

Marijuana and Immunity

LEO E. HOLLISTER, M.D.*

Few areas of scientific research have been as controversial as the effect of marijuana on immune defenses. The effects of marijuana on health in general have been marked by polarities of belief or interpretation of evidence often due to the particular prejudices of investigators. In addition, evidence of altered immune functions is derived mainly from in vitro tests or ex vivo experiments, which employed doses of cannabinoids far in excess of those that prevail during social use of marijuana. Finally, the clinical significance of the experimental observations is difficult to assess.

The present review will attempt to objectively assess the evidence. Other recent reviews of the subject have also appeared, with varying degrees of intensity of coverage (Hollister 1986; Maykut 1985; Munson & Fehr 1983; Rosenkrantz 1976). For purposes of a more systematic discussion, immunity will be considered as several separate topics: (1) cell-mediated immunity, (2) humoral mechanisms, (3) cellular defenses, and (4) immunogenicity of marijuana or cannabinoids.

CELL-MEDIATED IMMUNITY

Lymphocyte Transformation

Lymphocytes exposed to several mitogens divide rapidly, increase protein and nucleic acid synthesis, and show morphological changes resembling blasts. This test of the

ability of T-lymphocytes to transform themselves measures one potential aspect of cell-mediated immunity. A direct way to measure the activation of lymphocytes is to measure the rate of incorporation of a nucleic acid, such as ^3H -thymidine, into the cells following addition of the mitogen to the culture. All studies are conducted in vitro.

An early study (Nahas et al. 1976) measured ^3H -thymidine uptake in normal human lymphocytes stimulated by both phytohemagglutinin (PHA) and allogenic cell mixed lymphocyte culture (MLC). The incorporation of ^3H -thymidine was equally inhibited by 10^{-5}M to 10^{-4}M concentrations of Δ^9 -tetrahydrocannabinol (THC), Δ^8 -tetrahydrocannabinol (Δ^8 -THC), their corresponding 11-OH metabolites, a variety of other inactive cannabinoids, and olivetol. THC in similar concentrations also depressed ^3H -leucine and ^3H -uridine uptake, indicating an effect of protein and RNA synthesis as well. These concentrations of THC were 10 to 20 times greater than those reported earlier by the same group (Nahas et al. 1974) as having similar effects. In this study, cell-mediated immunity was evaluated in 51 young, chronic marijuana smokers whose lymphocytes were stimulated in vitro by PHA and MLC. As compared with normal controls, ^3H -thymidine uptake was reduced.

Klein and colleagues (1985) added the predominantly T-cell mitogens, PHA and concanavalin A (Con A), and the B-cell mitogen, *E. coli* lipopolysaccharide (LPS), to mice spleen cells treated with varying concentrations of THC and its active metabolite 11-OH-THC. Both T-lymphocyte and B-lymphocyte proliferation in response to mitogens were suppressed by THC, but considerably less

*Professor of Psychiatry and Pharmacology, University of Texas Medical School, Houston, Texas. Please address reprint requests to the author at Harris County Psychiatric Center, P.O. Box 20249, Houston, Texas 77225-0249.

by 11-OH-THC. Proliferation of both types of lymphocytes was completely inhibited by concentrations of THC (10 µg/ml) that were not directly lytic to the cells. Lower concentrations of THC were found to inhibit B-lymphocytes than those required for T-lymphocytes, suggesting that humoral immunity was more impaired than cell-mediated immunity in this system.

By no means have all studies of cell-mediated immunity in marijuana smokers or in vitro exposure of T cells to cannabinoids—often conducted in exactly the same way—shown evidence of immunosuppression. Indeed, the inconsistency of study findings has led to the present state of ambiguity.

White, Brin and Janicki (1975) obtained peripheral blood lymphocytes from 12 healthy long-term marijuana smokers. The blastogenic response to PHA and pokeweed mitogen were measured in vitro by ³H-thymidine uptake. The responses of lymphocytes from the marijuana smokers were not significantly different from those who did not smoke the drug.

Lau and colleagues (1976) observed eight chronic smokers of marijuana in a hospital setting over a 30-day period. Each subject received a placebo during the first six days, followed by THC in oral doses up to 210 mg/day for the next 18 days, and then a placebo for the last six days. The response of their lymphocytes to PHA stimulation, as measured by ³H-thymidine uptake, was no different in either of the three periods.

