship between marijuana use and psychosis is a subject of ongoing controversy. In this study, a respected group of Australian researchers took the data on marijuana use rates and rates of schizophrenia and ran a series of computer models to test the possibilities that marijuana: a) causes schizophrenia, b) precipitates schizophrenia in vulnerable persons, c) aggravates schizophrenia in people who already have it, or d) that schizophrenics are more likely to use marijuana (i.e. that marijuana use is the effect, not the cause, of schizophrenia).
- Some Go Without a Cigarette - This study examined differences between youth who use both tobacco and marijuana compared to youth who use marijuana only, and to youth using neither substance. The marijuana-only adolescents showed better functioning than those who also use tobacco.
- A Review of the Published Literature Into Cannabis Withdrawal Symptoms in Human Users - We hear regularly from prohibitionists that marijuana is addictive, but some experts consider the evidence unconvincing.

- A Preliminary DTI Showing No Brain Structural Change Associated With Adolescent Cannabis Use - The question of whether marijuana causes brain damage, especially among adolescents, remains controversial even though most recent evidence indicates no correlation.
- Predictors of Marijuana Use in Adolescents Before and After Licit Drug Use: Examination of the Gateway Hypothesis - This prospective, decade-long study finds no support for the "gateway theory" that marijuana causes youth to move on to hard drug use.
- Polydrug Use, Cannabis, and Psychosis-Like Symptoms - Much of the purported link between marijuana use and psychosis is based on correlations between marijuana use and schizophrenia-like symptoms or traits, called "schizotypal personality." But this study suggests that the effects of other drugs also used by some who use marijuana may be confounding such findings.
- A Pilot Clinical Study of 9-Tetrahydrocannabinol in Patients With Recurrent Glioblastoma Multiforme - THC and other cannabinoids have been shown to have marked anti-cancer action in laboratory and animal studies. This article describes a clinical pilot study in which THC was injected directly into tumors in terminal brain cancer patients via catheter (tube) to assess feasibility and safety of the procedure.
- Neuroscience of Psychoactive Substance Use and Dependence - While by no means an anti-prohibitionist document, this World Health Organization report makes a number of interesting points. The report notes, "despite intensive interdiction efforts, there always seems to be enough [drugs] available to users."
- The Neuropsychological Correlates of Cannabis Use in Schizophrenia: Lifetime Abuse/Dependence, Frequency of Use, and Recency of Use - Schizophrenia, a chronic mental illness, is often accompanied by poorer cognitive functioning, and some research has suggested that marijuana may worsen schizophrenia. But this case-control study shows enhanced cognitive functioning in schizophrenic subjects who use marijuana.
- Neuropsychiatry: Schizophrenia, Depression and Anxiety - Scientific consensus on the role of marijuana in psychological disorders is still lacking, after hundreds of years of speculation and study. Recent evidence of dysregulation of the body's endocannabinoid system in schizophrenics is beginning to shed new light on some of these questions.
- Motives for Cannabis Use as a Moderator Variable of Distress Among Young Adults - A number of studies have found higher rates of various psychiatric problems among marijuana users, and there has been much debate about whether marijuana causes these problems or whether those with psychological issues are simply more likely to use it. In this study, Swiss youth were followed for two years to determine how their motive for marijuana use interacts with levels of psychological distress.
- Marijuana Use and the Risk of Lung and Upper Aerodigestive Tract Cancers: Results of a Population-Based Case-Control Study - This study, co-authored by Donald Tashkin of UCLA, one of the world's leading experts on the effects of marijuana on the lungs, compared 1,212 cancer patients with 1,040 cancer-free controls matched for age, gender and neighborhood in order to see if there was a relation between marijuana use and cancers of the lungs, throat and mouth (cancers commonly caused by cigarette smoking).
- Long-Term Effects of Exposure to Cannabis - Oxford University pharmacologist Leslie Iversen reviews the literature on the effects of long-term marijuana use. Iversen finds that most purported cognitive impairment associated with marijuana dissipates when use ceases.
- Human Cannabinoid Pharmocokinetics - This review provides in-depth evaluation of marijuana absorption, metabolism and excretion.
- Further Consideration of the Classification of Cannabis Under the Misuse of Drugs Act 1971 - In 2005, concerned about reports linking marijuana use to mental illness, the British government asked the Council to take another look at the 2004 "downgrading" of marijuana, which had placed it in the least harmful category of illicit drugs and eliminated most marijuana possession arrests.
- Evidence-Based Answers to Cannabis Questions - This 60-page report is an evidence-based literature review of marijuana, based only upon research that followed well-accepted research

designs, included strong statistical and procedural controls and passed a careful review by independent scientists.

- The Evidence Base for the Classification of Drugs - As part of its evaluation of Britain's system for classifying illicit drugs, Parliament commissioned the European branch of RAND Corporation, one of the world's most respected think-tanks, to study the evidence underlying the classification of several specific drugs, including marijuana.

End

Prenatal Marijuana Exposure and Neonatal Outcomes in Jamaica: An Ethnographic Study

Melanie C. Dreher, PhD; Kevin Nugent, PhD; and Rebekah Hudgins, MA

---

http://www.druglibrary.org/Schaffer/hemp/medical/can-babies.htm

ABSTRACT.

Objective. **To identify neurobehavioral effects of prenatal marijuana exposure on neonates in rural Jamaica.**

Design. **Ethnographic field studies and standardized neurobehavior assessments during the neonatal period.**

Setting. **Rural Jamaica in heavy-marijuana-using population.**

Participants. **Twenty-four Jamaican neonates exposed to marijuana prenatally and 20 nonexposed neonates.**

Measurements and main results. **Exposed and nonexposed neonates were compared at 3 days and 1 month old, using the Brazelton Neonatal Assessment Scale, including supplementary items to capture possible subtle effects. There were no significant differences between exposed and nonexposed neonates on day 3. At 1 month, the exposed neonates showed better physiological stability and required less examiner facilitation to reach organized states. The neonates of heavy-marijuana-using mothers had better scores on autonomic stability, quality of alertness, irritability, and self-regulation and were judged to be more rewarding for caregivers.**

Conclusions. **The absence of any differences between the exposed on nonexposed groups in the early neonatal period suggest that the better scores of exposed neonates at 1 month are traceable to the cultural positioning and social and economic characteristics of mothers using marijuana that select for the use of marijuana but also promote neonatal development.**
Pediatrics **1994;93:254-260;** ***prenatal marijuana exposure, neonatal outcomes, Jamaica, Brazelton scale supplementary items.***

ABBREVIATIONS. NBAS, Neonatal Behavioral Assessment Scale; SES, Socioeconomic status.

