

INTERNATIONAL JOURNAL OF LEPROSY and Other Mycobacterial Diseases

OFFICIAL ORGAN OF THE INTERNATIONAL LEPROSY ASSOCIATION

EDITORIAL OFFICE

Gillis W. Long Hansen's Disease Center
Carville, Louisiana 70721, USA

VOLUME 54, NUMBER 3

SEPTEMBER 1986

EDITORIALS

Editorial opinions expressed are those of the writers.

Mycobacterium avium-complex Infections and Development of the Acquired Immunodeficiency Syndrome: Casual Opportunist or Causal Cofactor?

Since its first recognition in 1981 as a new immunodeficiency disease afflicting homosexual men in New York and San Francisco,^{1,2} the number of cases of acquired immunodeficiency syndrome (AIDS) reported each year to the Centers for Disease Control (CDC) in Atlanta, Georgia, U.S.A., has increased exponentially, reaching epidemic proportions in the U.S.A.,³ in Europe,⁴ and

in Africa.⁵ The total number of cases in the U.S. presently meeting CDC criteria for this disease⁶ now exceeds 16,000,³ continues to double yearly (Fig. 1), and is expected to reach more than 40,000 over the next two years.⁷ Although this figure is still relatively small, the overall mortality for this disease presently stands at 50% (with a two-year survival rate approaching zero). This chilling statistic, combined with recent reports that the AIDS virus is spreading into the heterosexual population⁸ has generated a level of public awareness and concern about

¹ Gottlieb, M. S., Schroff, R., Schanker, H. M., Weisman, J. D., Peng Thim Fan, Wolf, R. A. and Saxon, A. *Pneumocystis carinii* pneumonia and mucosal candidiasis in previously healthy homosexual men. Evidence of a new acquired cellular immunodeficiency. *N. Engl. J. Med.* **305** (1981) 1425-1431.

² Hymes, K. B., Cheung, T., Greene, J. B., Prose, N. S., Marcus, A., Ballard, H., William, D. C. and Laubenstein, L. J. Kaposi's sarcoma in homosexual men—a report of eight cases. *Lancet* **2** (1981) 598-600.

³ Update: acquired immunodeficiency syndrome (AIDS)—United States. *Morb. Mort. Wkly. Rep.* **34** (1985) 245-248.

⁴ Update: acquired immunodeficiency syndrome (AIDS)—Europe. *Morb. Mort. Wkly. Rep.* **33** (1984) 21-31.

⁵ Clumeck, N., Van de Perre, P., Carael, M., Rouvroy, D. and Nzaramba, D. Heterosexual promiscuity among African patients with Aids. (Letter) *N. Engl. J. Med.* **313** (1985) 182.

⁶ Jaffe, H. W., Bregman, D. J. and Selik, R. M. Acquired immune deficiency syndrome in the United States: the first 1,000 cases. *J. Infect. Dis.* **148** (1983) 330-345.

⁷ Wong-Staal, F. and Gallo, R. C. Human T-lymphotrophic retroviruses. *Nature* **317** (1985) 395-403.

⁸ Landesman, S. H., Ginzburg, H. M. and Weiss, S. H. The AIDS epidemic. *N. Engl. J. Med.* **312** (1985) 521-525.

this new disease far out of proportion to its present incidence.

The primary causative agent of AIDS is a retrovirus^{9,10} called human T-lymphotropic virus-III (HTLV-III) or lymphadenopathy-associated virus (LAV). The disease is spread via infected blood, semen, and saliva, with the virus parasitizing the T4 lymphocyte population¹¹ to produce declining T4/T8 cell ratios and an increasing level of immunodepression.¹² Only 5%–10% of AIDS-virus infected individuals go on to develop the terminal form of the disease,¹³ which is usually diagnosed following the development of a life-threatening opportunistic lung infection or an unusually malignant form of Kaposi's sarcoma.¹⁴ Death is most frequently due to disseminated *Pneumocystis carinii*, *Candida albicans*, *Histoplasma capsulatum*, *Toxoplasma gondii*, or *Mycobacterium avium* lung disease (Fig. 2). However, a number of other lung, intestinal, and urogenital pathogens have also been recovered from these patients, many of whom go on to develop severe intestinal, central nervous system, and septicemic complications.¹² Most of these opportunist-

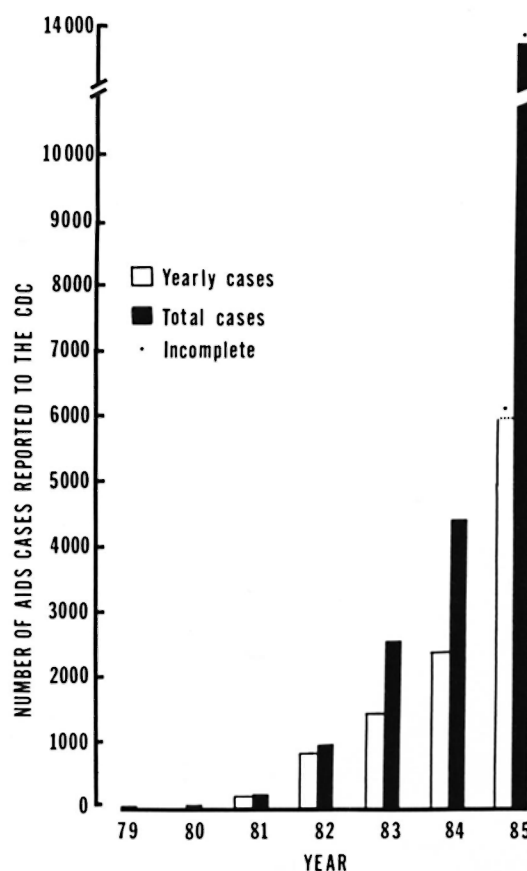


FIG. 1. Numbers of patients reported yearly to the U.S. Centers for Disease Control suffering from clinical AIDS, together with total number of cases reported up to September 1985. Data from footnote references 3 and 14.

⁹ Gallo, R. C., Salahuddin, S. Z., Popovic, M., Shearer, G. M., Kaplan, M., Haynes, B. F., Palker, T. J., Redfield, R., Oleske, J., Safai, B., White, G., Foster, P. and Markham, P. D. Frequent detection and isolation of cytopathic retroviruses (HTLV-III) from patients with AIDS and at risk for AIDS. *Science* **224** (1984) 500–502.

¹⁰ Montagnier, L., Gruest, J., Chamaret, S., Dauguet, C., Axler, C., Guétard, D., Nugeyre, M. T., Barré-Sinoussi, F., Chermann, J.-C., Brunet, J. B., Klatzmann, D. and Gluckman, J. C. Adaptation of lymphadenopathy associated virus (LAV) to replication in EBV-transformed B lymphoblastoid cell lines. *Science* **225** (1984) 63–66.

¹¹ Katzmann, D., Barré-Sinoussi, F., Nugeyre, M. T., Dauguet, C., Vilmer, E., Griscelli, C., Brun-Vezinet, C., Gluckman, J. C., Chermann, J.-C. and Montagnier, L. Selective tropism of lymphadenopathy associated virus (LAV) for helper-induced T lymphocytes. *Science* **225** (1984) 59–63.

¹² Fauci, A. S. Acquired immunodeficiency syndrome: epidemiologic, immunologic and therapeutic considerations. *Ann. Intern. Med.* **110** (1984) 92–106.

¹³ Lane, H. C. and Fauci, A. S. Immunologic aspects of acquired immunodeficiency syndrome. *Adv. Host Defense Mech.* **5** (1985) 131–148.

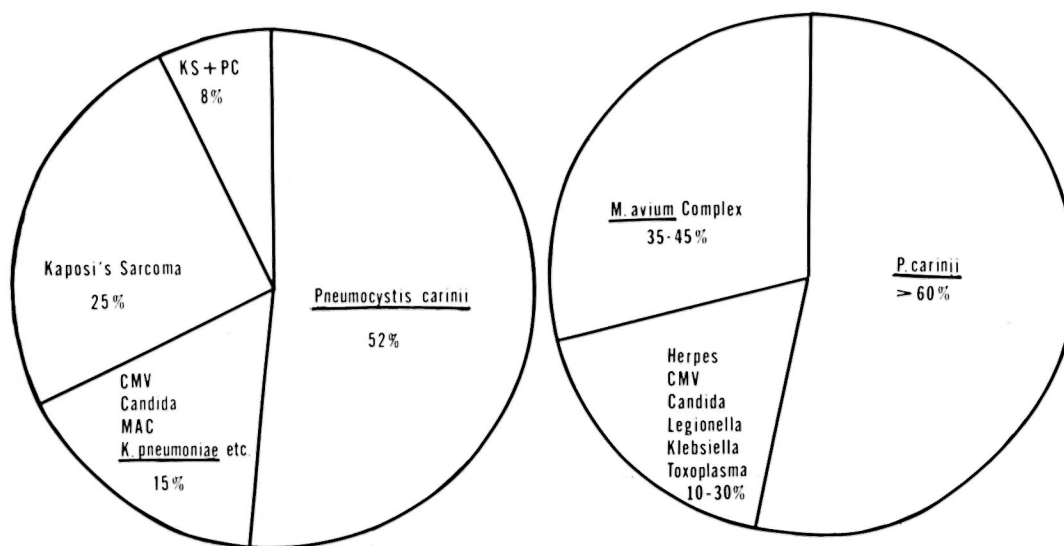
¹⁴ Acquired immunodeficiency syndrome—an assessment of the present situation in the world: memorandum for a WHO meeting. *Bull. WHO* **62** (1984) 419–432.

tic pathogens appear to be members of the normal nasopharyngeal, intestinal, and genitourinary flora, and are able to invade the tissues only after the normal T-cell defenses have been depleted in some manner. Many of these organisms have also been isolated from leukemia, organ and bone-marrow transplant, and cancer chemotherapy patients.^{15–17}

¹⁵ Feld, R., Bodey, G. P. and Groschel, D. Mycobacteriosis in patients with malignant disease. *Arch. Intern. Med.* **136** (1976) 67–70.

