Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Clinical Microbiology Newsletter

Vol. 15, No. 3 February 1, 1993

Psychoimmunology and Infection

Thomas W. Klein, Ph.D.
Department of Medical Microbiology and Immunology
University of South Florida College of Medicine
Tampa, FL 33612

The terms psychoimmunology and psychoneuroimmunology define the emerging science devoted to studying the two-way relationship between the nervous system and the immune system. The accumulating evidence now strongly supports the concept that the brain and peripheral nervous system, either directly through neurotransmitters or indirectly through endocrine hormones, can modulate the function of immune cells such as lymphocytes, natural killer (NK) cells, and macrophages. On the other hand, the cells of the immune system, through the mediation of released cytokines, can modulate the normal physiology and homeostasis of brain and endocrine systems. Because there is a direct relationship between the function of the immune system and resistance to infectious diseases, it is reasonable to suspect that alterations in the brain transmitted to the immune system would result in variations in host resistance to infectious diseases. Indeed, it has been observed and reported since ancient times that stressful situations in life are associated with unfavorable outcomes in patients suffering from infectious diseases and tumors. Many of us in our present day lives have witnessed and discussed this relationship between stress, immunity, and infections.

Stress to the nervous system is now viewed as emanating from a variety of sources. Events of day-to-day living, such as deadlines, bereavement, and perceived personal failure often lead to an individual's inability to cope with these challenges. The inability to cope results in psychological stress, resulting in an imbalance in the functioning of the central and peripheral nervous systems. In this case, the stress comes from within. Stress to the nervous system, however, can also come from the environment. Infections and other physical ailments can stress the nervous system, as can other environmental factors such as exercise and exposure to extremes of cold and heat. A form of environmental stress of particular relevance today is that induced by abusing psychoactive drugs, which can directly affect the nervous system. Because of their psychoactive nature, these agents can profoundly stress the normal homeostasis of the nervous system.

The soluble mediators of the reciprocal communication between the nervous system and the immune system have been elucidated in some detail over the past several decades. Molecules originating from the central nervous system, such as endorphins, enkephalins, corticotropin-releasing factor, and thyrotropin-releasing hormone, can affect immune cell function and are produced and released by cells of the immune system. Peripheral (and central) nervous system agents, such as somatostatin, substance P, vasoactive intestinal peptide, and norepinephrine, can likewise modulate the function of cells involved in immunity and inflammation, as can endocrine hormones from the pituitary and adrenal glands. On the other hand, cytokines, such as IL-1, IL-3, IL-6, interferon, and tumor necrosis factor, which regulate immunity and inflammation, can also influence the homeostasis of the brain and endocrine organs.

In the following, I will review recent experimental animal studies that show the effects of stress on resistance to infection. Also discussed will be studies dealing with the influence of drugs of abuse and resistance to infection. Other excellent and more comprehensive reviews in this area have appeared previously (1–6).

Stress and Resistance to Infection

Although the major emphasis of this review concerns the results of animal studies, a recent report by Cohen et al. (7) of a study that used human subjects deserves mention. This report describes a prospective study designed to examine the relationship between psychological stress and the frequency of colds in

In This Issue

subjects intentionally exposed to either rhinoviruses, respiratory syncytial virus, or coronavirus. Men and women, ranging in age from 18 to 54 yr, were admitted into the study at the Medical Research Council's Common Cold Unit, Salisbury, England. Initially, subjects were given a complete medical examination and a series of questionnaires designed to assess behavior, psychological stress, personality, and health practices. Blood was drawn for baseline respiratory virus antibody titers and groups of different subjects were infected by nasal drops with low infectious doses of the respiratory viruses—rhinovirus types 2, 9, 14, respiratory syncytial virus, and coronavirus type 229E. Following infection, the subjects were quarantined for up to 7 d, during which time they were examined daily by a clinician to observe and record symptoms of respiratory infection. Nasal wash samples were collected for virus isolation. Approximately 28 d after challenge, a second convalescent serum sample was collected. The psychological stress questionnaires measured the number of major stressful life events, the ability of the individual to cope, and an index of current negative affect. From these measurements, a stress index that ranged from 3 to 12 was formulated and used as an indicator of the degree of psychological stress experienced by the subjects. Laboratory and clinical assessment data were combined to yield profiles for either infected individuals or subjects with clinical colds. The results from this remarkable study showed that the rates of both respiratory infections and clinical colds increased in accordance with an increase in the stress index. For example, the infection rate at a low stress index was 74%, whereas the rate at a high index was 90%. Likewise, the rate of clinical colds was 27% at the low index and 47% at the high. Lifestyle factors such as age, sex, smoking, alcohol, exercise, and diet were excluded as contributors to the association between stress and illness. Although previous studies in humans pointed to a relationship between stress and alterations of immune cell functions (8), the report by Cohen and another by Glaser et al. (9) are among the first to suggest a strong correlation between stressful life situations and increased susceptibility to infection.