The purpose of this study was to identify the effects of marijuana (or "ganja" as it is called in Jamaica) consumption during pregnancy and lactation on offspring during the neonatal period. Despite the prevalence of marijuana use among women of childbearing age, 1-3 reports on the behavioral teratogenic effects of prenatal marijuana exposure have been conflicting and inconclusive. Fried and Makin, 4 for example, found that moderate levels of marijuana use in their middle-class Ottawa sample (7.0 joints per week) were associated with poorer habituation to light, higher levels of irritability, and increased tremors and startles as assessed by the Brazelton Neonatal Behavioral Assessment Scale (NBAS) between the third and sixth days of life. Tennes et al, 5 on the other hand, found no relationship between exposure to marijuana and the neonates' behavior as rated by the NBAS. Similarly, a recent study of 373 lower socioeconomic status (SES) mothers and their neonates by Richardson and colleagues 6 found no relationship between moderate levels of marijuana use during pregnancy and neonate behavior on the NBAS on the second day of life. Yet Chasnoff, 7 lending support to Fried's findings, observed that marijuana use during pregnancy made a significant contribution to variance in the Brazelton State Regulation cluster scores, including habituation, in neonates a few days of age.

More recently, Coles et al, 8 studied the effects of maternal drug use on the neurobehavioral status of 107 neonates and found maternal marijuana use had depressed effects on the Orientation cluster of the NBAS at 14 days and on the Range of State cluster at the end of the first month. The interaction of marijuana use and cocaine and alcohol, however, was responsible for significant amounts of the variance in neonate behaviors over the first month of life. Nevertheless, they concluded that although the influence of drug and alcohol exposure could be noted statistically, the effects on neonate behavior were small and behavior was not clinically aberrant.

It is likely that many of conflicting results among published studies on the effects of prenatal drug exposure are due to methodological problems in (1) the measurement of neonatal outcomes and (2) the context in which the research is conducted. With the exception of the analysis of cries of neonates in Jamaica 9 and the work of Scher et al 10 and Dahl et al 11 that demonstrated altered sleep cycling and motility among North American neonates, most research has used the Brazelton Neonatal Behavioral Assessment Scale as an outcome measure in examining the effects of prenatal drug exposure. Inconsistencies in the use of the scale, however, have included the timing of the administration, the degree to which examiners were trained to reliability, 12, 13 and the approach to data reduction and analysis. Perhaps most important, only the 28 neurobehavioral items on the NBAS have been used in any analysis to date. Although supplementary items were added to the second edition of the Brazelton Neonatal Behavioral Assessment Scale 12 to be used with high-risk or fragile neonates, the items have not yet been employed in any published study of the effects of in utero drug exposure. This may mean that the more subtle differences that could distinguish marijuana-exposed neonates simply may not have emerged in the traditional scoring schemes and neurobehavioral cluster analysis.

With regard to the research context, it should be noted that virtually all the studies of prenatal exposure have been conducted in the United Sates and Canada where marijuana use is primarily recreational. This is in marked contrast to other societies, such as Jamaica, where scientific reports have documented the cultural integration of marijuana and its ritual and medicinal as well as recreational functions. 14, 15 Previous studies have had difficulty controlling possible confounding effects of factors such as polydrug use, antenatal care, mothers' nutritional status, maternal age, SES and social support, as well as the effects of different caretaking environments, which could lead to differences in neonate behavior. 8, 16 The legal and social sanctions associated with illicit drug use often compromise self-report data and render it almost impossible to obtain accurate prenatal exposure levels. 17

The Jamaican perinatal marijuana study provides a unique opportunity to address several of these methodological issues. First, although the study employed the NBAS to assure comparability with other studies, it was assumed that the full-term scale might not be sensitive to less obvious effects of risk status. Because the effects of marijuana were expected to be subtle, 4 and because the results of studies using the NBAS to examine the effects of substance abuse on neonatal behavior have been inconclusive, 6, 8, 16 the new supplementary items were administered to better capture the more latent effects of maternal marijuana use on neonatal behavior.

In Jamaica the use of marijuana is culturally integrated and governed by social rules that guide consumption and distribution and inhibit abuse. 14, 15 Because the cultural meanings that attend marijuana use and users have been documented to influence the outcomes of consumption, 14, 18 the Jamaican study permits cross-cultural scrutiny of the concepts and assumptions formulated in Eurocentric cultures. Also unlike the United States and Canada where polydrug use prevails, marijuana use by women in Jamaica has been relatively uncontaminated by other drugs; even alcohol and tobacco are used only minimally by women. 14, 15, 18, 19 Furthermore, conducting the study in one rural parish (county) provided an opportunity to compare users and nonusers who are drawn from the same population in which there is little variation in such factors as nutrition and prenatal care. Finally, field workers resided in the communities and developed long-term, trusting relationships with participants. This enhanced the credibility of self-reports of consumption and permitted confirmation by direct observations of marijuana-linked behavior.

Previously reported findings from this study suggested a biological vulnerability associated with prenatal exposure to marijuana in the immediate postnatal period. 9 This paper explores the influence of the cultural context of caregiving by evaluating the infants both at the beginning and the end of the neonatal period with assessment measures specifically designed to capture the subtle effects of maternal marijuana use on neonatal behavior.

CULTURAL CONTEXT

This project was based in the southeastern part of Jamaica in which there is a well-known and documented widespread use of marijuana. 19 Consistent with the working class throughout Jamaica, residents in the rural communities from which the sample for this study is drawn view marijuana not only as a recreational drug but one that also has ritual and medicinal value. Rastafarians, members of a political-religious movement that endorses marijuana as a sacred substance, may smoke ritually on a daily basis. Marijuana also is known for its therapeutic and health-promoting functions. It is consumed as a tea by family members of all ages for a variety of illnesses and to maintain and promote health. 14, 15 Although the consumption of marijuana tea transcends class, age, and gender divisions, marijuana smoking traditionally has been an adult male, working class activity. 14, 15 The female marijuana smoker was a rarity and the few women who engaged in smoking were considered base and undignified and often held in contempt by both men and women. Instead, women prepared marijuana for themselves and their families in the form of teas and tonics.