¹⁶ Millar, J. W. and Horne, M. W. Tuberculosis in immunosuppressed patients. *Lancet* **1** (1978) 1176–1178.

¹⁷ Winston, D. J., Gale, R. P., Meyer, D. V. and Young, L. S. Infectious complications of human bone marrow transplantation. *Medicine (Baltimore)* **58** (1979) 1–31.



PRIMARY CAUSE OF DEATH IN AIDS PATIENTS IN U.S.A. OPPORTUNISTIC PATHOGENS PRESENT IN AIDS PATIENTS

FIG. 2. Primary cause of death in AIDS patients diagnosed over the period 1981–1983. Total percentage of infections in the right hand pie exceeds 100% because many patients were multiply infected with opportunistic pathogens. Data from footnote references 12 and 14.

One unexpected finding to emerge from the early AIDS autopsy data was the presence of disseminated *M. avium*¹⁸ and *M. intracellulare* infections in a surprisingly high proportion of these patients.¹⁹ These infections often present a picture of massive tissue involvement²⁰ analogous to that noted previously in human lepromatous leprosy²¹ and bovine paratuberculosis.²² Cultural studies quickly confirmed the presence of mycobacteria in the lungs, liver, spleen, bone marrow, and intestines of these patients who came from all of the major high-risk groups (Table 1). On the average, up to 40% of patients examined for acid-

fast bacilli (AFB) were found to be culture positive for *M. avium* complex (MAC) (Fig. 2), together with a few strains of *M. tuberculosis*, *M. gordonae* and *M. fortuitum*.²³ While some of these patients may have been tuberculous²⁴ prior to their exposure to the AIDS virus (especially those of Haitian origin), surprisingly few cultures of virulent tubercle bacilli were recovered from the AIDS population as a whole.²⁵ Out of a total of 421 AIDS patients examined in 30 separate investigations, only 46 (11%) were infected with *M. tuberculosis*, and most of them were Haitians living in Miami.²⁶ Cul-

¹⁸ Berlin, O. G., Zakowski, P., Bruckner, D. A., Clancy, M. N. and Johnson, B. L., Jr. *Mycobacterium avium*: a pathogen of patients with acquired immunodeficiency syndrome. *Diagn. Microbiol. Infect. Dis.* 2 (1984) 213–218.

¹⁹ Welch, K., Finkbeiner, W., Alpers, C. E., Blumenfeld, W., Davis, R. L., Smuckler, E. A. and Beckstead, J. H. Autopsy findings in the acquired immune deficiency syndrome. *JAMA* 252 (1984) 1152–1159.

²⁰ Dryjanski, J. and Gold, J. W. M. Infections in AIDS patients. *Clin. Hematol.* 13 (1984) 709–726.

²¹ Bullock, W. E. Immunobiology of leprosy. *Comp. Immunol.* 8 (1981) 369–390.

²² Merkel, R. S. Paratuberculosis. *Microbiol. Ser.* 15 (1984) 1237–1250.

²³ Armstrong, D., Gold, J. W. M., Dryjanski, J., Whimbey, E., Polsky, B., Hawkins, C., Brown, A. E., Bernarad, E. and Kiehn, T. E. Treatment of infections in patients with the acquired immunodeficiency syndrome. *Ann. Intern. Med.* 103 (1985) 738–743.

²⁴ Pitchenik, A. E., Burr, J. and Cole, C. H. Tuberculin testing for persons with positive serologic studies for HTLV-III. *N. Engl. J. Med.* 314 (1986) 447.

²⁵ Pitchenik, A. E., Cole, C., Russell, B. W., Fischl, M. A., Spira, T. J. and Snider, D. E., Jr. Tuberculosis, atypical mycobacteriosis and the acquired immunodeficiency syndrome among Haitian and non-Haitian patients in South Florida. *Ann. Intern. Med.* 101 (1984) 641–645.

²⁶ Pitchenik, A. E. and Fischl, M. A. Disseminated tuberculosis and the acquired immunodeficiency syndrome. *Ann. Intern. Med.* 97 (1983) 112.

TABLE 1. *Opportunistic pathogens, including M. avium complex recovered from AIDS patients.*

Patient population	No.	P.C. ^a	K.S. ^b	CMV ^c	Mtb ^d	MAC ^e	% Mortality	Footnote reference
Homosexual males	17	17	6	15	— ^f	4	100	106
Homosexual males	36	24	18	25	—	6	100	19
Homosexual males	38	16	—	7	—	6	21	107
Homosexual males	32	—	4	—	—	2	0	104
Homosexual males	5	2	—	4	—	5	80	108
Homosexual males	4	2	1	—	—	4	100	109
Homosexual males	9	8	4	5	—	8	90	110
Homosexual males	13	8	10	12	—	1	100	111
Homosexual males	2	—	—	—	—	2	100	112
Homosexual males	2	—	2	—	—	2	50	103
Homosexual males	1	—	—	—	—	1	0	113
Homosexual male	1	—	1	1	—	1	100	114
Homosexual male	1	—	1	—	—	1	100	40
Homosexual male	1	—	—	—	—	1	100	115
Homosexual male	1	—	1	—	—	1	0	116
Hemophiliac	1	1	—	1	—	1	100	117
Hemophiliac	1	1	—	—	—	1	0	118
Haitian	45	—	—	—	27	5	—	25
Haitian	29	2	1	4	6	1	62	119
Haitian	20	7	1	4	7	1	50	120
Haitian	10	4	—	—	6	1	60	121
Drug-abuse males	14	7	—	12	—	1	36	122
Male	1	1	—	—	—	1	100	123
Males	7	—	1	—	—	1	100	31
Males	30	—	21	—	—	10	—	101
Female consorts	5	—	—	5	—	2	0	124
Female consorts	5	5	—	—	—	5	60	125
Various	71	—	—	—	—	30	100	27
Various	13	—	—	—	—	8	—	126
Various	9	2	—	—	—	9	—	29
Total	421				46 (11%)	122 (29%)		

^a P.C. = *Pneumocystis carinii*.^b K.S. = Kaposi's sarcoma.^c CMV = cytomegalovirus.^d Mtb = *M. tuberculosis*.^e MAC = *M. avium* complex.^f — = Not reported.

tural and serological typing of the 168 mycobacterial isolates indicated that 3 out of 4 were members of the *M. avium* complex (Table 1). In one recent study, 30/55 (55%) of the AIDS patients were infected with *M. avium* or *M. intracellulare*;²⁷ in another, 18/36 (50%) were similarly infected.²⁰ Such infections may precede clinical AIDS by months or years, and are sufficiently frequent to justify routine tuberculin skin test-

ing of all HTLV-III/LAV antibody-positive individuals.²⁴ The use of PPD-A and PPD-B²⁸ could also be useful. Many of these patients exhibit extensive lung and intestinal involvement,²³ with the tissue sections being filled with large, foamy macrophages packed with AFB.²⁹ This histological picture resembles that once seen in children suffering with tuberculous ileitis after drinking unpasteurized cow's milk,³⁰ in some

²⁷ Kiehn, T. E., Edwards, F. F., Brannon, P., Tsang, A. Y., Maio, M., Gold, J. W., Whimbey, E., Wong, B., McClatchy, J. K. and Armstrong, D. Infections caused by *Mycobacterium avium* complex in immunocompromised patients: diagnosis by blood culture and fecal examination, antimicrobial susceptibility tests, and morphological and seroagglutination characteristics. *J. Clin. Microbiol.* **21** (1985) 168-173.

²⁸ Snider, D. E., Jr. The tuberculin skin test. *Am. Rev. Respir. Dis.* **125** (1982) S108-118.

²⁹ Damsker, B. and Bottone, E. J. *Mycobacterium avium-M. intracellulare* from the intestinal tracts of patients with acquired immunodeficiency syndrome: concepts regarding acquisition and pathogenesis. *J. Infect. Dis.* **151** (1985) 179-181.

³⁰ Francis, J. *Tuberculosis in Animals and Man*. London: Cassell and Co., 1958.

cases of Whipple's disease,³¹ and in John's disease in cattle.²² A similar type of histopathology has also been reported in tuberculous monkeys.³²

The data in Table 1 raise a number of important questions regarding the role played by these opportunistic mycobacteria during the development of AIDS. The small number of *M. tuberculosis* isolates (compared to MAC) in the American patients²⁷ was reversed in the Haitian AIDS population, although they must have been just as widely exposed to the atypical mycobacteria as their American counterparts. The incidence of nontuberculous mycobacterial disease in both populations has not changed greatly over the past two decades,³³ suggesting that infection by the atypical mycobacterial species should have been equally widespread in AIDS patients from both countries. Possibly, the Haitians have a genetic predisposition toward *M. tuberculosis* infections (childhood exposure to this organism is also known to be very high in Haiti) but, at present, there is little direct evidence for such a genetic effect.³⁴

MAC infections usually take the form of a self-limiting lymphadenitis in infants and young children.³⁵ *M. scrofulaceum* isolates outnumber both *M. avium* and *M. intracellulare*.³⁶ However, asymptomatic infections (colonization) of the nasopharyngeal and intestinal membranes by the latter species may be more widespread than commonly believed.³⁷ In the past, the presence

of atypical mycobacteria in clinical specimens collected from apparently normal adults has been accorded only minimal pathologic significance.³⁸ However, with the growing number of immunosuppressed patients in the community, this assumption may no longer be valid, and the presence of these AFB in lung³⁹ or intestinal²⁹ biopsy material taken from high-risk and AIDS-related complex (ARC) patients must now be recognized as being diagnostic of AIDS.²⁶

Intestinal involvement of immunocompetent adults by members of the MAC is relatively unusual,³⁵ but may be more common in ARC patients.²⁷ Colonization probably follows the ingestion of contaminated food or water.⁴⁰ It usually leads to systemic involvement only after the local cellular defenses have been depleted in this case by the HTLV-III/LAV infection.⁴¹ If the opportunistic pathogen can cross the intestinal or bronchial mucosae, it will drain to the lymphatics and enter the bloodstream.⁴² From there, the infection spreads to the lungs to produce a life-threatening tuberculous pneumonia in the immunodepressed patient.⁴³

The dearth of *M. tuberculosis* and *M. kansasii* infections in these patients cannot be readily explained, and may indicate some kind of potentiative relationship between the MAC and AIDS.¹³ The present review examines some of these possible relation-

³¹ Roth, R. J., Owen, R. L. and Keren, D. F. AIDS with *Mycobacterium avium-intracellulare* lesions resembling those of Whipple's disease. (Letter) *N. Engl. J. Med.* **309** (1983) 1324-1325.