Rachelfsky and Opedz (1977) stimulated normal human lymphocytes with PHA and with MLC, and ³H-thymidine uptake was measured. The uptake of thymidine was unchanged in lymphocytes exposed to 1.9×10^{-4} M or 12.0×10^{-4} M concentrations of THC. Higher concentrations of THC precipitated in the medium. Changes were comparable in cells exposed to THC and in those not so exposed.

Kaklamani and colleagues (1978) obtained peripheral lymphocytes from 12 chronic users of marijuana and 15 nonusing control subjects. Lymphocytes from the experienced marijuana users were obtained both before and after smoking hashish. Incorporation of ¹⁴C-thymidine, after PHA stimulation and formation of rosettes of sheep erythrocytes, was no different between the normal controls and the marijuana users either before or after the latter had smoked hashish.

Whatever immunosuppressive effects marijuana may have, they are not dependent on psychoactive components. A variety of cannabinoids, which have no apparent central nervous system activity, share an apparent immunosuppressive action (Smith et al. 1978).

T-Lymphocyte Rosette Formation

Another commonly used measure of cell-mediated immunity is the ability of T-lymphocytes to form in vitro

rosettes of sheep erythrocytes surrounding T cells. A dose-related decrease in rosette formation was found in sensitized T cells exposed in vitro to various concentrations of THC in this medium (Cushman, Khurana & Hashim 1976). Cushman and Khurana (1977) tested 10 subjects during a four-week cycle of marijuana smoking, so that the subjects were exposed chronically rather than acutely, and the results showed a decrease in early T-cell rosette formation, but no change in either late T-cell or B-cell rosettes. When Gupta, Grieco and Cushman (1974) compared 23 chronic marijuana smokers with 23 nonsmokers, T-cell rosettes were decreased in the users as compared with the nonusers, but rosettes associated with B-lymphocytes were not different, suggesting a selective effect on cell-mediated immunity.

Petersen, Grahan and Lemberger (1976) tested three subjects who smoked "street" marijuana for rosette formation and blastogenesis. Two of the three showed decreased rosette formation and impaired blastogenesis following stimulation of their lymphocytes with PHA. In another trial, rosette formation was measured in six persons three to six hours after they smoked a marijuana cigarette containing 10 mg of THC. Rosette formation was impaired in five of the subjects, and became normal 24 hours later in all but one subject. Thus, it appeared that the effects of marijuana on T-lymphocytes are variable and reversible, suggesting that factors other than exposure to marijuana itself may be involved.

Mice immunized with sheep erythrocytes were treated with intraperitoneal doses of 10, 25, and 40 mg/kg/day of THC for seven to eight days. Both plaque-forming and rosette-forming cells were decreased by the 25 mg/kg/day dose (Lefkowitz et al. 1978). Monkeys were exposed to three levels of marijuana smoke over a six-month period. Plasma immunoglobulins (IgG and IgM) were decreased in those monkeys exposed to medium and high concentrations of smoke. In vitro tests by Dual and Heath (1975) of the response of lymphocytes to Con A were decreased. Thus, both humoral and cell-mediated immunity appeared to be affected. However, the authors asserted that it is impossible to assess the in vivo implications from tests of this sort.

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These studies also indicated that T-lymphocyte function, as measured by rosette formation, was decreased when the cells are exposed to cannabinoids either in vitro or ex vivo. However, these impairments were rapidly reversible.

Other Measurements of Cell-mediated Immunity

A number of other measurements of cell-mediated immunity have pointed in the same direction. Although both impaired allograft rejection and decreased hemagglutinin titers were found in animals treated with cannabinoids, the effect on allograft rejection as a measure of cell-mediated immunity was greater (Munson et al. 1976). Susceptibility to infection with herpes simplex virus type 2 applied directly to the vagina was increased in mice that had received doses of 100 mg/kg/day of THC (Mishkin & Cabral 1985). A similar increased susceptibility was found in guinea pigs treated with doses of 4.0 and 10 mg/kg/day (Cabral et al. 1986).