More recently, however, increasing numbers of women have begun to smoke marijuana regularly. 20 To some extent, this was attributed to the increasing participation of women in Rastafarianism, but the practice has spread to nonRastafarian women as well. Not only are such women now grudgingly tolerated by their communities, many of the heavy-marijuana-users, particularly if they were Rastafarians, have been given the commendatory title of "Roots Daughter." Roots Daughters are described as women "with a purpose," who can "think, reason and smoke like a man" and who are self-reliant and dignified. They smoke marijuana on a daily basis, in a manner not unlike that of their male counterparts, and continue to smoke during pregnancy and the breast-feeding period.

Although marijuana use during pregnancy is discouraged in prenatal clinics and through government-sponsered prevention programs, the consumption of marijuana during pregnancy by Jamaican women is not necessarily indicative of a mother's lack of concern about the health and development of her infant. Supported by the folk belief that marijuana has health-rendering properties and by the experience of relatives and neighbors, women use it as a vehicle for dealing with the difficult circumstances surrounding pregnancy and childbirth. For instance, 19 of the marijuana smokers in the sample reported that it increased their appetites throughout the prenatal period and / or relieved the nausea of pregnancy. Fifteen reported using it to relieve fatigue and provide rest during pregnancy. All the mothers considered the effects of marijuana on nausea and fatigue to be good for both themselves and their infants.

The responsibilities that accompany pregnancy and infant care in an unyielding economic environment are not trivial. The multigravidas, in particular, reported that the feelings of depression and desperation attending motherhood in their impoverished communities were alleviated by both social and private smoking. Despite these reports of the benefits of marijuana to both mother and baby, the women who smoke marijuana with any regularity continue to be in the minority. Most women in Jamaica refrain from smoking the substance and those who do smoke marijuana represent a departure from the norms regarding standard female behavior. 20

METHOD

An ethnographic design, combining community and household naturalistic observations and interviews of 60 women with standardized testing of their neonates using the NBAS, was employed. With the assistance of local midwives, the field workers identified and recruited pregnant women who used marijuana until a sample of 30 was obtained. After each participant agreed to participate and informed consent was obtained, she was then matched (again, with the assistance of local midwives) with a gravid woman who did not use marijuana, according to age, parity, and SES. The study was fully explained to both the marijuana users and the companion group and none refused to participate. During the course of the study, three of the mothers designated as nonusers were discovered to be tea drinkers and were transferred to the users category, resulting in a sample of 33 users and 27 nonusers. Further losses to the sample include two spontaneous abortions in the users category and one stillbirth and a preterm in the nonuser category, yielding a maternal sample of 31 users and 25 nonusers. Social, medical, and obstetrical histories were determined via maternal interviews. Naturalistic observations of the women in their homes and communities were conducted by the field workers who maintained routine contact with the participants throughout the prenatal period. Data concerning labor and delivery and the status of the neonate, details of labor, any anomalies or complications, birth weight, and length of gestation were abstracted from hospital records for each birth event.

The sample was drawn from the vast category of "rural poor," which constitute the majority of the population of this region of Jamaica. The two groups were matched for SES, based on income and employment, parity (0 to 8 for both smokers and nonsmokers) and age . The 60 women ranged in age from 15 to 42 and all were of Afro-Jamaican descent. None were gainfully employed in permanent jobs although many worked occasionally outside their homes as agricultural or domestic laborers or as "higglers" (vendors). Only one of the women was legally married, although more than half of the women were living in a more or less permanent common-law arrangement with their infant's father. Three of the women were members of a Rastafarian sect and lived in a communal "Rasta Camp." All had regular prenatal care from at least the second trimester to birth. The use of alcohol and tobacco was minimal in both groups and did not exceed 3 beers or 15 tobacco cigarettes per week for any of the women in the study. Based on self reports, reports of community residents and direct observations by field workers, the group of marijuana-using mothers was further designated as "light," "moderate," or "heavy" users, depending on the frequency the amount of use. Light users

were defined as those women who consumed marijuana tea only or smoked infrequently, averaging less than 10 cigarettes per week. Moderate users were those women who smoked 3 or more days a week, averaging between 11 and 20 marijuana cigarettes. Heavy users smoked daily, usually more than 21 marijuana cigarettes per week. Many moderate and heavy users also were regular marijuana tea drinkers. Although it was not by design, the user group was divided into almost equal categories of heavy (n = 10), moderate (n = 9), and light (n = 12).

Although the sample was matched on three major variables, the social histories revealed subtle and unanticipated differences both within the using group and between the two groups. First, as a group, the heavy users had the highest level of education. All the heavy users had had some schooling beyond the primary school level and three had had some post secondary training. Although SES was a matching variable in the selection of the sample, the roots daughters (heavy-marijuana-users) were distinguishable by the source of support. None relied exclusively on the father of the study child for support whereas most of the sample was either solely or heavily dependent on their infant's father. Although none of the women in the sample was routinely employed, the alternative sources of income for the roots included their own cash-generating activities such as running an illegal gambling operation or selling marijuana, remittances from relatives living abroad, support from parents or from former mates in the form of cash, food, housing, clothing and/or child care, and for the three Rastafarian women, housing and food in a communal living arrangement. The heavy-marijuana-users did not have more income and status than the other women, but they did have more control over how they acquired and spent their resources. Closely linked to this greater economic independence is the lower level of conjugal stability among users compared with nonusers. Because they did not rely on male support, they were relatively free to separate and form new relationships if their current relationship was not to their liking. 21 Among the women using marijuana heavily, only 48% were in common-law unions compared with 71% of the nonusing women. Among the 10 heavy-marijuana-users, only 3 lived in more or less permanent, co-residential relationships with the fathers of their infants. The remaining seven maintained their own households, although 3 were visited regularly by their infant's father.

Newborn Assessments

The newborn assessments were administered in the hospital on the first and third days and at 1 month of the newborn's life in the hospital maternity ward. To keep the conditions of birth as comparable as possible, only those newborns who were born in the hospital and remained there for 3 days were included in the analysis. Therefore, although the maternal sample was 31 users and 25 nonusers the newborn sample was reduced to 24 exposed and 20 nonexposed newborns.