³² Good, R. C. Diseases in non-human primates. In: *The Mycobacteria—A Source Book*. Kubica, G. P. and Wayne, L. G., eds. New York: Marcel Dekker, Inc., 1984, Part A, pp. 903-924.

³³ Farer, L. S., Lowell, A. M. and Meador, M. P. Extrapulmonary tuberculosis in the United States. *Am. J. Epidemiol.* **109** (1979) 205-217.

³⁴ Fine, P. E. M. Immunogenetics of susceptibility to leprosy, tuberculosis and leishmaniasis. An epidemiological perspective. *Int. J. Lepr.* **49** (1981) 437-454.

³⁵ Wolinsky, E. Nontuberculous mycobacteria and associated diseases. *Am. Rev. Respir. Dis.* **119** (1979) 107-159.

³⁶ Codias, E. K. and Reinhardt, D. J. Distribution of serotypes of the *M. avium-intracellulare-scrofulaceum* complex in Georgia. *Am. Rev. Respir. Dis.* **119** (1979) 965-970.

³⁷ Tsukamura, M. Clinical significance of casual isolation of acid-fast organisms from sputum of tuberculosis patients. *Am. Rev. Respir. Dis.* **108** (1973) 1429-1430.

³⁸ Atwell, R. J. and Pratt, P. C. Unclassified mycobacteria in gastric contents of healthy personnel and patients of a tuberculosis hospital. *Am. Rev. Respir. Dis.* **81** (1960) 888-892.

³⁹ Hopewell, P. C. and Luce, J. M. Pulmonary involvement in the acquired immunodeficiency syndrome. *Chest* **87** (1965) 104-112.

⁴⁰ Strom, R. L. and Gruninger, R. P. AIDS with *Mycobacterium avium-intracellulare* lesions resembling those of Whipple's disease. (Letter) *N. Engl. J. Med.* **309** (1983) 1323-1324.

⁴¹ Mosier, D. E., Yetter, R. A. and Morse, H. C. Retroviral induction of acute lymphoproliferative disease and profound immunosuppression in adult C57BL/6 mice. *J. Exp. Med.* **161** (1985) 766-784.

⁴² Collins, F. M. Cellular antimicrobial immunity. *CRC Crit. Rev. Microbiol.* **7** (1979) 27-91. [496 ref.]

⁴³ Sinkovics, J. G., Gyorkey, F., Melnick, J. L. and Gyorkey, P. Acquired immune deficiency (AIDS); speculations about its etiology and comparative immunology. *Rev. Infect. Dis.* **6** (1984) 745-760.

TABLE 2. Distribution of *M. tuberculosis*, *M. kansasii*, and *M. avium* complex in normal, immunosuppressed, and AIDS patients.

Population	No. patients	Case rate per 10 ⁵ per year	Mycobacterial isolates			Footnote reference
			<i>M. tuberculosis</i>	<i>M. kansasii</i>	<i>M. avium</i>	
Normal U.S.A.	— ^a	14	90%	5%	14%	127
High risk U.S.A.	—	270	70%	15%	11%	28
Normal Japan	—	50	95%	—	4%	37
Normal Haitian	—	650	98%	—	5%	25
Tuberculosis U.K.	100	—	70%	—	27%	127
Tuberculosis U.S.A.	100	—	85%	3–10%	3%	47
Tuberculosis Japan	40	—	30%	—	70%	84
Tuberculosis U.S.A.	576	—	32%	42%	20%	128
Atypical U.S.A.	340	—	—	66%	33%	57
Atypical Japan	537	2	—	8%	90%	84
Immunodepressed patients						
Renal disease	172	—	7%	—	—	54
Kidney transplant	13	—	60%	7%	25%	129
Cancer patients	162	—	75%	14%	13%	130
Silicotics	83	—	12%	10%	4%	55
AIDS patients						
Homosexual	77	—	5%	9%	40% ^b	
Hemophiliac	2	—	0%	0%	100% ^b	
Drug abuser	52	—	10%	0%	25% ^b	
Female consort	10	—	0%	0%	70% ^b	
Haitian	59	—	35%	0%	5% ^b	

^a — = Not reported.^b Consolidated data taken from Table 1.

ships using an experimental mouse infection model to explore the nature of the host-parasite interactions as they develop in normal and immunosuppressed animals. This could provide a better assessment of the potential role played by these opportunistic pathogens during the development of the terminal stages of this important new human immunodeficiency disease.

MAC infections seen in normal individuals

Pulmonary tuberculosis is usually caused by *M. tuberculosis*,⁴⁴ but about 5% of these infections are due to a number of atypical mycobacterial species.³⁵ More than half of these isolates have been classified as *M. kansasii*,⁴⁵ while most of the rest are members of the MAC.⁴⁶ Tuberculin skin testing

using PPD-A and PPD-B,²⁸ as well as isolation data obtained from around the country,⁴⁷ indicate a widespread (though usually low grade) exposure to these organisms, most of which are probably of environmental origin.⁴⁸ However, some of them may be primary bird and animal pathogens.⁴⁹ Most normal adults are resistant to systemic infection by these organisms although several small outbreaks of MAC disease have been reported.^{36, 50, 51} This suggests that exposure

⁴⁴ Tuberculosis—United States 1984. Morb. Mort. Wkly. Rep. **34** (1985) 299–307.

⁴⁵ Ahn, C. H., Lowell, J. R., Onstad, G. D., Shuford, E. H. and Hurst, G. A. A demographic study of disease due to *Mycobacterium kansasii* or *M. intracellulare-avium* in Texas. *Chest* **75** (1979) 120–125.

⁴⁶ Chapman, J. S. The atypical mycobacteria. *Am. Rev. Respir. Dis.* **125** (1982) S119–124.

⁴⁷ Good, R. C. and Snider, D. E. Isolation of nontuberculous mycobacteria in the United States, 1980. *J. Infect. Dis.* **146** (1982) 829–833.

⁴⁸ Falkinham, J. O., Parker, B. C. and Gruft, H. Epidemiology of infection by nontuberculous mycobacteria. I. Geographic distribution in the eastern United States. *Am. Rev. Respir. Dis.* **121** (1980) 931–937.

⁴⁹ Meissner, G. and Anz, W. Sources of *M. avium* complex infection resulting in human disease. *Am. Rev. Respir. Dis.* **116** (1977) 1057–1064.

⁵⁰ Rosenzweig, D. Y. Pulmonary mycobacterial infections due to *Mycobacterium intracellulare-avium* complex. *Chest* **75** (1979) 115–119.

⁵¹ Weisenthal, A. M., Powell, K. E., Kopp, J. and Splinter, J. W. Increase in *M. avium*-complex isolates among patients admitted to a general hospital. *Public Health Rep.* **97** (1982) 61–65.

to these opportunistic pathogens occurs in many parts of this country, and that colonization of the bronchial and intestinal membranes may be quite frequent,⁵² especially in heavy smokers or individuals suffering from chronic bronchitis or colitis.²⁹ However, few of these mucosal "infections" go on to produce active lung disease unless some other potentiating factor (emphysema, silicosis, Hodgkin's disease) is also present.⁵³

One of the most intriguing questions to emerge from these studies is: Why should a relatively rare group of opportunistic mycobacteria infect the lungs (and intestines) of so many AIDS patients coming from various parts of the country and all of the major high-risk groups? If it were simply a matter of the virally induced T-cell depletion enhancing susceptibility to intracellular pathogens in general, one would expect to find more *M. tuberculosis* and *M. kansasii* infections in both AIDS and chemotherapy patients. In fact, more than 60% of mycobacterial isolates from silicotic and terminal renal failure patients are *M. tuberculosis* or *M. kansasii*.^{54, 55} On the other hand, those cancer and transplant patients who are infected with MAC^{15, 17} seem to yield dominant serotypes which are different from those found in AIDS.²⁷ Finally, *M. scrofulaceum* infections are relatively common in young children,⁵⁶ but are virtually absent from AIDS and leukemia patients.⁵⁷ Thus, the distribution pattern for mycobacteria in both ARC and AIDS patients fails to conform to that predicted on the basis of infections seen in the rest of the population (Table 2).

⁵² Singer, E. Non-specific sensitization to old tuberculin: asymptomatic infection with mycobacteria. *Tubercle* **46** (1965) 270-272.

⁵³ Wolinsky, E. When is an infection disease? (Editorial) *Ref. Infect. Dis.* **3** (1981) 1025-1027.

⁵⁴ Andrew, O. T., Schoenfeld, P. Y., Hopewell, P. C. and Humphreys, M. H. Tuberculosis in patients with end-stage renal disease. *Am. J. Med.* **68** (1980) 59-65.

⁵⁵ Bailey, W. C., Brown, M., Buechner, H. A., Weill, H., Ichinose, H. and Ziskind, M. Silico-mycobacterial disease in sandblasters. *Am. Rev. Respir. Dis.* **110** (1974) 115-125.

⁵⁶ Saitz, E. W. Cervical lymphadenitis caused by atypical mycobacteria. *Pediatr. Clin. North Am.* **28** (1981) 823-839.

⁵⁷ Lincoln, E. M. and Gilbert, L. A. Disease in children due to mycobacteria other than *M. tuberculosis*. *Am. Rev. Respir. Dis.* **105** (1972) 683-714.