Morohan and colleagues assessed the LD₅₀ dose of *Listeria monocytogenes* in mice treated with THC in doses of 38, 75 and 150 mg/kg. The LD₅₀ was decreased 10-, 17- and 657-fold by each dose, respectively. Marijuana extract was less active. A similar challenge with herpes simplex type 2 virus showed a 96-fold decrease following administration of THC, with no decreased resistance following administration of marijuana extract. These situations are not at all comparable to human exposure.

The vast majority of people can be made sensitive to dinitrochlorobenzene (DNCB), a powerful skin sensitizer. DNCB is often used with "recall" antigens (e.g., tuberculin and mumps) to test patients for anergy. Sensitivity to DNCB was found in all 34 chronic marijuana smokers who were tested as compared with 96 percent of 279 healthy nonsmokers. On the other hand, 384 patients with cancer, whose cell-mediated immunity is sometimes decreased, showed a positive reaction in only 70 percent of those tested (Silverstein & Lessin 1974). Such evidence raises questions about the clinical significance of experiments that have shown evidence of cell-mediated immunity from cannabinoids.

It has been hypothesized that the membrane-disordering effects of THC may affect the binding of antigens to cellular receptors, accounting for a decrease in cell-mediated immunity. On the other hand, the combination of increased membrane disorder and inhibition of acyltransferase activity in B cells and T cells could impair the transfer of cellular constituents (Baczynsky & Zimmerman 1983b). Regardless of whether the action is a nonspecific one at the cell membrane or at a more primary site, impaired immunity remains precisely that. However, a cell membrane site of action could explain the apparent transitory nature of the observed alterations in cell-mediated immunity, as well as the requirement for much larger concentrations of cannabinoids than those usually encountered during social use of marijuana.

Summary of Effects of Cell-mediated Immunity

In summary, the effects of cannabinoids on cell-mediated immunity are contradictory. Such evidence as

has been obtained to support such an effect has usually involved doses and concentrations that are orders of magnitude greater than those obtained when marijuana is used by human subjects. Clinically, one might assume that sustained impairment of cell-mediated immunity might lead to an increased prevalence of opportunistic infections, or an increased prevalence of malignancy, as seen in the current epidemic of acquired immune deficiency syndrome (AIDS). No such clinical evidence has been discovered or has any direct epidemiological data incriminated marijuana use with the acquisition of human immunodeficiency virus infection or the clinical development of AIDS. Even though some degree of impairment of immune responses were to occur, the remaining immune function may be adequate, especially in the young persons who are the major users of cannabis.

HUMORAL IMMUNITY

Transformation of B-Lymphocytes

Transformation of B cells stimulated by the mitogen LPS was inhibited more than were T cells stimulated by PHA following the same doses of THC in mice (Klein et al. 1985). This evidence of diminished B-cell reactivity following the administration of THC was confirmed in another study (Munson et al. 1976) that showed a dose-dependent suppression from doses of 50, 100, and 200 mg/kg of THC in mice. These doses are enormous, of course.

Antibody Formation

A frequently used measure of humoral immunity is the ability of splenic lymphocytes from mice that are immunized against sheep erythrocytes to form plaques when exposed in vitro to sheep erythrocytes. Levy and Heppner (1981) found that both THC and haloperidol produced dose-dependent reductions in hemolytic plaque-forming cell (PFC) numbers at the time of peak reactivity (day 4) in control mice. Treatment with THC and haloperidol only delayed the time of peak PFC formation by 24 to 48 hours (doses were high enough to produce signs of gross behavioral toxicity). Neither THC nor other cannabinoids had any effect on the titer of serum hemagglutinating antibody measured seven days after immunization.

Baczynsky and Zimmerman (1983a) immunized mice with sheep erythrocytes on Day 1 (primary immune response) and on Days 1 and 28 (secondary immune response) and measured hemagglutinin titers. Mice treated with 10 mg or 15 mg of THC during the primary immunization period exhibited a suppression of the primary humoral immune response. These doses also suppressed the secondary immune response, even when given during the period of primary immunization. Mice treated with THC during the secondary immunization period showed no measurable response. Other cannabinoids had no effect.