The bulk of existing literature concerning the effects of stress on resistance to infection has been obtained from animal infection models and stressors, such as forced exercise, avoidance learning, restraint, isolation, and cold. The literature was recently reviewed by Peterson et al. (5), wherein a variety of animal models and viral and bacterial infections were discussed. The majority of these studies involved use of the relatively simple experimental paradigm of stressing animals in various ways and then recording mortality following infection with a variety of microorganisms. Infections with human viruses, such as polio, coxsackie virus, herpes simplex, influenza, rabies, and coronavirus were reported to result in greater mortality or pathogenesis in stressed experimental animals, such as mice, monkeys, and swine (5). Similarly, increased mortality was also reported in response to bacterial pathogens such as *Bacillus anthracis, Staphylococcus aureus, Escherichia coli,* and *Mycobacterium tuberculosis.* Interestingly, however, increased survival was noted with other bacterial infections with *Streptococcus pneumoniae, E. coli,* and *M. tuberculosis.* It can be concluded from these results that stressing experimental animals physiologically (i.e., forced exercise, cold, crowding, and surgery) reproducibly alters susceptibility to a challenge infection with viral and bacterial pathogens. However, it is also clear that currently there is little understanding of the changes in immune and neuroendocrine function responsible for the altered susceptibility.

Two recent reports have addressed the issue of mechanisms. Bonneau et al. (10) studied the development of selected cellular immune functions in restraint-stressed mice simultaneously infected in the footpad with herpes simplex virus (HSV) type 1. They observed that the numbers of lymphocytes, the lymphocyte proliferation responses, as well as the generation of HSV-specific CTLs and NK cells, were depressed in restrained mice receiving a footpad injection of HSV. In addition, the depressed cellular immunity coincided with a higher titer of infectious virus at the site of infection. In a similar study, Sheridan et al. (11) observed a reduced pulmonary mononuclear cell infiltrate and lung consolidation along with elevated levels of plasma corticosterone in stressed mice infected intranasally with influenza virus. In addition, lymphocytes obtained from these animals were deficient in IL-2 production when cultured with viral antigens. Interestingly, however, the antiviral IgG antibody response in stressed animals was similar to that in controls. These two reports show a strong correlation between immune dysfunction and the progression of viral pathogenesis, and the authors speculate that the link between the physiological stress and immune dysfunction might be mediated by alterations in the hypothalamic-pituitary-adrenal axis.

Opiates and Resistance to Infection

Heroin addicts are known to present with a high rate of infections. However, the many lifestyle practices associated with these individuals, such as the sharing of needles and poor nutrition, have frustrated efforts to define the precise role that heroin contributes to the increased susceptibility to infection. For this reason, investigators have studied

Clinical Microbiology Newsletter (ISSN 0196-4399) is issued twice monthly in one indexed volume per year by Elsevier Science Publishing Co., Inc., 655 Avenue of the Americas, New York, NY 10010. Subscription price per year: $145.00 including postage and handling in the United States, Canada, and Mexico. Add $56.00 for postage in the rest of the world. Second-class postage paid at New York, NY and at additional mailing offices. Postmaster: Send address changes to *Clinical Microbiology Newsletter*, Elsevier Science Publishing Co., Inc., 655 Avenue of the Americas, New York, NY 10010.

the effects of opiates on immune cell function in vitro, using cells from experimental animals. These reports (12–15) have shown that opiates do modulate the function of immune cells. However, the relevance of these findings to susceptibility to infection remains to be determined.