The Jamaican examiner, who was blind to the neonates group assignment, was a registered nurse who had worked for several years on the maternity unit and was trained by the Child Development Unit Harvard Medical School both to the .90 reliability criterion and to administer the NBAS supplementary items. 12 Three examination data collection points were used to embrace the entire neonatal period: 1 day, 3 days, and 1 month. Given the great disparity within the sample regarding the timing and place of birth, the day assessments were omitted from the analysis because of possible differences in recovery time, in keeping with the recommendations of the NBAS manual. 12 Based on the developmental assumptions underlying the NBAS, 13 the assessment of neonate behavior at the end of the first month also can provide a functional assessment of the effects of the caregiving environment on neonate behavior. The Brazelton scores at the end of the first month, therefore, can be interpreted not only in terms of direct marijuana effects but also as a result of the effects of the environment on behavior. 12

The supplementary items assess behavior such as the quality of the neonate's attention or the cost of this level of responsivity to the neonate's physiological or motor system. The supplementary items

also assess the extent of examiner effort that may be necessary to facilitate the neonate's performance. This, in turn, may be a critical area that differentiates the fragile neonate, who has difficulty in coping with the demands of the examination, from the less stressed, healthy neonate. These additional supplementary items also identify the threshold of responsivity in neonates and the degree to which they are vulnerable to external environmental stimulation.

Quality of Alert Responsiveness is an assessment of the overall capacity of the neonate to respond to both human and nonhuman stimuli. Cost of Attention describes the degree to which the neonate's motor, state, and physiological systems are stressed or compromised as the neonate interacts with the environment. Examiner Persistence is a measure of the amount of examiner facilitation that is necessary to enable the neonate to maintain homeostasis or to be able to respond optimally to the challenges of the examination. General irritability is an extension of the irritability item in the Scale proper and describes the overall amount of fussing or crying during the course of the examination. The Robustness and Endurance item assesses the degree to which neonates become exhausted or stressed during the course of the assessment or the extent to which their "energy" resources enable them to organize or recover in the face of stress. The Regulatory Capacity score is an index of the strength of the regulatory system and of the neonate's ability to self-regulate. State Regulation provides a measure of the range of the neonate's six states and the degree to which the states are robust and stable and contribute to the overall organization of the neonate. Balance of Motor Tone Examines the consistency of motor tone throughout the body and is demonstrated by the balance between the flexor and extensor motor groups. The final item, Reinforcement Value of the Infant's Behavior, is a measure of the examiner's reaction to the neonate and a clinical rating of the degree to which the neonate was easy or difficult to manage through the course of the examination. Of these nine items, only Regulation of State and the Cost of Attention items were not scored. On the basis of the individual item scores, each subject was assigned a score for each of the seven clusters, and a score for each of the seven summary supplementary items.

For the analysis of the NBAS data, the 3-day and 1-month individual scores were reduced to the seven clusters described by Lester et al. 22 These clusters and the supplementary items were used as dependent measures in the subsequent analyses. The clusters are Habituation, Orientation, Motor Organization. Range of State, Regulation of State, Autonomic Regulation, and the number of Abnormal Reflexes.

The groups were first dichotomized into marijuana-exposed versus nonexposed and, using SPSS-X statistical software,The tests were performed to compare the performance of these neonates on the NBAS clusters and on the supplementary items. Because the neonates of the heavy users received the most frequent and consistent exposure both prenatally and during the first month of life they served as the "extreme" cases in which to search for specific developmental and behavioral effects. To examine these effects, the scores of the neonates of heavy-marijuana-using and neonates of nonusing mothers were also compared using t tests.

RESULTS

The course of the pregnancies were similar in each group and the two groups of neonates were not significantly different according to physical examination data, including birth weight and length and gestational age. 23 Because Apgar scores were not recorded by hospital nurses at standard time intervals, they were less reliable. Nevertheless, there were no significant differences in the Apgar scores between the two groups.

t tests were used to compare the performance of neonates of users (n = 24) and nonusers (n = 20 on the NBAS cluster scores and on the supplementary items on the third day of life. Table 1 shows that there were no significant differences on the seven clusters. There also were no differences on the

seven supplementary items. To examine the degree to which heavy marijuana use may have an effect on neurobehavioral outcome, we then compared the performance of the heavily exposed and nonexposed neonates on the NBAS on day 3, by examining group differences on the seven Brazelton cluster scores and on the supplementary items scores. As Table 2 reveals, there were no significant differences in performance on the Brazelton cluster scores on day 3. Similarly, no differences were found on the supplementary item summary scores.

At 1 month, however, comparisons between exposed and nonexposed neonates revealed that the neonates of using mothers had significantly higher scores on the Autonomic and Reflex clusters of the NBAS (see Table 3). On the supplementary items, these neonates scored higher (were less irritable) on the General Irritability item.

Comparing the heavily exposed and the nonexposed infants, the Brazelton clusters on day 30, showed that the offspring of heavy-marijuana using mothers had significantly higher scores on the Orientation cluster, on the Autonomic Stability cluster, and on Reflexes (see Table 4). Due to the intercorrelation among the variables comprising each cluster, no *t* scores or *P* values are reported for individual items. Nevertheless, a comparison of individual item scores showed that neonates of heavy users had higher scores on habituation to auditory and tactile stimuli, and to animate auditory stimuli, the degree of alertness, capacity for consolability, irritability (ie, less irritable), and had fewer startles and tremors. The comparisons on the supplementary items revealed significant differences on all seven variables, with the neonates of mothers who were heavy-marijuana users performing more optimally on these items.

DISCUSSION

Although no positive or negative neurobehavioral effects of prenatal exposure were found at 3 days of life using the Brazelton examination, there were significant differences between the exposed and nonexposed neonates at the end of the first month. Comparing the two groups, the neonates of mothers who used marijuana showed better physiological stability at 1 month and required less examiner facilitation to reach an organized state and become available for social stimulation. The results of the comparison of neonates of the heavy-marijuana-using mothers and those of the nonusing mothers were even more striking. The heavily exposed neonates were more socially responsive and were more autonomically stable at 30 days than their matched counterparts. The quality of their alertness was higher; their motor and autonomic systems were more robust; they were less irritable; they were less likely to demonstrate any imbalance of tone; they needed less examiner facilitation to become organized; they had better self-regulation; and were judged to be more rewarding for caregivers than the neonates of nonusing mothers at 1 month of age.