The MAC consists of at least 31 serotypes,⁵⁸ most of which are environmental (soil and water) species.³⁵ Some of the more virulent of these serotypes may invade the nasopharyngeal, bronchial, and intestinal membranes of normal individuals,⁴⁶ resulting in some local inflammation which may be detected by means of fiber optic examination or by culturing biopsy specimens.^{59, 60} Detection of small numbers of AFB in specimens collected from apparently normal individuals is a technically demanding procedure, especially if their presence is only ephemeral and the specimen is heavily contaminated with commensal organisms.⁶¹ However, many ARC patients develop chronic diarrhea as their disease progresses, and these individuals may excrete large numbers of AFB in their feces, greatly simplifying this diagnostic procedure.⁶²

The recovery of MAC serotypes 1, 4, and 8 from so many AIDS patients²⁷ could simply reflect their higher virulence for man and experimental animals, compared to that for other serotypes.⁴⁹ Significantly, these same serotypes have also been isolated from a number of cases of simian AIDS.⁶³ However, the presence of *M. avium* in AIDS patients from New York, Miami, and San Francisco (and the corresponding lack of *M.*

⁵⁸ McClatchy, J. K. The seroagglutination test in the study of nontuberculous mycobacteria. *Rev. Infect. Dis.* **3** (1981) 867-870.

⁵⁹ Caya, J. G., Cohen, E. B., Allendorph, M. M., et al. Atypical mycobacterial and cytomegalovirus infection of the duodenum in a patient with acquired immunodeficiency syndrome: endoscopic and histopathologic appearance. *Wisconsin Med. J.* **83** (1984) 33-36.

⁶⁰ Stover, D. E., White, D. A., Romano, P. A. and Gellene, R. A. Diagnosis of pulmonary disease in acquired immune deficiency syndrome (AIDS). Role of bronchoscopy and bronchoalveolar lavage. *Am. Rev. Respir. Dis.* **130** (1984) 659-662.

⁶¹ Runyon, E. H., Karlson, A. G., Kubica, G. P. and Wayne, L. G. Mycobacterium. In: *Manual of Clinical Microbiology*. 2nd ed. Washington, D.C.: American Society for Microbiology, 1974, pp. 148-174.

⁶² Burnham, W. R., Lennard-Jones, J. E., Stanford, J. L. and Bird, R. G. Mycobacteria as a possible cause of inflammatory bowel disease. *Lancet* **2** (1978) 693-696.

⁶³ Henrickson, R. V., Maul, D. H., Osborn, K. G., Sever, J. L., Madden, D. L., Ellingsworth, L. R., Anderson, J. H., Lowenstein, L. J. and Gardner, M. B. Epidemic of acquired immunodeficiency in rhesus monkeys. *Lancet* **1** (1983) 388-390.

kansasii) does reflect known differences in the distribution of these organisms across the United States.⁴⁷ The question then becomes: Do these atypical mycobacteria behave as simple opportunistic bystanders in these patients, or do they also make a direct contribution to the immunodepression initiated by the retroviral infection? Put another way, does the HTLV-III/LAV infection simply increase the frequency and severity of existing mycobacterial infections by depleting those T-cell defenses which, until then, had limited the systemic spread of the infection, or does the *M. avium* population actively contribute to the immunosuppressive process? If the latter is true, then why do only three *M. avium* serotypes seem to provide the secondary infectious stimulus needed to drive the ARC patient into the terminal stage of this disease? One possible explanation could be the presence of specific receptors on *M. avium* and *M. intracellulare* which permit them to adhere preferentially to nasopharyngeal or intestinal mucosal cells, thus allowing more effective colonization of those membranes. The more virulent MAC serotypes thus persist within the tissues where the presence of some unique metabolic or antigenic factor allows them to interact during the final immunosuppressive phase of the disease more effectively than other mycobacterial species. The immunological characteristics of AIDS differ substantially from those seen in most other immunodeficiency diseases,⁶⁴ and it may be that a secondary infectious²⁰ and allogenic stimulus⁶⁵ is necessary before the immunosuppression characteristic of AIDS can reach life-threatening proportions.¹³ At present, it is unclear how much this disease depends upon the nature of this secondary stimulus and how much on the immunosuppressive effect of the AIDS-virus infection per se.⁴ In an attempt to obtain answers

to this last point, some of the interactions which occur between *M. avium* and the cellular defenses of increasingly immunosuppressed mice will be examined.

MAC infections in the immunosuppressed host

Different *M. avium* and *M. intracellulare* serotypes can vary extensively in their ability to multiply and survive within the tissues of intravenously challenged mice (Fig. 3). *M. avium* TMC 724 (serotype 2) was selected as the most mouse-virulent strain available. It will induce a slowly progressive lung and spleen infection which eventually kills most of the animals.⁶⁶ Other *M. avium* strains (such as TMC 702) will produce persistent infections, but little active growth of the organisms occurs in either the lungs or the spleen (Fig. 3). On the other hand, *M. intracellulare* serotypes 14 and 16 fail to establish active systemic infections in any of the test organs,⁶⁷ even when injected in very large doses.⁶⁸ The reason(s) for these differences in growth behavior are still unclear, but seem to correlate with colony morphology (flat, translucent vs opaque, domed) and antigenic composition.^{69, 70} However, the nature of these so-called "virulence" factors remains elusive, and may also involve some host responses⁷¹ which makes comparison of virulence data obtained in different laboratories more difficult to evaluate objectively.

Most human isolates of *M. avium* are also virulent for mice, rabbits, and monkeys.⁴⁹ On the other hand, most *M. intracellulare* strains are far less virulent for experimental

⁶⁴ Fahey, J. L., Prince, H., Weaver, M., Groopman, J., Visscher, B., Schwartz, K. and Detels, R. Quantitative changes in T helper or T suppressor/cytotoxic lymphocyte subsets that distinguish acquired immune deficiency syndrome from other immune subset disorders. *Am. J. Med.* **76** (1984) 95–100.

⁶⁵ Tung, K. S. K., Koster, F., Bernstein, D. S., Kriebel, P. W., Payne, S. M. and Shearer, G. M. Elevated allogeneic cytotoxic T lymphocyte activity in peripheral blood leukocytes of homosexual men. *J. Immunol.* **135** (1985) 3163–3171.

⁶⁶ Collins, F. M., Morrison, H. E. and Montalbino, V. Immune response to persistent mycobacterial infection in mice. *Infect. Immun.* **19** (1978) 430–438.

⁶⁷ Schaefer, W. B. Incidence of serotypes of *M. avium* and atypical mycobacteria in human and animal disease. *Am. Rev. Respir. Dis.* **97** (1968) 18–23.

⁶⁸ Watson, S. A. & Collins, F. M. The specificity of suppressor T cells induced by *M. avium* infections in mice. *Clin. Exp. Immunol.* **43** (1981) 10–19.

⁶⁹ Brennan, P. J. Antigenic peptidoglycolipids, phospholipids and glycolipids. *Microbiol. Series* **15** (1984) 467–490.

⁷⁰ Schaefer, W. B., Davis, C. L. and Cohn, M. L. Pathogenicity of translucent, opaque and rough variants of *M. avium* in chickens and mice. *Am. Rev. Respir. Dis.* **102** (1970) 499–506.

⁷¹ Segal, W. Growth dynamics of *in vivo* and *in vitro*-grown mycobacterial pathogens. *Microbiol. Series* **15** (1984) 547–573.

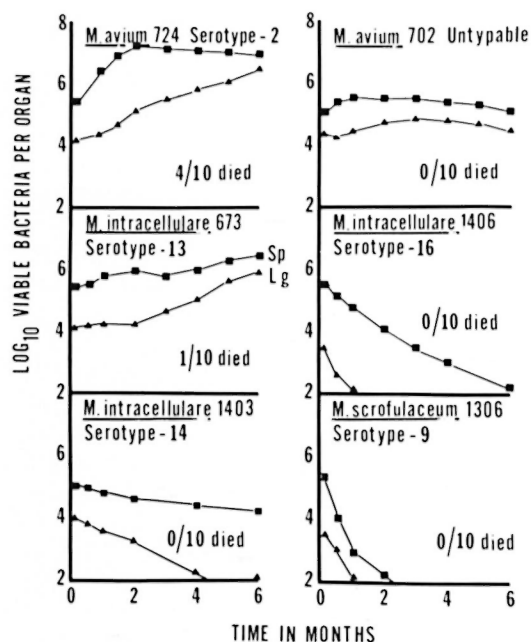


FIG. 3. Growth curves for *M. avium*, *M. intracellulare*, and *M. scrofulaceum* in intravenously infected B6D2 hybrid mice. ▲ = lungs; ■ = spleen. Standard error for 5 determinations per time point was usually less than 10% of the mean. Numbers of deaths were recorded up to 12 months following challenge.

animals, and can be eliminated from the normal host with little sign of an acquired immunity.⁷² The mouse virulent strain of *M. intracellulare* (D673) will induce an initial cellular response, followed by a prolonged period of antigenic unresponsiveness with minimal signs of a cellular response by the host defenses.⁷³ This lack of antimicrobial resistance in the MAC-infected host contrasts sharply with that seen when equivalent numbers of virulent tubercle bacilli or BCG are introduced into the tissues.⁷⁴ This persistently unresponsive state has been variously ascribed to the devel-

⁷² Collins, F. M. Kinetics of the delayed-type hypersensitivity response in tuberculous guinea pigs and mice tested with several mycobacterial antigen preparations. *Am. Rev. Respir. Dis.* **127** (1983) 599–604.

⁷³ Collins, F. M. and Watson, S. R. Immune responses to atypical mycobacterial lung infections. *Rev. Infect. Dis.* **3** (1981) 981–989.

⁷⁴ Collins, F. M. Tuberculosis. In: *Bacterial Vaccines*. Germanier, R., ed. New York: Academic Press, 1984, pp. 373–418.