A few studies, however, directly address the influence of these drugs on susceptibility to infection. One of these examines the influence of morphine administration on the survival of mice infected with either *Klebsiella pneumoniae* or *Candida albicans* (16). Animals infected intraperitoneally with *K. pneumoniae* were significantly more susceptible to infection when also injected subcutaneously at 3, 24, and 48 h after infection with 25 mg/kg of morphine. Also, mice given either several drug doses before and after infection with *Candida albicans* or continuously infused with morphine by an implanted osmotic minipump were significantly more susceptible to infection with the yeast. These effects were observed at morphine doses considerably below the LD_{50} dose and were related to a suppressive effect on phagocytic cell function in the animals.

Similar results were reported in a model system that used morphine pellet implantation in mice and challenge infection with *Listeria monocytogenes* (17). Corticosteroids are known to suppress the functioning of macrophages and other cells involved in immunity. Recently, increases in serum corticosterone levels, after implantation of morphine pellets, were shown to at least partially mediate morphine-induced immunosuppression (18). These data suggest that corticosteroids may be mediating morphine-induced increased susceptibility to infections by causing the suppression of immune cells such as macrophages. However, a recent report by Chao et al. (19) suggests that other factors may be involved. In their study, mice repeatedly injected every 36 h with morphine sulphate (300 mg/kg) following infection with *Toxoplasma gondii* displayed 86% mortality relative to control mice not receiving the drug. Interestingly, a single injection of morphine also markedly increased mortality when given at 13 d postinfection. The authors suggested that the increased mortality following the single morphine injection was probably caused not by a drug-induced immunosuppression but perhaps by host factors associated with the immune response to *Toxoplasma* antigens. This hypothesis was supported by the finding that sulfadiazine therapy in infected mice totally abrogated the lethal effect of a single morphine injection and that a single morphine injection induced mortality in mice immunized 10 d previously with heat-killed *Corynebacterium parvum*.

It is noteworthy that the phenomenon of enhanced mortality following a single morphine injection has also recently been observed in an infection model involving Friend leukemia virus (FLV) (20). Here, 100% mortality was observed in mice receiving a single drug injection at either 14 or 21 d postinfection. Taken together these studies suggest that morphine may alter susceptibility to infection through either steroid-induced immunosuppression or by acutely exacerbating the potentially lethal release of inflammatory cytokines such as IL-1, IL-6, and TNF.

Cocaine and Resistance to Infection

Various reports have shown that cocaine can modulate the function of human (21, 22) and experimental animal (23–25) lymphoid cells. However, only a few reports have appeared wherein the drug effect on resistance to challenge infection was tested in experimental animals. In one study, multiple cocaine injections were not associated with altered resistance of mice to a challenge infection with *Streptococcus pneumoniae* (26). However, in this study mice were challenged with *S. pneumoniae* 5 d following the cessation of cocaine treatment, which may have contributed to the failure to demonstrate a drug effect. In another study, cocaine was shown to increase the susceptibility of mice to infection with influenza virus (27). Mice given either a single intraperitoneal dose of cocaine (1 mg/kg) 24 h prior to infection or given a 1 mg/kg dose per day for 7 d consecutively prior to infection were shown to be significantly more susceptible to the lethal effects of virus infection than control mice. Coincident with these effects, a drug-induced suppression of splenic NK and CTL activity was also observed.

Enhanced mortality induced by cocaine was also observed in a murine FLV model (20). FLV, a murine retrovirus, is viewed as a relevant model for several aspects of human AIDS. Mice were injected intraperitoneally with 50 mg/kg cocaine twice daily for 5 d before infection, followed by 30 mg/kg per day for 14 d postinfection. Survival was significantly decreased in drug-treated mice and, as expected, FLV-induced splenomegaly was significantly increased. In addition, delayed hypersensitivity, in terms of the ear thickness response to oxazolone application, was significantly reduced, as were serum antibody titers to sheep red blood cells in cocaine-treated animals (20). Taken together, these studies suggest that reduced resistance to viral infections following cocaine treatment is associated with a decrease in cell-mediated immunity.

