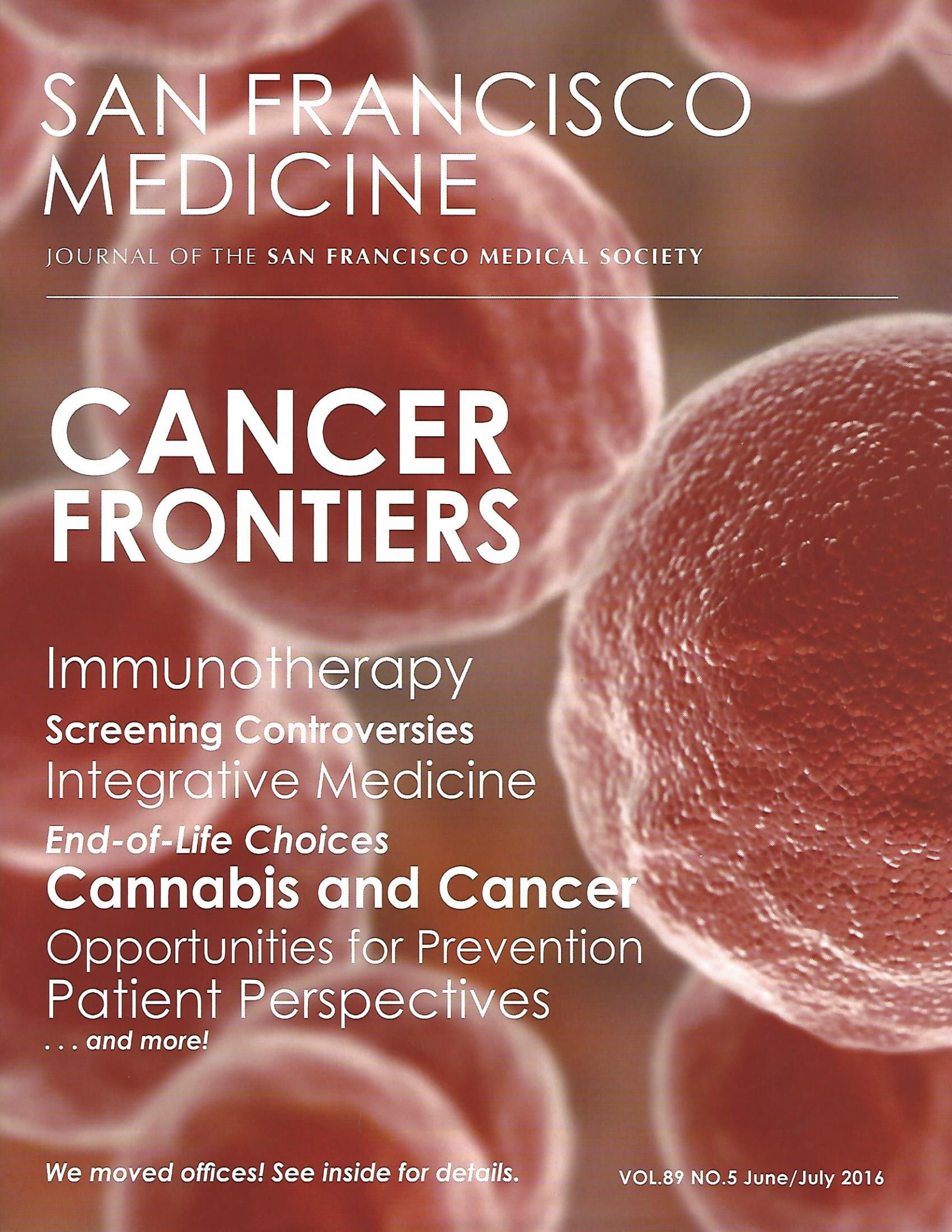

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CANNABIS AND CANCER

Decoding the Connection

Donald I. Abrams, MD

It seems like just yesterday that claims were being made that cannabis caused cancer. Epidemiologic reports suggested that regular cannabis use might be connected with the obvious head and neck malignancies and lung cancer, but also some that seemed more far-fetched such as cervical, prostate, and testicular. Subsequent analyses called most of these associations into question. One data set from Kaiser Northern California suggested that cannabis use might actually decrease the risk of lung cancer, a finding supported by a later case-controlled investigation from the pulmonologist at UCLA who has spent forty years studying the potential adverse effects of cannabis on the lungs. Then came the report suggesting that cannabis might decrease the risk of bladder cancer. And now, as the pendulum continues to swing, suddenly we are faced with increasing claims being made that cannabis actually cures cancer. What is the origin of such a notion?