TABLE 1. Neonatal Behavioral Assessment Scale Cluster and Supplementary Scores, Day 3

Users	Nonusers (n = 24)		*t* Score (n = 20)	
	Mean	SD	Mean	SD	
Habituation	6.83	0.804	6.82	0.835	-.06
Orientation	5.87	0.953	5.45	1.324	-1.10
Motor organization	5.39	0.576	5.42	0.405	0.22
Range of state	4.15	0.415	4.07	0.474	-.57

Regulation of state	5.43	1.163	5.73	0.664	1.06
Autonomic stability	7.59	1.350	7.41	2.020	-.35
Reflexes	15.15	2.240	13.82	3.264	-1.47
Quality of alertness	5.69	1.692	6.05	1.298	0.80
Robustness	7.46	0.811	7.64	1.115	0.59
Regulatory capacity	5.80	1.767	6.00	1.458	0.39
Motor tone	6.76	0.992	6.94	1.249	0.48
General irritability	7.70	0.806	7.75	0.447	0.21
Examiner's persistence	5.42	1.653	5.58	2.002	0.28
Reinforcement value	5.88	1.451	5.94	1.435	0.13

TABLE 2. Neonatal Behavioral Assessment Scale Cluster and Supplementary Scores, Day 3

Heavy users	Nonusers (n = 10)		Heavy users (n = 20)		*t* Score
	Mean	SD	Mean	SD	
Habituation	6.45	0.683	6.82	.835	1.10
Orientation	5.87	0.655	5.45	1.324	-1.05
Motor organization	5.42	0.484	5.42	0.405	0.01
Range of state	4.13	0.427	4.07	0.474	-.31
Regulation of state	5.43	0.836	5.73	0.664	0.93
Autonomic stability	8.13	1.200	7.41	2.020	-1.18
Reflexes	15.66	2.180	13.82	3.264	-1.72
Quality of alertness	5.77	1.856	6.05	1.298	0.40
Robustness	7.22	0.441	7.64	1.115	1.38
Regulatory capacity	5.33	1.871	6.00	1.458	0.93
Motor tone	6.77	1.093	6.94	1.249	0.34
General irritability	7.85	0.378	7.75	0.447	-.59
Examiner's persistence	6.00	1.581	5.58	2.002	-.57
Reinforcement value	5.77	1.716	5.94	1.435	0.24

TABLE 3. Neonatal Behavioral Assessment Scale Cluster and Supplementary Scores, One Month

Users	Nonusers (n = 24)		*t* Score (n = 20)		
	Mean	SD	Mean	SD	
Habituation	7.20	0.877	6.53	1.503	−1.50
Orientation	6.63	1.439	6.45	1.310	−.45
Motor organization	6.45	0.669	6.36	.715	−.41
Range of state	3.88	0.748	4.03	.614	0.80
Regulation of state	5.62	1.074	5.47	1.415	−.39
Autonomic stability	8.69	0.549	7.33	2.260	−2.63*
Reflexes	15.55	1.88	13.40	2.990	−2.85*
Quality of alertness	7.28	1.357	6.65	1.496	−1.51
Robustness	8.78	0.499	8.47	.841	−1.45
Regulatory capacity	7.00	1.633	6.15	1.725	−1.72
Motor tone	7.46	1.105	7.50	0.513	0.15
General irritability	8.37	0.565	7.75	0.716	−3.20*
Examiner's persistence	7.25	1.666	6.55	1.877	−1.33
Reinforcement value	7.28	1.512	6.70	1.418	−1.37

* *P* <(on top of) (symbol) .01.

Cry changes reported for this population [9] had suggested a biological vulnerability [24] in the immediate postnatal period that was not evident in the supplementary item results of this study. A possible explanation for this discrepancy is that the Brazelton supplementary items, conducted under more controlled conditions, simply provided a more comprehensive and reliable assessment of the neonates' neurobehavioral status. It also is possible that the social effects [25] of the neonate's cry characteristics may even have elicited a quality of caregiver responses that could contribute to better outcomes at 1 month. It should be pointed out that Coles et al [8] also reported more significant differences at 1 month on the Brazelton Scale clusters than at earlier assessments, suggesting environmental effects. In this case, the direction of the differences in performance on the Brazelton examination between 3 days and 1 month suggest not only that the environment may be more influential than prenatal exposure in predicting outcomes but that the environment of the exposed group may be superior to that of the nonexposed group.

Conventional wisdom would suggest that mothers who are long-term marijuana users are less likely to create optimal caregiving environments for their neonates. In this area of rural Jamaica, however, where marijuana is culturally integrated, and where heavy use of the substance by women is associated with a higher level of education and greater financial independence, it seems that roots daughters have the capacity to create a postnatal environment that is supportive of neonatal development. Indeed, Pearson's correlations, performed determine whether there was an association between the mother's education and neonatal outcomes at 1 month, revealed that maternal education

was significantly correlated with the Autonomic cluster at 1 month ($r = .27$, $P = .031$) and approached significance with all the supplementary items.

Although it is tempting to explain the 1-month outcomes by simply appealing to the correlation evidence linking performance to maternal characteristics, the question remains as to how these characteristics are translated to the formation of a better environment for neonatal development, particularly given the higher level of conjugal instability among users. Ethnographic observations of the postnatal environments identified that, despite the higher level of single mother households among the users, they had fewer children at home and thus fewer child care responsibilities compared with their nonusing counterparts. They also had more adults living in their households. Pearson's correlations revealed that the household child / adult ratio was significantly correlated with the Habituation clusters at 1 month ($P = .046$, $r = .30$) and with later child development outcomes. [21] Although the exact mechanism linking child / adult ratio to 1 month outcomes requires further delineation, it is possible that with more adults present to assist the mother and respond to the neonate and / or with fewer children to compete for attention, the mother is better equipped to facilitate the neonate's interaction with his / her environment. The lower child / adult household ratios and the mother's characteristics are not unrelated. The dispersal or outplacement of older children to their respective father's households as a new child is brought in is a common practice, facilitated by the pattern of serial mating in which the using mothers are more likely to engage. Thus, in this Jamaican rural working class context, conjugal instability is associated with greater rather than diminished access to the resources that influence child development.