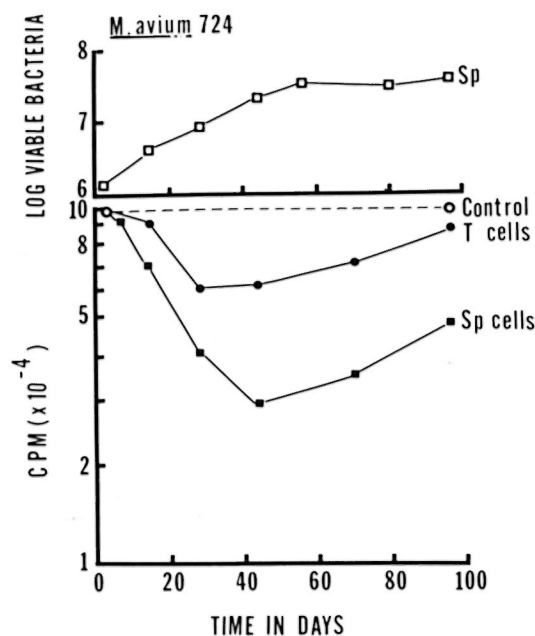


FIG. 4. Growth curve for *M. avium* 724 in intravenously infected normal B6D2 hybrid mice (top). Spleens were removed at intervals during the infection, and whole spleen cells (■) and T-cell enriched (●) suspensions were tested for blastogenic activity to PHA *in vitro*.

opment of an infectious tolerance,⁷⁵ to some sort of antigenic "overload" phenomenon,⁷⁶ or to the development of a population of suppressor cells within the heavily infected spleen.⁷⁷ The concomitant loss of tuberculin hypersensitivity by these mice can be correlated with a sharp reduction in mitogenic responsiveness when spleen cells from the anergic host are exposed to PHA or PPD *in vitro*.⁶⁸ This sharp decline in tritiated thymidine (³H-TdR) uptake (70% or more) coincides with the beginning of a prolonged plateau in the growth curve (Fig. 4). However, as the infection continues, so the ³H-TdR uptake rate slowly returns toward control levels, despite the continued pres-

⁷⁵ Gershon, A. R. K. and Kondo, L. Infectious immunological tolerance. *Immunology* **21** (1971) 903–914.

⁷⁶ Rook, G. A. W. The immunological consequences of antigen "overload" in experimental mycobacterial infections in mice. *Clin. Exp. Immunol.* **19** (1975) 167–178.

⁷⁷ Watson, S. R. and Collins, F. M. Development of suppressor T cells in mice heavily infected with mycobacteria. *Immunology* **39** (1980) 367–373.

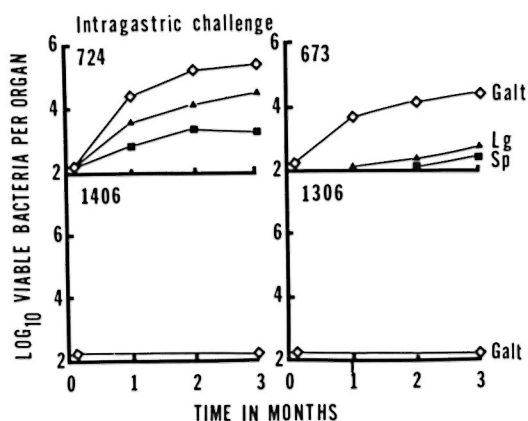


FIG. 5. Growth of *M. avium* 724 (top left), *M. intracellulare* 673 (top right), *M. intracellulare* 1406 (bottom left), and *M. scrofulaceum* 1306 (bottom right) following intragastric inoculation of C57BL/b mice with approximately 10^8 viable units in 0.2 ml of 5% bicarbonate solution. $\diamond$ = gut-associated lymphoid tissues (GALT) Peyer's patches and mesenteric lymph nodes; $\blacksquare$ = spleen; $\blacktriangle$ = lungs.

ence of large numbers of viable mycobacteria within the spleen. Cell-mixing experiments indicate that both T cells and adherent cells (macrophages) harvested from these heavily infected animals will block the mitogenic and allogenic activity of an indicator T-cell suspension taken from normal donors.⁶⁸ However, much of this putative suppressor cell activity can be reversed by the addition of an exogenous source of interleukin-2 (IL-2) to the culture medium, suggesting that the suppression may be due to the absorption or destruction of this essential T-cell growth factor by activated cells present in the heavily infected spleen.⁷⁸ Non-persisters MAC strains do not induce this type of suppression,⁷⁹ and spleen cells taken from these mice may even be mildly stimulatory when assayed in this system.⁸⁰ However, it is still not clear whether this *in vitro* data can be extrapolated to the whole ani-

mal,⁸¹ and its relevance to human AIDS remains in doubt.

The virulence of many mycobacteria depends on the medium and the age of the culture used to prepare the inoculum.⁸² Presumably, these differences depend on nutritional, metabolic, and antigenic variations in the resulting cell suspensions. *In vivo*-grown cells also differ in their virulence from the corresponding *in vitro*-grown preparations.⁷¹ Much of this effect can be explained as differences in the degree of dispersion of the two preparations. Substantial differences also occur if the challenge inoculum is introduced into the tissues by different routes.⁸³ For instance, intravenous injection of 10^6 viable mycobacteria into normal B6D2 hybrid mice results in lung and splenic growth curves which differ substantially from those seen when the same inoculum is introduced via the foot pad route (Collins and Stokes, unpublished data). On the other hand, if equivalent numbers of tubercle bacilli (10^3 to 10^4 CFU) are introduced into the lungs by the aerogenic and intravenous routes, extensive growth will occur in the lungs of both groups of animals but the resulting disease will be much more severe in the aerogenic group, with death usually occurring in a matter of weeks instead of months. On the other hand, if the mice were challenged orally, very large doses of viable bacilli (10^8 to 10^9 CFU) would be required in order to infect the gut-associated lymphoid tissues, even in a highly susceptible strain of mouse. The resulting systemic infection will be relatively indolent but eventually some systemic spread does occur (Fig. 5). Similar data were obtained using the mouse virulent strain of *M. intracellulare* D673, but not when the non-per-

⁷⁸ Orme, I. M., Ratcliffe, M. J. H. and Collins, F. M. Acquired immunity to heavy infections with *M. bovis* (BCG) and its relationship to the development of non-specific unresponsiveness *in vitro*. *Cell. Immunol.* **88** (1984) 285–296.

⁷⁹ Hepper, K. P. and Collins, F. M. Immune responsiveness of mice heavily infected with *M. kansasii*. *Immunology* **53** (1984) 357–364.

⁸⁰ Hepper, K. P. and Collins, F. M. Adoptive transfer of acquired resistance to *M. kansasii* infection by splenic T cells harvested from chronically infected mice. *Immunology* **53** (1984) 819–825.

⁸¹ Orme, I. M. and Collins, F. M. Immune response to atypical mycobacteria: immunocompetence of heavily infected mice measured *in vivo* fails to substantiate immunosuppression data obtained *in vitro*. *Infect. Immun.* **43** (1984) 32–37.

⁸² Collins, F. M., Wayne, L. G. and Montalbino, V. The effect of cultural conditions on the distribution of *M. tuberculosis* in the spleens and lungs of specific pathogen-free mice. *Am. Rev. Respir. Dis.* **110** (1974) 147–156.

⁸³ Collins, F. M. and Montalbino, V. Relative immunogenicity of streptomycin-susceptible and -resistant strains of BCG. II. Effect of the route of inoculation on growth and immunogenicity. *Am. Rev. Respir. Dis.* **111** (1975) 43–51.

sistent *M. intracellulare* TMC 1406 or *M. scrofulaceum* TMC 1306 were used. Presumably, the avirulent MAC strains were inactivated as fast as they were able to cross the intestinal mucosa.

The relevance of this oral mouse infection data to the human AIDS patient remains largely speculative at this time. However, it seems likely that *M. avium* enters the body via the respiratory or intestinal mucosae. In most cases, the resulting colonization produces nothing more than a self-limiting lymphadenitis.⁸⁴ However, the continued entry of the MAC antigen(s) into the mucosa-associated lymphoid tissues (MALT) could induce a state of specific immune tolerance or feedback suppression within the host.⁸⁵ In effect, the virulent *M. avium* becomes a part of the commensal nasopharyngeal or intestinal flora which causes this antigenic unresponsiveness to continue indefinitely, just as it does in other chronic human diseases such as lepromatous leprosy, systemic leishmaniasis, and mucocutaneous candidiasis.²¹ Experimentally, this type of effect can be induced by heavily infecting normal mice with *M. avium* TMC 724 or *M. intracellulare* D673.⁶⁶ This type of experimental model may, therefore, be useful in the study of some of the immunological parameters associated with the development of this type of acquired immunodeficiency.

Effect of immunodepletion on the growth and survival of MAC *in vivo*

Virulent mycobacteria can survive within normal mouse macrophages, multiplying intracellularly until they kill the phagocyte.⁴² Following inoculation, the challenge organisms are quickly taken up by the resident tissue macrophages to establish a primary granuloma or tubercle by drawing large numbers of blood-derived monocytes into the developing lesion.⁷⁴ During this process,

many of the macrophages become sufficiently nonspecifically activated to restrict the further intralesional growth of the pathogen, and the growth curve passes into a prolonged plateau.⁷⁹ However, these phagocytic cells cannot eliminate the virulent mycobacteria from the tissues, a process which requires the entry of specifically sensitized T cells into the granuloma.⁷⁴ On exposure to the specific sensitizer, these cells release lymphokines which can immunologically arm the macrophage in such a way that it kills the pathogen.⁴² Depletion of the host of its T-cell population prior to challenge has little effect on the early stages of the infection (phagocytosis and granuloma formation), but will ablate the cell-mediated immunity (CMI) needed to eliminate the pathogen from the tissues. Many of these T-cell-depleted mice die from an uncontrolled, ongoing lung infection, with progressive tissue consolidation and fibrosis. Tissue sections prepared from these mice are filled with foamy macrophages packed with AFB.⁸⁶ However, the spleens of these animals can still express substantial levels of nonspecific antibacterial activity against an unrelated intracellular pathogen such as *Listeria monocytogenes*.⁷⁹ For this reason, it is important to distinguish between nonspecific and specific macrophage activity in the lungs and spleen, especially when using inherently resistant and susceptible inbred strains of mice. For instance, both resistant (A/J) and susceptible (BALB/c) mice possess equivalent numbers of T cells and macrophages within their spleens and peritoneal cavities, so that the reasons for the striking differences in the growth of *M. avium* in these two strains of mouse is still not clearly understood (Stokes, unpublished data). This effect should be taken into account when comparing virulence data obtained in mice from differing genetic backgrounds.⁸⁷

T-cell depletion greatly enhances the severity of a tuberculous challenge,⁸⁸ even by

⁸⁴ Tsukamura, M., Shimoide, H., Kita, N., Kawakami, K., Ito, T., Nakajima, N., Kondo, H., Yamamoto, Y., Matsuda, N., Tamura, M., Yoshimoto, K., Shirota, N. and Kuse, A. Epidemiological studies of lung disease due to mycobacteria other than *Mycobacterium tuberculosis* in Japan. *Rev. Infect. Dis.* **3** (1981) 997-1007.