Marijuana and Resistance to Infection

The major psychoactive component of marijuana is delta-9-tetrahydrocannabinol (THC). THC suppresses the function of immune cells from humans (28–30) and experimental animals (31–35). As with immune assessment following treatment with other drugs of abuse, relatively few studies are designed to examine THC effects on resistance to challenge infection. Cabral et al. (36) reported on an infection model employing guinea pigs and HSV type 2. Animals were given daily doses of THC in amounts ranging from 0.2 to 25 mg/kg. On the second day following the beginning of the drug treatment, the guinea pigs were infected intravaginally with sublethal amounts of HSV-2 and then observed for virus shedding, lesion expression, and morbidity and mortality. The frequency of vaginal lesion expression and the mortality was observed to be higher in THC-treated guinea pigs than in control animals. Virus shedding in the vagina was also increased in drug-treated guinea pigs (36). Another study employed THC treatment of mice co-infected with

0196-4399/93/$0.00 + 03.00

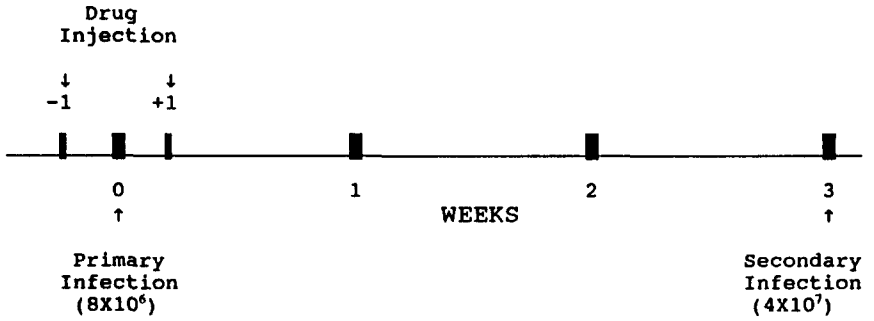

Figure 1. Primary and secondary infection model involving THC and Legionella pneumophila.

murine FLV and HSV type 1 (37). Here, groups of mice were infected either with FLV alone, FLV plus a THC injection, FLV followed 7 d later by an HSV infection, or FLV infection and HSV co-infection along with THC administration. The combination treatment of FLV, HSV, and THC caused enhanced mortality relative to FLV infection only or FLV combined with THC. Interestingly, the combination of FLV and HSV seemed to enhance the survival of the mice over FLV only. This study points out the potential cofactor effect of underlying virus infection and drug treatment which is a common problem in drug-abusing individuals. The cellular mechanisms responsible for the enhanced susceptibility to viral infections in these models may be related to drug-induced suppression of NK activity (37) or a drug-induced decrease in the interferon α/β response following virus challenge (38).

Effects of marijuana on challenge injections with bacterial antigens have also been reported. In one of these studies, groups of mice were infected with increasing numbers of *Listeria monocytogenes* and treated on days 1 and 2 following infection with doses of THC ranging from 38 to 200 mg/kg (39). The 38 mg/kg dose of THC significantly suppressed the LD_{50} dose of bacteria; however, maximum suppression occurred at drug doses in excess of 10 mg/kg. Coincident with the increased susceptibility to *L. monocytogenes* the authors also observed a drug-induced decrease in the delayed type hypersensitivity response.

Host susceptibility to gram-negative infections following marijuana treatment have also been studied (40). Combination injections of mice with nonlethal doses of THC and nonlethal doses of either endotoxin, killed gram-negative bacteria, the lipid A component of endotoxin, or live *E. coli* resulted in animal mortalities, suggesting additive toxic interactions of the drug and endotoxin components. The mechanism of this enhanced lethal interaction was not presented; however, it was speculated that it resulted from impaired liver metabolism of THC or disruption by endotoxin of the blood brain barrier, allowing THC to reach vulnerable sites in the brain (40).