Immature mice immunized with sheep erythrocytes also showed suppression of the immune response when treated with THC in doses of 1.0, 5.0, and 10.0 mg/kg. Splenic weight was reduced and PFC as well as hemagglutinin titers were lower than controls. The suppression was specific for THC and was not observed with cannabidiol or cannabinal, even at doses of 25 mg/kg (Zimmerman et al. 1977). Some evidence of tolerance or hyporesponsiveness to this humoral antibody suppression by THC was found when mice were treated with THC for five days prior to immunization as well as afterward (Loveless, Harris & Munson 1981-1982).

Rosenkrantz, Miller and Esber (1975) immunized rats with a single intraperitoneal dose of sheep erythrocytes during, before and after administration of THC in order to determine its effect on the inductive and productive phases of the primary immune response. Following a dose of 10 mg/kg, THC decreased the primary immune response by 33 to 40 percent; the inductive phase was decreased by 48 to 78 percent by all doses of THC and the productive phase was decreased by 26 to 59 percent by the higher doses.

The same group (Luthra et al. 1980) tested the primary immune response of rats to intraperitoneal administration of sheep erythrocytes after five to 26 days following pretreatment with THC in order to determine if tolerance developed to the immunosuppressant effects. As measured by splenic antibody-forming cells and hemagglutinin/hemolysin titers, no evidence of tolerance was found.

Summary of Effects of Humoral Immunity

In summary, humoral immunity, as tested by a number of *in vitro* procedures, seems also to be impaired by cannabinoids, but this effect was most evident for THC. The clinical significance of such changes is questionable due to the great concentrations of cannabinoids used and the lack of any epidemiological evidence of increased bacterial infections in chronic users of marijuana.

CELLULAR DEFENSES

Leukocytes and Lymphocytes

When 10 subjects were followed through a four-week cycle of marijuana smoking, no change was observed either in peripheral leukocyte or absolute lymphocyte counts (Cushman & Khurana 1977). Leukocytes from five chronic marijuana smokers were compared with those from five nonusers of the drug for their ability to migrate after exposure to THC or marijuana extract. Both treatments inhibited leukocyte migration without killing the cells, both in cells from users and nonusers of marijuana. The prevailing THC concentration needed to accomplish this was 2.0 µg/ml, a couple of orders of magnitude greater than any THC plasma concentrations usually found clinically (Schwartzfarb, Needle & Chavez-Chase 1974).

Natural Killer-cell Activity

Natural killer-cell activity in rats was decreased by subchronic treatment (25 days) with THC, but not after acute treatment (one day). This effect was not found in rats treated simultaneously with naloxone, suggesting possible involvement of the opiate system (Patel et al. 1985). When injected into mice, both THC and its active metabolite 11-OH-THC suppressed splenic natural killer-cell activity *in vitro*. The tissue concentrations of the cannabinoids were reported as being 5.0-10.0 µg/ml, about two orders of magnitude greater than those that might be experienced during the social use of marijuana (Klein, Newton & Friedman 1987).

Macrophages

Macrophages work closely with T cells as part of the immunological defense system. On glass surfaces, macrophage cultures normally show spreading, which is an indication of their mobility. The addition of THC to the medium inhibited the degree of spreading. It also inhibited the phagocytosis of yeast particles (Lopez-Cepero et al. 1986). However, another experiment (Munson et al. 1976) using intact mice that were treated with a single dose or multiple doses of THC could not demonstrate impairment in reticuloendothelial activity, as measured by the intravascular clearance of colloidal carbon.

Summary of Effects on Cellular Defenses

It is somewhat surprising that newer techniques of cell sorting, which permit determination of absolute counts of T- and B-lymphocytes as well as subsets of T-lymphocytes, have not been utilized. The evidence from the *in vitro* studies is weakened by the high concentrations of drug that were used. Clinically, evidence for impairment of cellular defenses has not been forthcoming.