⁸⁵ Waksman, B. H. Tolerance, the thymus and suppressor T cells. *Clin. Exp. Immunol.* **28** (1977) 363-374.

⁸⁶ Morrison, N. E. and Collins, F. M. Immunogenicity of an aerogenic BCG vaccine in T-cell depleted and normal mice. *Infect. Immun.* **11** (1975) 1110-1121.

⁸⁷ Goto, Y., Nakamura, R. M., Takahashi, H. and Tokunaga, T. Genetic control of resistance to *M. intracellulare* infection in mice. *Infect. Immun.* **46** (1984) 135-140.

an attenuated species such as BCG which induces a potentially lethal mycobacteriosis in severely immunosuppressed individuals.⁷⁴ When normal mice are depleted of their T-cell defenses (usually by thymectomy and lethal irradiation, but also by the use of congenitally athymic mice), viable BCG will persist within the lymphoreticular organs for many months, with little or no sign of either tuberculin hypersensitivity or acquired antituberculous immunity.⁸⁶ As a result, many of these mice will die from a widely disseminated disease unless the cellular defect is reversed by an infusion of immunocompetent T cells harvested from an immunized donor.⁸⁹

When T-cell-depleted mice are challenged with a virulent strain of *M. avium*, little difference is seen in early growth behavior within the immunodeficient host compared to the normal controls (Fig. 6). However, after about 40 days of infection, the growth curve for the athymic mouse lung increases sharply and many of these mice ultimately die. Bacterial growth within the thymectomized-irradiated (Thxb) mouse is not as greatly affected, and most of these animals will survive the challenge despite the presence of large numbers of viable mycobacteria within the lung and spleen at the completion of the experiment.

One of the most puzzling features about the MAC infections seen in the AIDS patient population has been the lack of *M. scrofulaceum* isolates, despite its known presence both in the environment⁴⁸ and in pediatric populations.⁵⁶ Normal mice are highly resistant to infection with *M. scrofulaceum* (Fig. 3), so attempts were made to infect T-cell-depleted mice with this species using *M. vaccae* as a known avirulent control.⁹⁰ Both organisms were eliminated from nude and Thxb mice with no obvious dif-

ference from the control response. Presumably, the nonpersister MAC species were inactivated by a nonspecific killing mechanism which could not be enhanced by T-cell depletion.⁸³ For this reason, *M. scrofulaceum* would not be expected to induce

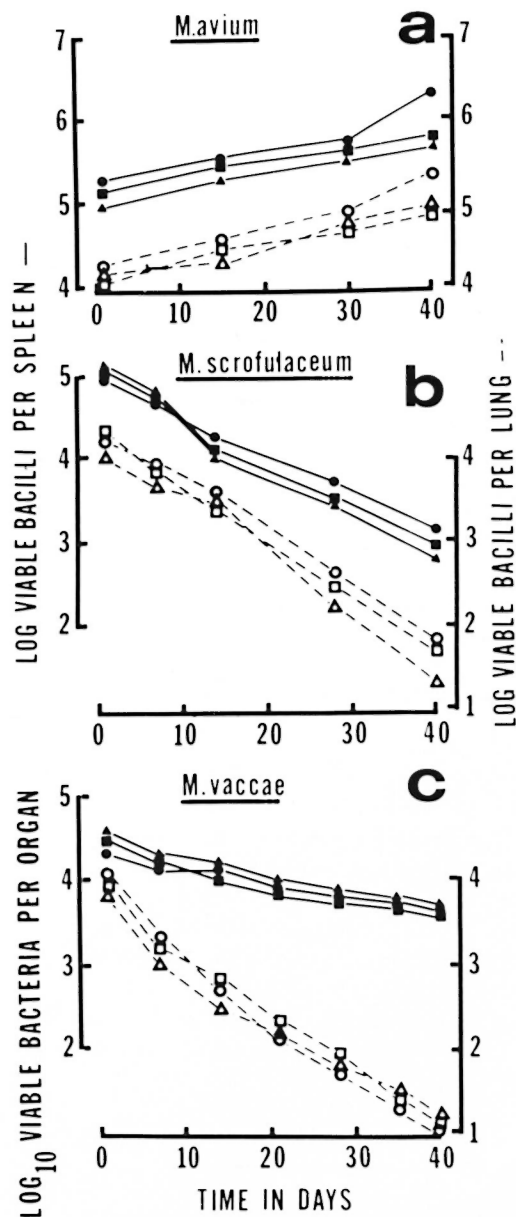


FIG. 6. a = Growth of *M. avium* 724 in nu/nu (●), Thxb (■), or normal (▲) mouse spleens (—) or lungs (---) following an intravenous challenge. b = *M. scrofulaceum*-challenged mice. c = *M. vaccae*-challenged mice.

⁸⁸ Ueda, K., Yamazaki, S. and Someya, S. Experimental mycobacterial infection in congenitally athymic "nude" mice. *J. Reticuloendothel. Soc.* **19** (1976) 77-90.

⁸⁹ Orme, I. M. and Collins, F. M. Protection against *M. tuberculosis* infection by adoptive immunotherapy. *J. Exp. Med.* **158** (1983) 74-83.

⁹⁰ Watson, S. R., Morrison, N. E. and Collins, F. M. Delayed hypersensitivity responses in mice and guinea pigs to *M. leprae*, *M. vaccae*, *M. nonchromogenicum* cytoplasmic proteins. *Infect. Immun.* **25** (1979) 229-236.

disseminated lung or bowel disease in either ARC or AIDS patients.²³

It is still not clear whether the HTLV-III/LAV-induced T-cell depletion allows the MAC species to invade the gut or lung mucosae or merely exacerbates an already established involvement into life-threatening proportions. However, atypical mycobacteria have been isolated from bone-marrow biopsy samples taken from some ARC patients,⁹¹ suggesting that these infections may be already established within the tissues before the AIDS virus plays a direct immunosuppressive role in the development of this disease.

Potentiative effects of MAC infections in ARC patients

Clinical AIDS usually develops after some sort of secondary infectious or alloantigenic stimulus which drives the disease into its terminal phase.⁹² Concomitant infections with cytomegalovirus, herpes, or hepatitis B virus may provide such a trigger in many homosexual AIDS patients,¹³ but other bacterial, fungal, and parasitic agents are also likely to perform this function.¹⁴ The more virulent *M. avium* serotypes appear to be especially effective in providing this kind of immunosuppressive trigger, possibly by disrupting normal lymphocyte recirculation patterns and thereby reducing the ability of the host to mount an effective T-cell-mediated response.⁹³ They can also act as potent polyclonal B-cell activators, resulting in a persistent hyper-gammaglobulinemia, with excess antigen-antibody complex formation and a reduced CMI.⁹⁴ In effect, this systemic MAC infection deflects an already limited T-cell resource in the AIDS-virus-infected individual into an enhanced, though nonprotective humoral response (a char-

acteristic also noted in lepromatous leprosy patients).²¹ The HTLV-III/LAV virus also acts as a potent B-cell mitogen, and the two effects may combine in an immunological defect not unlike that of systemic lupus erythematosus.¹³

Conclusions

The interrelationships which may exist between MAC and AIDS can be summarized as follows:

The relationship may be entirely fortuitous. The MAC are widely distributed throughout the environment,⁴⁸ and silent infections caused by aerosols of these opportunistic pathogens may be relatively common in many communities,⁹⁵ judging from the widespread tuberculin hypersensitivity expressed against PPD-A and PPD-B observed in a number of epidemiological surveys.²⁸ Thus, the presence of the MAC in AIDS patients from New York, Miami, and San Francisco could simply reflect this widespread natural geographic distribution. However, one would also expect a larger number of AIDS patients to be infected with *M. kansasii*, *M. gordonae* or *M. fortuitum*, since these species are just as widely distributed in the community.⁴⁷

Tolerance induction by intestinal MAC infections. A relatively small number of *M. avium* serotypes (1, 2, 4, 8, 12, and 16) seem to be responsible for most of the nontuberculous infections seen in normal adults.⁵⁸ These strains are also more virulent for chickens, rabbits, pigs, and monkeys.³² MAC infections are not uncommon in children,⁹⁶ and so it seems likely that silent colonization of the bronchial membranes by these organisms may be relatively common in the pediatric population.⁴⁹ The more virulent serotypes should also have some survival advantage, since they would be present for longer periods of time within the lymphoid organs of the normal host. The continued presence of their sensitin(s) within the mucosa-associated lymphoid tissues could in-

⁹¹ Pitchenik, A. E. and Robinson, H. A. The radiographic appearance of tuberculosis in patients with acquired immune deficiency syndrome (AIDS) and pre-AIDS. *Am. Rev. Respir. Dis.* **131** (1985) 393-396.

⁹² Fauci, A. S. and Lane, H. C. The acquired immunodeficiency syndrome (AIDS): an update. *Int. Arch. Allergy Appl. Immunol.* **77** (1985) 81-88.

⁹³ Bullock, W. E., Evans, P. E., and Filomeno, A. R. Impairment of cell-mediated immune responses by infection with *Mycobacterium lepraemurium*. *Infect. Immun.* **18** (1977) 157-164.

⁹⁴ Bloom, B. R. and Mehra, V. Immunological unresponsiveness in leprosy. *Immunol. Rev.* **80** (1984) 5-28.