These studies with marijuana, as well as most studies examining the effects of drugs of abuse on resistance to infection, have emphasized how drugs affect resistance to primary infection. However, it is widely appreciated that secondary or anamnestic immune responses to infection are as important, if not more important, than the primary or initial immune response. The immune potential of animals (including humans) increases with age as a result of continuous exposure and re-exposure to potentially lethal microbial antigens. With these thoughts in mind, we decided to examine the influence of THC on the anamnestic or secondary response in mice infected with *Legionella pneumophila*. We selected a THC dose of 5 mg/kg, which has some relevance to the human experience (41, 42). The mice were first injected intraperitoneally with a sublethal dose of *L. pneumophila* (8×10^6), followed 3 wk later by a lethal challenge dose (4×10^7) (Fig. 1). Drug-treated groups were injected with THC either 24 h before or 24 h after the primary *L. pneumophila* infection or with the drug vehicle (DMSO) or saline at these times. Under these conditions, none of the animals died at the time of the primary infection (data not shown). Furthermore, less than 20% of the animals died following challenge with a lethal dose when previously primed with a sublethal dose and injected with either DMSO or saline (Fig. 2). This indicates that the mice developed an anamnestic protective response following the primary infection. However, the mortality increased to around 80% if the primary infection was followed 24 h later by a single injection of THC (Fig. 2). If the primary infection was preceded by a THC injection, there was no drug effect on mortality. These results suggest that THC may have subtle and insidious effects on immune function, such as the suppression of the anamnestic response. This drug effect may prevent the long-term accumulation of enhanced immunity to various infectious agents. It is also of interest that this immune memory infection model demonstrates drug effects at doses not active on primary infection, suggesting the memory model is more sensitive for detecting THC effects.

Summary

Many studies have contributed to our understanding of the interactions between the nervous system, endocrine system, and immune system. These studies have required collaboration among neuroscientists, endocrinologists, and immunologists. However, further study of host resistance to infectious diseases and neoplasms will require collaboration with microbiologists and oncologists also. Stress and drugs of abuse do modulate immune function and this effect results in significant modulation of the host resistance to infection. However, the molecular and cellular mechanisms mediating these interactions are poorly understood.

Experimental animal studies have contributed to our understanding in this area and document that increased susceptibility to primary infection following stress or drug treatment occurs in association with dysfunction of immune cells such as macrophages, T lymphocytes, and NK cells. These changes appear to emanate partially from altera-