The unearthing of the tomb of the Siberian Ice Maiden in 1993 revealed the well-preserved remains of a young woman presumed to have lived twenty-five hundred years ago. The maiden had metastatic breast cancer and was found buried with a pouch of cannabis, suggesting to the archeologists that she was using cannabis for symptom management as well as possibly a direct anti-cancer effect. Fast forward to 1974 when scientists at the National Cancer Institute published their findings that cannabinoids—delta-9-tetrahydrocannabinol (THC), delta-8-THC, and cannabidiol (CBD)—were all able to suppress the growth of Lewis lung adenocarcinoma cells *in vitro* and in mice. An increasing body of pre-clinical evidence from investigators predominantly in Spain and Italy supports the possibility of cannabinoids having anti-cancer effects, but to date there has only been one human study. Because the brain is enriched for the cannabinoid-1 receptor, it makes some sense that gliomas are a particularly responsive to the antineoplastic effects of cannabinoids. This led to a study conducted on patients with recurrent glioblastoma multiforme in the Canary Islands, where investigators applied topical delta-9-THC via a catheter directly into the tumors. The results were not impressive.

Certainly it cannot be the underwhelming result of that single human trial that is fanning the flames of the "Cannabis Cures Cancer" movement. A Canadian boiler maintenance worker heard of the news that cannabis may suppress tumors in 1974, two years after a cousin had died an agonizing death from cancer. Thirty years later when he was dealing with three basal cell carcinomas, he decided to treat them with a highly concentrated cannabis oil preparation. When the lesions disappeared, the highly concentrated cannabis oil took on his name and, with the impact of social media, went viral so that people all over were seeking such preparations for topical treatment of skin cancers and subsequently oral ingestion for diverse malignancies. Patients posted radiographic evidence of their tumors shrinking or disappearing on the internet, and a mass movement had begun. Interestingly, a number of the most vocal advocates for the benefits of cannabis oil seem oddly amnesiac that they were also treated with chemotherapy or other conventional means.

As an oncologist in San Francisco for the past thirty-three years, I often say that I would venture to guess that the majority of the patients I have cared for have used cannabis during their treatment. Thus, if cannabis cured cancer, I would have a lot more survivors. Granted, the plasma concentration of inhaled cannabis, as most of my patients have likely used in the past, probably does not approach that which can be achieved with the highly concentrated oil preparations (no data available on this as yet), but still, oncologists maintain that the plural of anecdote is not evidence! What saddens and disturbs me the most is when I see a patient in consultation with a potentially curable malignancy who is foregoing conventional cancer therapy in hopes that cannabis oil will be a kindler, gentler treatment. The fact remains, there is no evidence at this time to support such a decision. Having completed a number of clinical trials investigating the effect of inhaled cannabis on the pharmacokinetics of protease inhibitors and sustained release opioids without seeing clinically significant perturbations of plasma concentrations of the pharmaceuticals, I hopefully extrapolate that the cannabis oil preparations will behave similarly. But again, the reality is that we have no such information. And if we were to study it, would we use a high THC oil, or a high CBD oil, or one that has one of the magic THC:CBD ratios touted by those who purvey them?