TABLE 4. Neonatal Behavioral Assessment Scale Cluster and Supplementary Scores, One Month

Heavy users	Nonusers (n = 10)		*t* Score (n = 20)		
	Mean	SD	Mean	SD	
Habituation	6.75	1.521	6.53	1.503	-.22
Orientation	7.40	0.457	6.45	1.310	-2.87+
Motor organization	6.33	0.374	6.36	0.715	0.16
Range of state	3.41	0.984	4.03	0.614	1.75
Regulation of state	6.20	1.007	5.47	1.415	-1.57
Autonomic stability	9.00	0	7.33	2.260	-3.30+
Reflexes	15.78	2.220	13.40	2.990	-2.38*
Quality of alertness	8.00	0.500	6.65	1.496	-3.61+
Robustness	9.00	0.000	8.47	.841	-2.73+
Regulatory capacity	7.77	1.093	6.15	1.725	-3.07+
Motor tone	7.88	0.333	7.50	.513	-2.44*
General irritability	8.75	0.463	7.75	.716	-4.37+
Examiner's persistence	8.33	0.707	6.55	1.877	-3.70+
Reinforcement value	8.00	0.707	6.70	1.418	-3.29+

* *P* <(on top of) (symbol) .03.

+ *P* <(on top of) (symbol) .01.

Cross-societal research 14, 15, 26 has identified the importance of understanding the cultural context of drug use to explain outcomes. Whether or not the effects of marijuana during the prenatal period are real or only perceived, it is clear that for them, it has at least symbolic value in assisting them through the physical, social, and psychological difficulties of pregnancy and the postnatal experience. Furthermore, unlike the United States, in which heavy marijuana use often is associated with maternal incompetence and a suboptimal caregiving environment, the data from this study indicate that in Jamaica, the heavy-marijuana-using mother's education, independence, and greater access to resources converge in a constellation of maternal competence and a supportive context for neonatal development.

Strengths and Limitations

It should be noted that there are several limitations posed by this study and caution must be used in interpreting the results. First, the means by which the study participants were recruited may have introduced a bias in the sample. Second, the sample size is small, obviating the use statistical procedures that might be able to account for the many environmental variables that seem to influence some of the outcomes. Third, in a prospective study of this nature it is impossible to foresee and control for all the potential environmental and maternal confounders. Finally, this study has not eliminated alternative explanations. It is possible for example, that the outcomes at 1 month are related to neonatal exposure to marijuana constituents via breast milk or to prenatal influences that simply were not manifested at the 3-day examination.

On the other hand, the prospective design, using ethnographic techniques and inductive analyses, offers several advantages to the exploration of prenatal exposure to illicit drugs. First, given the difficulties encountered in recruiting participants who are engaging in an illegal activity and then retrieving credible data from them, identification by fieldworkers, with assistance from local midwives, represented a contributive alternative to a random sampling strategy. Second, although the sample size is small, it provided an opportunity to follow up drug-using women through pregnancy with the level of detail that often is lacking in retrospective studies of large numbers of women. Finally, the effects of prenatal exposure to drugs such as marijuana depend on several factors for which it is difficult and sometimes impossible to control in most clinical investigations. 8 Although this study was successful in controlling for polydrug use and SES, other variables (financial independence, mothers education, and household child / adult ratio) emerged as meaningful during the course of this study. Indeed a strength of the inductive design is its capacity to identify such unanticipated variables and to understand how they are linked in Jamaican culture with heavy marijuana use and a roots daughter syndrome. Although some might interpret this failure to identify the relevant variables at the outset of the study and control for them in a more experimental design as a weakness of the study, one could argue, conversely, that the project's greatest value is its capacity for discovery and the generation of hypotheses and research questions that can be explored in subsequent studies.

ACKNOWLEDGMENT

This work was supported by the March of Dimes Foundation.

REFERENCES

1. Negrete JC. What's happened to the cannabis debate? *Br J Addiction*. 1988:83:359-372

2. Schwartz RH. Passive inhalation of marijuana, phencyclidine, and freebase cocaine ('crack') by infants. *Am J Dis Child.* 1989:143:644

3. Zuckerman B. Frank. DA, Hingsem R, et al. Effects of maternal marijuana and cocaine use on fetal growth. *New Engl J Med.* 1989:32D:763-768

4. Fries PA, Makin JE. Neonatal behavioral correlates of prenatal exposure to marijuana, cigarettes and alcohol in a low risk population. *Neurotoxicol Teratol.* 1987:9:1-7

5. Tennes K, Avitable N, Blackard C, et al. Marijuana: prenatal and postnatal exposure in the human. In: Pinkert TM, ed. *Current Research on the Consequences of Maternal Drug Abuse*. Washington DC: US Government Printing Office: 1985. NIDA Research Monograph No. 59.

6. Richardson GA, Day NL, Taylor PM. The effect of prenatal alcohol, marijuana, and tobacco exposure on neonatal behavior. *Infant Behav Dev.* 1989:12:199-209

7. Chasnoff IJ. Cocaine use in pregnancy: effect on infant neurobehavioral functioning. Presented at the American Society for Pharmacology and Experimental Therapeutics, 1990, Washington DC

8. Coles CD, Platzman KA, Smith I, James ME, Falek A. Effects of cocaine, alcohol, and other drug use in pregnancy on neonatal growth and neurobehavioral status. *Neurotoxicol Teratol.* 1992:14:22-33

9. Lester B, Dreher M. Effects of marijuana use during pregnancy on newborn cry. *Child Dev.* 1989:(?):765-771

10. Scher MS, Richardson GA, Cuble PA, et al. The effects of prenatal alcohol and marijuana exposure: disturbances in neonatal sleep cycling and arousal. *Pedatr Res.* 1984:24:101-105

11. Dahl RE, Scher MS, Day NL, et al. The effects of prenatal marijuana exposure evidence of BEG sleep disturbances continuing through 3 years of age. *Dev Behav Pediatr.* 1989:19:264 Abstract