0196-4399/93/$0.00 + 03.00

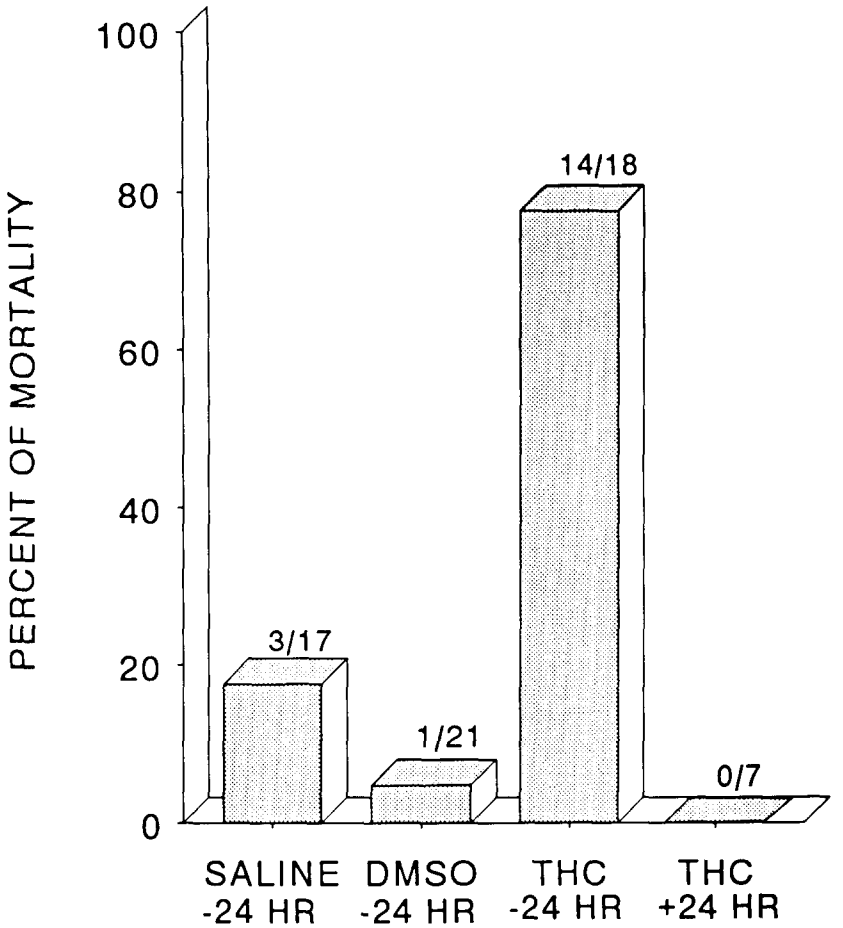

Figure 2. THC suppresses development of the immune memory response to infections with Legionella pneumophila.

tions in the hypothalamic-pituitary-adrenal axis. It now appears that drugs of abuse such as morphine and marijuana, when administered at high doses, might serve as harmful cofactors when combined with the endogenous release of inflammatory cytokines during the course of infection. Chronic drug administration, however, might depress cellular immune function (including decreased cytokine production) and contribute to harmful effects in the host. Much is known concerning the modulation of immune function by stress and drugs of abuse. However, much remains to be learned about the relevance of this immunomodulation to host susceptibility to infections.

References

1. Payan, D.G., J. P. McGillis, and E. J. Goetzl. 1986. Neuroimmunology. Adv. Immunol., 39:299–323.
2. Dantzer, R. and K. W. Kelley. 1989. Stress and immunity: an integrated view of relationships between the brain and the immune system. Life Sci. 44:1995–2008.
3. Dunn, A. J. 1989. Psychoneuroimmunology for the psychoneuroendocrinologist: a review of animal studies of nervous system-immune system interactions. Psychoneuroendocrinology 14:251–274.
4. Blalock, J. E. 1989. A molecular basis for bidirectional communication between the immune and neuroendocrine systems. Physiol. Rev. 69:1–32.
5. Peterson, P. K. et al. 1991. Stress and pathogenesis of infectious disease. Rev. Infect. Dis. 13:710–720.
6. Vollhardt, L. T. 1991. Psychoneuroimmunology: A literature review. Am. J. Orthopsychiatr. 61:35–47.
7. Cohen, S., D. A. J. Tyrrell, and A. P. Smith. 1991. Psychological stress and susceptibility to the common cold. N. Engl. J. Med. 9:606–612.
8. Kiecolt-Glaser, J. K. and R. Glaser. 1991. Psychosocial factors, stress, disease and immunity, p. 849–867. *In* R. Ader, D. L. Felten, and N. Cohen (eds.), Psychoneuroimmunology. Academic Press, Inc., San Diego.
9. Glaser, R. et al. 1991. Stress-related activation of Epstein-Barr virus. Brain Behav. Immunol. 5:219–232.
10. Bonneau, R. H. et al. 1991. Stress-induced suppression of herpes simplex virus (HSV)-specific cytotoxic T lymphocyte and natural killer cell activity and enhancement of acute pathogenesis following local HSV infection. Brain Behav. Immunol. 5:170–192.
11. Sheridan, J. F. et al. 1991. Restraint stress differentially affects anti-viral cellular and humoral immune responses in mice. J. Neuroimmunol. 31:245–255.
12. Gungor, M. et al. 1980. Effect of chronic administration of morphine on primary immune response in mice. Experientia 36:1309–1310.
13. Johnson, H. M. et al. 1982. Regulation of the in vitro antibody response by neuroendocrine hormones. Proc. Natl. Acad. Sci. U.S.A. 79:4171–4174.
14. Gilmore, W. and L. P. Weiner. 1988. β-endorphin enhances interleukin-2 (IL-2) production in murine lymphocytes. J. Neuroimmunol. 18:125–138.
15. Peterson, P. K. et al. 1990. Opiates and cell-mediated immunity, p. 1–18. *In* R.R. Watson (ed.), Drugs of abuse and immune function. CRC Press, Boca Raton, FL.
16. Tubaro, E. et al. 1983. Effect of morphine on resistance to infection. J. Infect. Dis. 148:656–666.
17. Bryant, H. U. et al. 1988. Abstr. Ann. Mtg. Fed. Am. Soc. Exp. Biol. Med. FASEB J. 5608:A1260.
18. Bryant, H. U. et al. 1991. Role of adrenal cortical activation in the immunosuppressive effects of chronic morphine treatment. Endocrinology 128:3253–3258.
19. Chao, C. C. et al. 1990. Lethality of morphine in mice infected with *Toxoplasma gondii*. J. Pharmacol. Exp. Ther. 252:605–609.
20. Starec, M. et al. 1991. Immune status and survival of opiate- and cocaine-treated mice infected with Friend virus. J. Pharmacol. Exp. Ther. 259:745–750.
21. Klein, T. W., C. A. Newton, and H. Friedman. 1988. Suppression of human and mouse lymphocyte proliferation by cocaine, p. 139–143. *In* T. P. Bridge, A. F. Mirsky, F. R. Goodwin (eds.), Psychological, neuropsychiatric and substance abuse aspects of AIDS. Raven Press, New York.
22. Delafuente, J. C. and C. L. DeVane. 1991. Immunologic effects of cocaine and related alkaloids. Immunopharmacol. Immunotoxicol. 13–23.
23. Ou, D. W., M-L. Shen, and Y-D. Luo. 1989. Effects of cocaine on the immune system of BALB/c mice. Clin. Immu-