⁹⁵ Paramasivan, C. N., Govindan, D., Prabhakar, R., Somasundaram, S., Subbammal, S. and Tripathy, S. P. Species level identification of non-tuberculous mycobacteria from South Indian BCG trial area during 1981. *Tubercle* **66** (1985) 9-15.

⁹⁶ Romanus, V. Childhood tuberculosis in Sweden. *Tubercle* **64** (1983) 101-110.

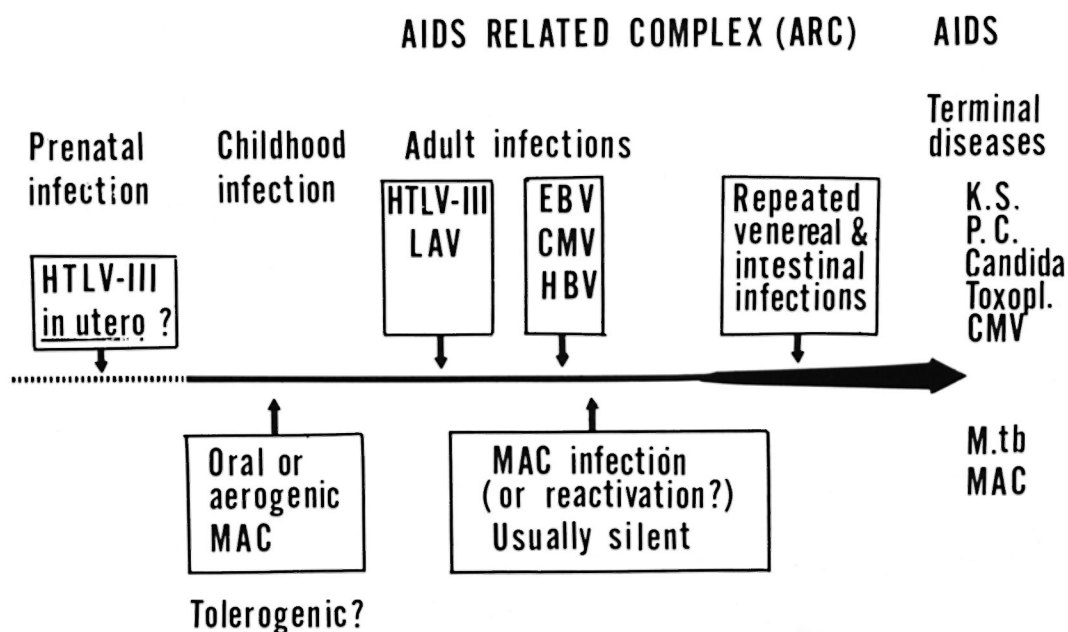


FIG. 7. Possible interactions between HTLV-III/LAV and various opportunistic pathogens during the evolution of acquired immune deficiency syndrome. EBV = Epstein-Barr virus; CMV = cytomegalovirus; HBV = hepatitis B virus; MAC = *M. avium* complex; K. S. = Kaposi's sarcoma; P.C. = *Pneumocystis carinii*; Toxopl. = toxoplasma; M.tb. = *M. tuberculosis*.

duce a persistent immune tolerance within the host.⁸⁵ This would, in turn, reduce the ability of the host to respond effectively against a subsequent re-infection by the same organism (Fig. 7). Intestinal colonization of normal healthy individuals by these opportunistic mycobacteria would be very difficult to detect, since they induce little obvious signs of inflammation or gut pathology.²⁹ The more virulent MAC serotypes will persist more effectively within the gut-associated lymphoid tissue (GALT) organs (Fig. 5), and so produce a more substantial systemic disease once the HTLV-III/LAV infection begins to deplete the T-cell defenses.

The systemic MAC infection will also induce a substantial T-cell proliferative response on the part of the host defenses^{79, 81} which provide an expanded source of activated T cells for the HTLV-III/LAV virus to multiply in.⁹⁷ Several investigators have

noted that enhanced allogenic and parasitically induced T-cell activation occurs in many high-risk males.^{65, 98} The presence of such cells in AIDS patients (as in attempts at T-cell replacement therapy) merely enhances HTLV-III/LAV growth *in vivo*, and does not appear to be therapeutically useful.⁹⁹ Thus, the MAC may provide a potent mitogenic stimulus to the T-cell population which, in turn, will increase the viral load within the tissues.⁴¹ The end result will be an overall acceleration to the virally induced immunodepression.

Immunodepletion by the systemic *M. avium* infection. Some mycobacterial infections modulate the cellular responsiveness within the heavily infected host,⁶⁸ probably by inducing some sort of antigen overload or tolerance.^{75, 76} This permits the organisms to continue multiplying *in vivo* without the expression of an effective cellular immune response within the lesions.⁸⁵ As the

⁹⁷ McDougal, J. S., Mawle, A., Cort, S. P., Nicholson, J. K. A., Cross, G. D., Scheppeler-Campbell, J. A., Hicks, D. and Sligh, J. Cellular tropism of the human retrovirus HTLV-III/LAV. I. Role of T cell activation and expression of the T4 antigen. *J. Immunol.* **135** (1985) 3151-3162.

⁹⁸ Singer, A. and Shearer, G. M. AIDS therapy by blocking CD4+ cells. *Nature* **320** (1986) 113.

⁹⁹ Lane, H. C. and Fauci, A. S. Immunological reconstitution in the acquired immunodeficiency syndrome. *Ann. Intern. Med.* **103** (1985) 714-718.

infectious load increases, so more and more viable bacilli will enter the bloodstream (persistent mycobacteremias have been reported in a number of ARC patients¹⁰⁰⁻¹⁰²). The resulting hematogenous spread will seed other uninvolved tissues throughout the body, including the bone marrow (another frequent source of MAC isolates from these patients^{103, 104}). As the resulting bone marrow granulomas increase, so lymphocyte and monocyte production will be affected, making it still more difficult for the host defenses to control the further growth and spread of this opportunistic pathogen.⁸⁶ Eventually, the infection reaches the point where so many AFB accumulate within the tissues (as many as 10^{10} AFB per gram have been reported in some infections²¹) that a permanent state of immunological tolerance is induced. Some investigators ascribe this to the presence of a population of suppressor cells within the spleen.⁹⁴ However, much of this suppressor-cell activity is based on *in vitro* mitogen assays⁶⁸ which may not always be validly extrapolated to the whole animal.⁸¹ In many cases, the anergic (suppressed) animal will still respond immunologically to other unrelated antigens,⁷⁹ and the spleen contains large numbers of activated macrophages which can partly compensate for any reduced T-cell activity seen in these animals.⁸⁰ Furthermore, the anergic host can express an enhanced humoral (helper T cell) response against many of the mycobacterial

antigens which one would have expected the suppressor cells to have blocked.¹⁰⁵ However, the deviative effect of the heavy mycobacterial infection on helper T-cell reactivity could intensify the HTLV-III/LAV-induced immunodeficiency, thus helping to drive the disease into its terminal mode.¹³

¹⁰⁵ Phung, P. D. and Davidson, P. T. Increased suppressor cell activity in a patient with *M. avium-intracellulare* pulmonary disease and hypergammaglobulinemia. *Ann. Allergy* **46** (1981) 204-207.

¹⁰⁶ Nash, G. and Fligel, S. Pathologic features of the lung in the acquired immune deficiency syndrome (AIDS): an autopsy study of seventeen homosexual males. *Amer. J. Clin. Pathol.* **81** (1984) 6-12.

¹⁰⁷ Blumenfeld, W., Wager, E. and Hadley, W. K. Use of the transbronchial biopsy for diagnosis of opportunistic pulmonary infection in acquired immunodeficiency syndrome. *Amer. J. Clin. Pathol.* **81** (1984) 1-5.

¹⁰⁸ Greene, J. B., Sidhu, G. S., Lewin, S., Levine, J. F., Masur, H., Simberkoff, M. S., Nicholas, P., Good, R. C., Zolla-Payne, S. R., Pollock, A. A., Tapper, M. L. and Holzman, R. S. *Mycobacterium avium-intracellulare*: a cause of disseminated life-threatening infection in homosexuals and drug abusers. *Ann. Intern. Med.* **97** (1982) 539-546.

¹⁰⁹ Wong, B., Edwards, F. F., Kiehn, T. E., Whimbey, E., Donnelly, H., Bernard, E. M., Gold, J. W. M. and Armstrong, D. Continuous high-grade *Mycobacterium avium-intracellulare* infection in patients with the acquired immune deficiency syndrome. *Am. J. Med.* **78** (1985) 35-40.

¹¹⁰ Zakowski, P., Fligel, S., Berlin, G. W. and Johnson, L., Jr. Disseminated *Mycobacterium avium-intracellulare* infection in homosexual men dying of acquired immunodeficiency. *JAMA* **248** (1982) 2980-2982.

¹¹¹ Guarda, L. A., Luna, M. A., Smith, J. L., Mansell, P. W. A., Gyorkey, F. and Roca, A. N. Acquired immune deficiency syndrome: postmortem findings. *Am. J. Clin. Pathol.* **81** (1984) 549-557.

¹¹² Sohn, C. C., Schroff, R. W., Kliewer, K. E., Lebel, D. M. and Fligel, S. Disseminated *Mycobacterium avium-intracellulare* infection in homosexual men with acquired cell-mediated immunodeficiency: a histologic and immunologic study of two cases. *Am. J. Clin. Pathol.* **79** (1982) 247-252.

¹¹³ Wolke, A., Meyers, S., Adelsberg, B. R., Bottone, E. J., Damsker, B., Schwartz, I. S. and Janowitz, H. D. *Mycobacterium avium-intracellulare* associated with colitis in a patient with the acquired immunodeficiency syndrome. *J. Clin. Gastroenterol.* **6** (1984) 225-229.

¹¹⁴ Gillin, J. S., Urmacher, C., West, R. and Shike, M. Disseminated *M. avium-intracellulare* infection in acquired immune deficiency syndrome mimicking Whipple's disease. *Gastroenterology* **85** (1983) 1187-1191.