Having lived through the rise and fall of many "alternative" cancer cures during these past three-plus decades, I fear that cannabis may go the way of laetrile or shark's cartilage, dismissed as bogus and fraudulent. The reality is that there is an increasing body of evidence that cannabinoids work against cancer cells from many angles—increasing apoptosis, decreasing angiogenesis through inhibition of vascular endothelial growth factor and thwarting invasion and metastases by matrix metalloproteinase-2. What is lacking is the demonstration that these *in vitro* effects translate into any benefit for people living with cancer. But there is a body of evidence that cannabis is an effective medicine for the management of symptoms arising from cancer or its treatment, so a blanket dismissal of cannabis as an invalid cancer treatment would deprive patients of a very valuable therapy.

Oncologists demand evidence before they embark on a therapeutic option. That makes sense because the diseases we treat and the interventions we employ are serious and potent, so data is essential before recommending any regimen. Similarly,

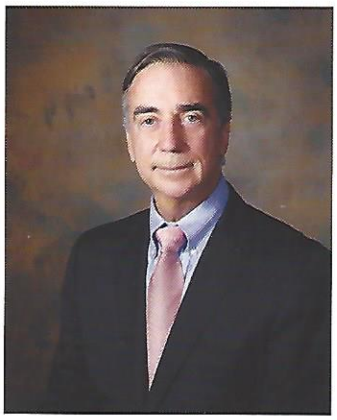
one would hope to see data supporting the effectiveness of cannabis as an antiemetic, appetite stimulant, analgesic, sleep aid or mood elevator before feeling confident suggesting its use.

It is important to recall, however, that the only legal source of cannabis for research in the United States is the National Institute on Drug Abuse (NIDA), and that they have a mandate from Congress to only study "substances of abuse" as substances of abuse and not therapeutic interventions. So if one wants to investigate the clinical effectiveness of cannabis as medicine, the drug can be obtained from NIDA, but funding must come from elsewhere. There are numerous additional regulatory hoops that must be surmounted before such a study can be conducted. Current data mainly involves the licensed delta-9-THC product, dronabinol, which has been the most widely studied cannabinoid medicine in the U.S. Dronabinol was licensed and approved for treatment of chemotherapy-induced nausea and vomiting in 1986, so oncologists theoretically should have the most experience using cannabis-based medicines. The fact that the single most active component of the parent plant is available supports the observation that the botanical itself is a useful antiemetic. Many of us have patients who forego the use of prescription anti-nausea medications in favor of using cannabis alone.

In animal models, cannabinoids are effective in both treatment and prevention of peripheral neuropathy caused by each of the three main classes of chemotherapy associated with this vexing symptom—the vinca alkaloids, the platinums and the taxanes. A number of studies, including one we conducted in HIV-related peripheral neuropathy, have suggested that inhaled cannabis is effective in various neuropathic syndromes. Interestingly, all of these studies suggest that the number of patients needed to treat for one to have a benefit (NNT) is consistently between three and one-half and four, which is identical to the NNT for gabapentin, one of the more widely used interventions for painful neuropathy. As yet, only one small study of an oromucosal spray preparation of whole cannabis extract has been completed in sixteen patients with chemotherapy-induced peripheral neuropathy with results that would support conducting a larger follow-on confirmatory trial.

Often cancer patients require opioid analgesics for management of pain. A small pharmacokinetic interaction study that we conducted found no significant alteration of plasma levels of sustained-release morphine or oxycodone when vaporized cannabis was inhaled three times daily. There was, however, a signal that pain relief may have been augmented. Animal studies support the synergy between cannabinoids and opioids in analgesia. This is another potential role for cannabis medicines in cancer patients.

Many patients are now seeking CBD-enriched preparations to avoid the psychoactivity associated with delta-9-THC. Although euphoria may be considered a side effect of cannabis use, I would not consider it an adverse experience. If I have one medicine that can decrease nausea and vomiting, enhance appetite, decrease pain, improve sleep and mood, I consider that to be a valuable intervention. Instead of writing prescriptions for five or six pharmaceuticals that could all interact with each other or the chemotherapy I prescribe, I can recommend one very safe botanical. On asking cancer patients "What brings you joy?" I am impressed by the number who answer that gardening does. It seems as if one is dying, or feels that a part of them has died, the ability to bring life out of the ground is a special gift. And if one can grow their own medicine, that is especially empowering.



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