12. Brazelton TB. *The Neonatal Behavioral Assessment Scale*. Philadelphia: JB Lippincott: 1984

13. Brazelton TB, Nugent KJ, Lester BM. The neonatal behavioral assessment scale. In; Osafsky J, ed. *The Handbook of Infant Development.* New York; Wiley; 1987

14. Rubin V, Comitas L. *Ganja in Jamaica.* The Hague: Mouton Press; 1975

15. Dreher M. *Working Men and Ganja.* ISHI; 1982

16. Zuckerman B, Hingson R. Alcohol consumption during pregnancy. *Dev Med Child Neurol,* 1987;28:6-19-653

17. Hingson R, Zuckerman B, Amaro H, et al. Maternal marijuana use and neonatal outcomes; uncertainty posed by posed by self-reports. *Am J Public Health.* 1986;76:667-669

18. Dreher M. School children and ganja. *Anthropol Educ Q.* 1984;15:131-150

19. Clayton RR, Lindblad R, Walden KP, Knight F, Campbell E, Eldemire D. Drug use and drug abuse in Jamaica: the 1987 Jamaica national household survey. Sponsored by USAID and the

National Council on Drug Abuse, Government of Jamaica, through the Pan America Health Organization, 1988

20. Dreher M. The evolution of a roots daughter. *J Psychoactive Drugs*. 1987;19:165-170

21. Dreher M, Gilbert D, Hudgins R. Conjugal multiplicity and child development in Jamaica. Presented at Society for Applied Anthropology; March 1992; Memphis Tennessee

22. Lester BM, Als H, Brazelton TB. Regional obstetrics anesthesia and newborn behaviors: a reanalysis toward synergistic effects. *Child Dev.* 1982;52:71-82

23. Hayes J, Dreher M, Nugent K. Neonatal outcomes with maternal marijuana use in Jamaican women. *Pediatr Nurs.* 1988;14:107-110

24. Zuckerman B, Bresnahan K. Developmental and behavioral consequences of prenatal drug and alcohol exposure. *Pediatr Clin North Am.* 1991;38:1387-1406

25. Lester BM. A biosocial model of infant crying. In: Lipsett L, ed. *Advances in Infancy Research*. New York: Ablex;1984

26. Carter W. *Cannabis in Costa Rica.* Philadelphia; ISHI; 1980

[End]

Boy, two, with brain cancer is 'cured' after secretly being fed medical marijuana by his father

By Daily Mail Reporter

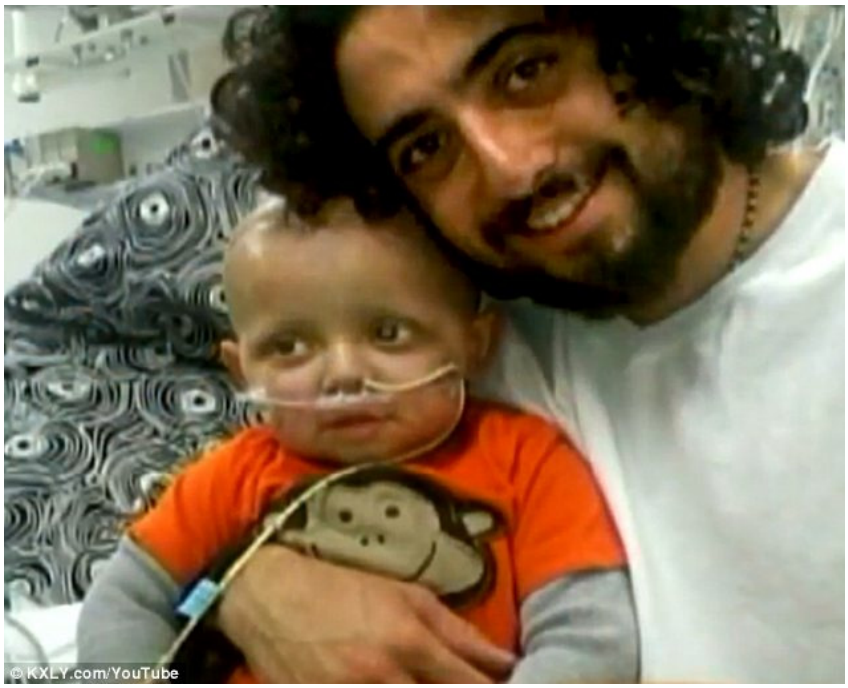
Last updated at 3:16 PM on 4th May 2011

A desperate father whose son was suffering from a life-threatening brain tumour has revealed he gave him cannabis oil to ease his pain. And he has now apparently made a full recovery.

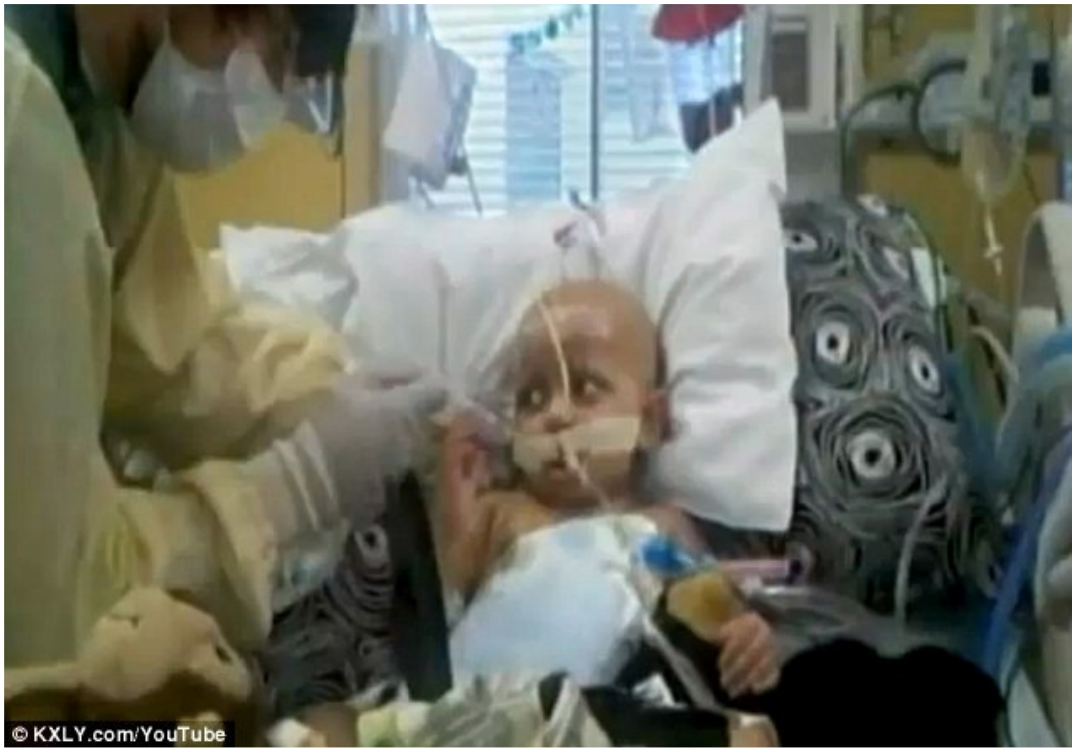
Cash Hyde, known as Cashy, was a perfectly healthy baby when he was born in June 2008 but became sick shortly before his second birthday.