IMMUNOGENICITY OF CANNABINOIDS

Laboratory Studies

It has been hypothesized that THC, a relatively simple chemical, can act as a hapten and become an immunogen. If such were the case, tolerance to THC might be explained on an immunological basis as well as the rare reports of allergic reactions. Azathioprine, an immunosuppressant, had a modest effect in mitigating the hypotensive effects of THC in spontaneously hypertensive rats. Spleen cells from mice treated with THC showed slightly more blast transformation in culture than untreated spleen cells, either with or without THC being added to the culture medium. However, the degree of blast transformation was far less than that produced by PHA. This somewhat weak evidence for an immunogenic action of THC came from a laboratory that later stressed the immunosuppressant effects of marijuana (Nahas, Zugury & Schwartz 1973).

Watson, Murphy & Turner (1983) employed a technique used to test compounds for their potential for producing allergic contact dermatitis and that also maximizes the degree of skin sensitization of guinea pigs. Sensitivity was greatly increased by THC and cannabinal, but less so with other cannabinoids.

Clinical Studies

In a clinical study conducted in the southwestern United States (Freeman 1983), skin tests were applied to 90 patients with various forms of atopy. The test was positive for 63 patients for marijuana pollen as compared to only 18 who had reacted to tobacco leaf. However, it is unlikely that marijuana pollen contains many cannabinoids, but rather contains proteins that may be sensitizing.

A series of 28 marijuana smokers showed precipitins for *Aspergillus* antigens: 13 were positive as compared to one of 10 controls. Lymphocytes showed significant blastogenesis in three of those subjects who tested positive. Seven of these 23 subjects reported bronchospasm following the smoking of marijuana, and one patient had evidence of systemic aspergilliosis (Kagen et al. 1983). As it is well known that marijuana contains contaminants, including molds and fungi, it is not surprising that these should cause allergic reactions in some users. The study does not indicate that cannabinoids themselves are immunogens.

Skin testing with cannabinoids seems to be useless for determining the rare patient with sensitivity to marijuana. A variety of intradermal tests with various cannabinoids and common allergens was applied to 63 marijuana users by Lewis and Slavin (1975). Two users, who were clearly atopic with a past history of bronchial asthma, also reported experiencing asthma after some exposures to marijuana. A third subject, with a history of allergic rhinitis, also experienced similar symptoms following marijuana use. All three of these subjects had negative skin tests to cannabinoids. On the other hand, seven subjects who tested positive for hemp and one who tested positive to Δ^8 -THC had no clinical manifestation of marijuana sensitivity.

A 29-year-old woman (known to be allergic to ragweed) experienced symptoms of an anaphylactoid reaction that lasted 20 to 30 minutes immediately after smoking marijuana. Skin tests with THC showed a 2+ reaction, and with cannabidiol a 1+ reaction (Liskow, Liss & Parker 1971). The weakly positive skin tests do not necessarily indicate that the reaction was due specifically to the cannabinoids.

Summary of Immunogenicity

While it is possible that a few persons may become truly allergic to cannabinoids, it is far more likely that allergic reactions, which have been exceedingly rare following the use of marijuana, are due to contaminants. Marijuana is grown in the field and harvested along with everything else (e.g., bacteria, fungi, molds, parasites, worms, chemicals) that may be found in such field plants. That such impure material, when smoked and inhaled into the lungs, causes so little trouble is really a marvel.

SUMMARY AND CONCLUSIONS

Despite the fairly large literature that developed during the past 15 years or so, the effect of cannabinoids on the immune system is still unsettled. The evidence has been contradictory and is more supportive of some degree of immunosuppression only when one considers in vitro studies. These have been seriously flawed by the very high concentrations of drug used to produce immunosuppression and by the lack of comparisons with other membrane-active drugs. The closer that experimental studies have been to actual clinical situations, the less compelling has been the evidence.

Although the topic was of great interest during the 1970's, as indicated by the preponderance of the references from that period, interest has waned during the present decade. This waning of interest suggests that perhaps most investigators feel that this line of inquiry will not be rewarding. The AIDS epidemic has also diverted the attention of immunologists to the far more serious problem of the truly devastating effects a retrovirus can have on a portion of the immune system.

The relationship between the use of social drugs and the development of clinical manifestations of AIDS has been of some interest, however. Persons infected with the virus but not diagnosed as AIDS have been told to avoid the use of marijuana and/or alcohol. This advice may be reasonable as a general health measure, but direct evidence that heeding this warning will prevent the ultimate damage to the immune system is totally lacking.

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