0196-4399/93/$0.00 + 03.00

nol. Immunopathol. 52:305–312.
24. Watson, E. S. et al. Effects of the administration of coca alkaloids on the primary immune responses of mice: interaction with Δ^9-tetrahydrocannabinol and ethanol. Toxicol. Appl. Pharmacol. 71:1–13.
25. Bagasra, O. and L. Forman. 1989. Functional analysis of lymphocyte subpopulations in experimental cocaine abuse. I. Dose-dependent activation of lymphocyte subsets. Clin. Exp. Immunol. 77: 289–293.
26. Havas, H. F. et al. 1987. Effect of cocaine on the immune response and host resistance in BALB/c mice. Int. Arch. Allergy Appl. Immunol. 83:377–383.
27. DiFrancesco, P. et al. 1990. Effect of acute or daily cocaine administration on cellular immune response and virus infection in mice. Nat. Immun. Cell Growth Regul. 9:397–405.
28. Specter, S., G. Lancz, and H. Friedman. 1990. Marijuana and immunosuppression in man, p. 74–83. *In* R. R. Watson (ed.), Drugs of abuse and immune function. CRC Press, Boca Raton, FL.
29. Nahas, G. G, A. Morishima, and B. Desoize. 1977. Effects of cannabinoids on macromolecular synthesis and replication of cultured lymphocytes. Fed. Proc. 36:1748–1752
30. Watzl, B., P. Scuderi, and R. R. Watson. 1991. Marijuana components stimulate human peripheral blood mononuclear cell secretion of interferon-gamma and suppress interleukin-1 alpha in vitro. Int. J. Immunopharmacol. 13:1091–1097.
31. Klein, T. W. and H. Friedman. 1990. Modulation of murine immune cell function by marijuana components, p. 88–111. *In* R. R. Watson (ed.), Drugs of abuse and immune function. CRC Press, Boca Raton, FL.
32. Rosenkrantz, H., A. J. Miller, and H. J. Esber. 1975. Δ^9-tetrahydrocannabinol suppression of the primary immune response in rats. J. Toxicol. Environ. Health 1:119–125.
33. Smith. S. H. et al. 1978. Structure-activity relationships of natural and synthetic cannabinoids in suppression of humoral and cell-mediated immunity. J. Pharmacol. Exp. Ther. 207:165–169.
34. Baczynsky, W. O. T. and A. M. Zimmerman. 1983. Effects of Δ^9-tetrahydrocannabinol, cannabinol and cannabidiol on the immune system in mice. II. In vitro investigation using cultured mouse splenocytes. Pharmacology 26:12–19.
35. Arata, S. et al. 1991. Tetrahydrocannabinol treatment suppresses growth restriction of *Legionella pneumophila* in murine macrophage cultures. Life Sci. 49:473–479.
36. Cabral, G. A. et al. 1986. Effect of Δ^9-tetrahydrocannabinol on herpes simplex virus type 2 vaginal infection in the guinea pig (42325). Proc. Soc. Exp. Biol. Med. 182:181–186.
37. Specter, S. et al. 1991. Δ-^{9}-tetrahydrocannabinol augments murine retroviral induced immunosuppression and infection. Int. J. Immunopharmacol. 13:411–417.
38. Cabral, G. A., J. C. Lockmuller, and E. M. Mishkin. 1986. Proc. Soc. Exp. Biol. Med. 181:305–311.
39. Morahan, P. S. et al. 1979. Effects of cannabinoids on host resistance to *Listeria monocytogenes* and herpes simplex virus. Infect. Immun. 23:670674.
40. Bradley, S. G. et al. 1977. Enhanced susceptibility of mice to combinations of Δ^9-tetrahydrocannabinol and live or killed gram-negative bacteria. Infect. Immun. 17:325–329.
41. Dax, E. et al. 1989. The effects of 9-ENE-tetrahydrocannabinol on hormone release and immune function. J. Steroid Biochem. 34:263–270.
42. Menkes, D. B. et al. 1991. Salivary THC following cannabis smoking correlates with subjective intoxication and heart rate. Psychopharmacology 103:277–279.