¹¹⁵ Fainstein, V., Bolivar, R., Mavligit, G., Rios, A. and Luna, M. Disseminated infection due to *Mycobacterium avium-intracellulare* in a homosexual man with Kaposi's sarcoma. *J. Infect. Dis.* **145** (1982) 586.

¹⁰⁰ Berlin, O. G., Zakowski, P., Bruchner, D. A. and Johnson, B. L. New biphasic culture system for isolation of mycobacteria from blood of patient with acquired immune deficiency syndrome. *J. Clin. Microbiol.* **20** (1984) 572-574.

¹⁰¹ Macher, A. M., Kovacs, J. A., Gill, V., *et al.* Bacteremia due to *Mycobacterium avium-intracellulare* in the acquired immunodeficiency syndrome. *Ann. Intern. Med.* **99** (1983) 782-785.

¹⁰² Waxman, J. S., Subietus, A., Malowany, M., *et al.* Overwhelming mycobacteriosis in an immunodeficient homosexual. *Mt. Sinai J. Med.* **50** (1985) 19-21.

¹⁰³ Cohen, R. J., Samoszuk, M. K., Busch, D. and Lagios, M. Occult infections with *M. intracellulare* in bone-marrow biopsy specimens from patients with AIDS. (Letter) *N. Engl. J. Med.* **308** (1983) 1475-1476.

¹⁰⁴ Osborne, B. M., Guarda, L. A. and Butler, J. J. Bone marrow biopsies in patients with the acquired immunodeficiency syndrome. *Hum. Pathol.* **15** (1984) 1048-1053.

Suppressor-cell induction by the systemic MAC infection. Many mycobacterial infections induce the production of large numbers of activated macrophages within the spleen which may limit the *in vivo* growth of the pathogen before the T-cell responses (DTH and CMI) can be fully expressed.⁸⁰ Often the only indication that activated macrophages are present within the infected tissues will be the appearance of a plateau in the growth curve (bacteriostasis). Adoptive transfer studies carried out with spleen cells harvested during the early phase of the infection suggest a lack of sensitized T cells.⁸⁰ While suppressor T cells may be responsible for this effect,⁷⁷ there is also evidence that activated macrophages are involved.⁷⁹ These cells may also be responsible for excessive antigen (sensitin) destruction within the

granuloma so that it does not reach the draining lymph node in sufficient quantities to stimulate a detectable T-cell response.⁸¹

Suppressor (modulator) T cells are known to be present in the lymphoreticular organs of the normal host.⁸⁵ The function of these cells is thought to be to down-regulate the cellular immune response once the infection has been brought under control. MAC serotypes 1, 4, and 8 may possess unique metabolic or antigenic factors able to stimulate the overproduction of these regulatory T cells early in the infection period. There may be some precedence for the existence of such a factor. Recently, a phenolic glycolipid antigen from *M. leprae* was postulated to induce the persistent lepromin anergy seen in human lepromatous leprosy patients.⁹⁴ The existence of such an antigen is still largely inferential, but the presence of such a factor in *M. avium* could help to explain the apparent association between these MAC serotypes and AIDS. In the same way, the absence of such a factor from other atypical mycobacteria such as *M. kansasii* and *M. simiae* would help to explain their absence from this immunosuppressed population. Avirulent members of the MAC may or may not possess this factor, but their inability to invade the normal tissues to reach the tolerogenic threshold would, in any case, explain their lack of involvement in this disease.

¹¹⁶ Croxson, T. S., Ebanks, D. and Mildvan, D. Atypical mycobacteria and Kaposi's sarcoma in the same biopsy specimens. (Letter) *N. Engl. J. Med.* **308** (1983) 1476.

¹¹⁷ Elliott, J. L., Hoppes, W. L., Platt, M. S., Thomas, I. G., Patel, I. P. and Gansar, A. The acquired immunodeficiency syndrome and *Mycobacterium avium-intracellulare* bacteria in a patient with hemophilia. *Ann. Intern. Med.* **98** (1983) 290-293.

¹¹⁸ Poon, M. C., Landay, A., Prasthofer, E. F. and Stagna, S. Acquired immunodeficiency syndrome with *Pneumocystis carinii* pneumonia and *Mycobacterium avium-intracellulare* infection in a previously healthy patient with classical hemophilia. *Ann. Intern. Med.* **98** (1983) 287-290.

¹¹⁹ Malebranche, R., Arnoux, E., Guérin, J. M., Pierre, G. C., Laroche, A. C., Péan-Guichard, C., Elie, R., Morisset, P. H., Spira, T., Mandeville, R., Drotman, P., Seemayer, T. and Dupuy, J.-M. Acquired immunodeficiency syndrome with severe gastrointestinal manifestations in Haiti. *Lancet* **2** (1983) 873-877.

¹²⁰ Pitchenik, A. E., Fischl, M. A., Dickinson, G. M., Becker, D. M., Fournier, A. M., O'Connell, M. T., Colton, R. M. and Spira, T. J. Opportunistic infections and Kaposi's sarcoma among Haitians: evidence of a new acquired immunodeficiency state. *Ann. Intern. Med.* **98** (1983) 277-284.

¹²¹ Vieira, J., Frank, E., Spira, T. J. and Landesman, S. H. Acquired immune deficiency in Haitians. Opportunistic infections in previously healthy Haitian immigrants. *N. Engl. J. Med.* **308** (1983) 125-129.

¹²² Small, C. B., Klein, R. S., Friedland, G. H., Moll, B., Emeson, E. E. and Spigland, I. Community-acquired opportunistic infections and defective cellular immunity in heterosexual drug abusers and homosexual men. *Am. J. Med.* **74** (1983) 433-441.

¹²³ Burmester, G. R., Gramatzki, M., Muller-Hermelink, H. K., Solbach, W., Djwari, D. and Kalden, J. R. Dissociation of helper/inducer T-cell functions: immunodeficiency associated with mycobacterial histiocytosis. *Clin. Immunol. Immunopathol.* **30** (1984) 279-289.

¹²⁴ Harris, C., Small, C. B., Klein, R. S., Friedland, G. H., Moll, B., Emeson, E. E., Spigland, I. and Steigbigel, N. H. Immunodeficiency in female sexual partners of men with acquired immunodeficiency syndrome. *N. Engl. J. Med.* **308** (1983) 1181-1184.

¹²⁵ Masur, H., Michelis, M. A., Wormser, G. P., et al. Opportunistic infection in previously healthy women. Initial manifestations of a community-acquired cellular immunodeficiency. *Ann. Intern. Med.* **97** (1983) 533-539.

¹²⁶ Wollschlager, C. M. and Khan, F. A. Pulmonary manifestations of acquired immunodeficiency syndrome (AIDS). *Chest* **85** (1984) 197-202.

¹²⁷ Comstock, G. W. Epidemiology of tuberculosis. *Am. Rev. Respir. Dis.* **125** (1982) S8-15.

¹²⁸ Hobby, G. L., Redmond, W. B., Runyon, E. H., et al. A study on pulmonary disease associated with mycobacteria other than *Mycobacterium tuberculosis*: identification and characterization of the mycobacteria. *Am. Rev. Respir. Dis.* **95** (1967) 954-971.

¹²⁹ Abbott, M. A. and Smith, D. D. Mycobacterial infections in immunosuppressed patients. *Med. J. Aust.* **1** (1981) 351-353.

¹³⁰ Ortbals, D. and Marr, J. A comparative study of tuberculosis and other mycobacterial infections and their association with malignancy. *Am. Rev. Respir. Dis.* **117** (1978) 39-45.

The data shown in Figure 1 and Table 1 forebode an increasing epidemic of MAC infections in the United States as the number of AIDS patients continues to increase.¹⁴ The ability of these organisms to multiply silently to enormous tissue loads, combined with their high degree of antituberculous drug resistance, makes the clinical management of these patients both difficult and frustrating.²⁷ At present, the prognosis for the MAC-infected AIDS patient is particularly bleak,¹² and we urgently need new immunological tools (recombinant interferon, IL-2, cloned T cells) to more effectively treat these patients. Before we can apply many of these reagents to this disease, however, we need to learn a lot more about the immunological parameters associated with the normal immune response to these opportunistic pathogens.⁸¹ The mouse infection model may help to throw new light on some of the parameters controlling the evolution of this disease.

In summary, the *M. avium* complex (MAC) can induce pulmonary infections in children and some immunocompetent adults, although they usually behave as simple opportunistic pathogens in the latter group. The MAC and *M. tuberculosis* are present in as many as 50% of AIDS patients examined for the presence of acid-fast bacilli. The pattern of MAC serotypes isolated from these patients differs from that seen in normal, cancer, and transplant patient groups. Thus, the presence of three MAC serotypes in so many AIDS patients suggests that they may play some sort of causative

role in the evolution of the terminal form of this immunodeficiency disease. Virulent MAC serotypes 1, 4, and 8 may possess some predisposing factor (possibly a receptor which enables them to attach to the nasopharyngeal or intestinal mucosae) which allows them to more effectively colonize and invade these membranes, compared to the other atypical mycobacteria. Avirulent MAC serotypes lack the ability to invade the normal host tissues and so are unable to establish a progressive systemic infection, even after the AIDS virus has depleted the T-cell defenses. A specific immune tolerance induced by the persistent colonization of the intestinal mucosa by members of the MAC may contribute to the HTLV-III/LAV-induced immunodepletion, thus helping to drive the ARC patient into the terminal stage of this disease. If this is true, then the *M. avium* complex could be considered a cofactor in the development of this important human immunodeficiency disease.

—Frank M. Collins, Ph.D., D.Sc.

Immunological Research Laboratories

Trudeau Institute, Inc.

P. O. Box 59

Saranac Lake, New York 12983, U.S.A.

Acknowledgments. I thank Vincent Montalbini, Linda Auclair, and Alan Roberts for their excellent technical assistance during these studies. The work was supported by a grant from the New York State AIDS Institute, Albany, and by grants AI-14065 and HL-19774 from the National Institutes of Health, Bethesda, Maryland, U.S.A.