At first he was misdiagnosed with glandular fever before his parents Mike and Kalli, from Missoula in Montana, were given the devastating news he had a serious brain tumour.

The little boy had to have arduous chemotherapy treatment to reduce the growth, which had drastic side effects including seizures and a blood infection.



Mike Hyde with his son Cash who was diagnosed with a severe brain tumour



Cash had to have high-dose chemotherapy which made him very ill

His distraught parents were repeatedly told he was likely to succumb to the illness because the condition was so bad.

After one bout of high-dose chemotherapy, Cash was so weak he could not lift his head and was too sick to eat any solid food for 40 days.

It was at this point that Mr Hyde decided to take action and go down the route of medical marijuana to try to help his young son.

Cash's doctors refused to even discuss the option but his father went and sought authorisation elsewhere and then secretly administered it through his son's feeding tube.

He also told doctors to stop giving Cash the cocktail of anti-nausea drugs he had been taking - although he never told them what he was doing.

Mr Hyde told KXLY News that his son started looking better right away.

The youngster with his older brother Colty as he is treated in hospital

Mr Hyde said: 'He hadn't eaten a thing in 40 days - and, it was really incredible to watch him take a bite of a piece of cheese. It shows that he wants to live'.

He credits the cannabis oil with helping his son get through the chemo, and say Cash has now been declared cancer free by doctors.

The boy is now back and home and living the life of a typical young boy, playing with his elder brother Colty.

Medical marijuana is legal in some states, including Montana, but its use for children is poorly understood and quite rate.

The US federal government does not recognise the legality of using the drug for medical reasons and frequently clashes with states over the issue.

Mr Hyde told KXLY: 'It's very controversial, it's very scary. But, there's nothing more scary than losing your child.'

Cash is now at home and able to live like a normal little boy

Read more: http://www.dailymail.co.uk/health/article-1383240/Boy-brain-cancer-cured-secretly-fed-medical-marijuana-father.html#ixzz1RVPQ2xF2

End.

New US Study Affirms Smoked Marijuana Protects Against Cancer.

Share:
by Brinna | August 10, 2009 at 09:12 pm

In 1974, University of Virginia researchers discovered something very unlikely. Cannabis, banned in the United States in 1937, and further demonized by the Nixon administration in 1968, had an unexpected property: it inhibited the growth of lung cancer cells. But, even more surprising was the response from the government: an apparent complete absence, even discouragement of any follow-up studies. The results were briefly mentioned in news reports at the time, but with the end of the Carter administration, cannabis became a step-child as far as scientific research was concerned.

Like any unloved step-child cannabis was treated with different rules, and made a scape-goat for social ills.

There was still research being done on cannabis, but funding was only available if the intent was to prove harm. In fact, it wasn't until the pioneering work done by Dr. Raphael Mechoulam, in Israel, and Dr. Manuel Guzman in Spain, that this startling anti-cancer property of cannabis sativa became public again.

What is even more troubling is that the United States Government actually did a secret follow up-study on the Virginia findings, in the mid '90's. When it only served to confirm the results of the 1974 research, and showed that THC (one of the main active ingredient in cannabis – and the one the government loves to hate), when administered to mice, protected them against malignancy, true to form, our government attempted to bury the results. Fortunately, a draft copy of the study was leaked to the journal, AIDS Treatment News, and the media covered the story. An excellent article by Paul Armentano, Deputy Director of NORML, covers this part of our shameful history.

By 2003, the cat was pretty much out of the bag, and a quick search onPubMed brings up at least 262 results when you put in "cannabis and cancer" in the search string. But, as late as this year, the US Government was still funding research meant to prove that cannabis causes cancer. The extremely flawed survey which attempted to link cannabis smoking with testicular cancerfalls into this category. In fact, in 2008, two years after Dr. Donald Tashkin research which showed that not only does cannabis not cause lung cancer, but appears to protect against it, three respected doctors from the cannabis research group felt compelled to write a letter to the European Respiratory Journal debunking a New Zealand study which claimed that smoking cannabis led to an increased risk of lung cancer.

Now, this month in Cancer Prevention Research Journal one can find a study demonstrating that chronic, long term of cannabis actually reduces the incidence of head and neck cancer. Specifically:

"10 to 20 years of marijuana use was associated with a significantly reduced risk of HNSCC" [head and neck squamous cell carcinoma].

Knowing this, are you angry? You should be. It's a safe bet to say you know someone who has cancer. Or died of it.

It's also a safe bet that you didn't hear any coverage of this story in the mainstream media.

For my money, it's way past time for the politics of prohibtion to be thrown aside, and hard science applied to what promises to be an extraordinary new era in the treatment and cure of cancer.

And... we need all the voices we can get saying: That time is now!

Requests for reprints of the study cited above can be made here: Karl T. Kelsey, Department of Community Health, Department of Pathology and Laboratory Medicine, Division of Biology and Medicine, Brown University, Providence, RI. Phone: 401-863-6420; Fax: 401-863-9008; E-mail: Karl_Kelsey@brown.edu.

Continue reading at NowPublic.com: New US Study Affirms Smoked Marijuana Protects Against Cancer. | NowPublic News Coverage http://www.nowpublic.com/health/new-us-study-affirms-smoked-marijuana-protects-against-cancer#ixzz1RvURxLZv

end