Case Report

Opportunistic Infections in a Patient with Chronic Myelogenous Leukemia

Sumit Majumder, M.D.
Jonathan Wright, M.D.
Michael Cynamon, M.D.
Department of Medicine
VA Medical Center, and
SUNY Health Science Center
Syracuse, NY 13210

Mycobacterium avium complex (MAC) has been known as a pathogen of fowl, birds, and swine since 1890 (1). Recently, MAC has been reported as an important and frequent pathogen in patients with AIDS (2). However, only a few patients with solid tumors or hematologic malignancies have been reported with MAC infection, despite their compromised condition. We report here on a patient with chronic myelogenous leukemia (CML) concurrent with disseminated MAC infection and pulmonary cryptococcosis.

Case Report

A 47-yr-old white female was diagnosed with Philadelphia chromosome–positive chronic myelogenous leukemia in January 1988. Over the next 2½ yr she received hydroxyurea, myleran, low-dose cytosine arabinoside, alpha-interferon, and anagrelide to control her disease. Thrombocytosis proved difficult to control and she required occasional platelet-pheresis to control symptomatic erythromelalgia. She also had chronic obstructive airway disease and was a two-pack-per-day smoker. In August 1989 during treatment with interferon, she developed low-grade fever, chills, weight loss, night sweats, and increasing shortness of breath. In October 1989 she was found to have right middle-lobe pneumonia. Mediastinal lymphadenopathy was noted on chest CT, but needle biopsy of the nodes demonstrated only hyperplasia. The right middle lobe was resected and was negative for malignancy. Routine culture and acid-fast smears were negative. CT of the abdomen showed multiple low-density areas in the spleen. Aspiration needle biopsy of the spleen was negative on routine culture. Bone marrow biopsy showed increased cellularity consistent with CML. Six weeks later all of these cultures (right middle lobe, mediastinal lymph node, bone marrow, and splenic puncture fluid) grew acid-fast organisms that were identified as MAC using an RNA-directed DNA probe (Gen Probe, San Diego, CA). She was started on rifampin

 0196-4399/93/$0.00 + 03.00