

# Longitudinal Study of Tuberculosis Outcomes Among Immunologically Naive Aché Natives of Paraguay

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**KEY WORDS** Indians; South America; tuberculosis; epidemiology; Th2; heterozygosity; extinction

**ABSTRACT** This study documents the course of a tuberculosis epidemic in an immunologically naive group of South American Indians within fewer than 20 years after first sustained contact with outsiders. Groups of Northern Aché (ah-CHAY) of eastern Paraguay were contacted and settled on reservations between 1971–1979. Not surprisingly, the Aché are very susceptible to tuberculosis, and the epidemiological characteristics of the disease are quite different from those of populations that have had tuberculosis for centuries. Within 6 years of the first detected case of tuberculosis among the Aché, the prevalence rate of active tuberculosis cases reached 18.2%, and of infected cases among adults, 64.6%, some of the highest rates ever reported for any human group. Remarkably, males and females are equally likely to have been diagnosed with active tuberculosis, Aché children between birth and 5 years of age are least vulnerable to tuberculosis, high nutritional and socioeconomic status do not decrease the

risk of disease or infection, and children immunized with BCG are less responsive to tuberculin challenge than are other children. Moreover, similar to the Yanomamö, but unlike populations of European or African descent, a high percentage of Aché with active disease test negative on tuberculin challenge tests (purified protein derivative; PPD). These differences may be due to a high prevalence of diminished cell-mediated immunity, and T-helper 2 dominance. We also hypothesize that these immunological characteristics, low genetic diversity, hostile intergroup interactions, and behavioral noncompliance to treatment protocols together contribute to the high rates of active disease observed. Existing tuberculosis control programs are poorly equipped to handle the impact of these causal complexities on the course of recent tuberculosis epidemics that have quickly spread throughout native communities of Latin America during the last decade. *Am J Phys Anthropol* 121:134–150, 2003. © 2003 Wiley-Liss, Inc.

Tuberculosis is caused by mycobacteria of different species (e.g., *M. tuberculosis*, *M. bovis*, and *M. africanum*), but *M. tuberculosis* is responsible for most cases worldwide. The pathogen stays dormant in hosts for many days, if not weeks, months, or life, as occurs with other mycobacteria such as *M. leprae*. It usually takes at least 1 year for individuals exposed to the tubercle bacilli to convert from negative to positive tuberculin reaction, i.e., to have a positive skin PPD test result. This test is a measure of adaptive immunity, a response by the immune system that involves B and/or T cells (Janeway et al., 1999). Some studies show that only 1% of individuals with a positive PPD test develop active disease within the first year. In addition, when clinical manifestations of pulmonary tuberculosis appear, they do so gradually over a period of months or years. They include malaise, anorexia, weight loss, fever, night sweats, and mucoid or purulent cough. In contrast, the clinical course of extrapulmonary tuberculosis can take on different forms, depending on the tissue affected: skin, genitourinary tract, bone, liver, lymph, heart, muscle, or other tissues. In general, *M. tuberculosis*

thrives in the lungs (Robbins and Kumar, 1987), although close to 15% of active cases develop extrapulmonary tuberculosis (Cook, 1996).

When first introduced into populations of Europeans, it did not take long for tuberculosis to reach epidemic levels. However, once tuberculosis took hold, epidemics ran their full course in about 300 years (Cook, 1996). Tuberculosis epidemics in Western Europe, Eastern Europe, and North America reached their peak in the early 1800s, mid-1800s, and early 1900s, respectively. After the introduction

Grant sponsor: National Science Foundation; Grant sponsor: Avina Foundation.

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Received 17 April 2001; accepted 29 October 2002.

DOI 10.1002/ajpa.10228

of antimicrobial agents for the treatment of tuberculosis, tuberculosis epidemics took much less time to wane (Braun et al., 1990).

In many countries of Asia, Africa, and Latin America, epidemics have not reached their peak (Cook, 1996), and in others, including industrialized countries, new epidemics are beginning to emerge. This is due to the deterioration of public health services, socioeconomic decline, the AIDS epidemics, migration, and ironically, due to widespread use of chemotherapeutic agents which cause the proliferation of multidrug-resistant strains of tuberculosis (Freiden et al., 1993). Still, in other populations of industrialized nations, the epidemic began to wane significantly in recent decades. Among many natives of North America, tuberculosis rates remained high throughout the 1900s until the late 1970s, and reached their lowest levels in 1985. Nevertheless, the rate of tuberculosis among American Indians and Alaskan Natives was still 4.4 times higher than the rate among whites during that year (25 per 100,000 vs. 5.7 per 100,000; Rieder, 1989).

In response to emerging epidemics, in many parts of the world, public health departments have increased surveillance and treatment of tuberculosis. According to recent estimates, from 1990–1999, 8.8 million new active cases of tuberculosis were diagnosed, and 3 million people died of the disease per year (Johns Hopkins University, 2002). Ninety-five percent of all cases occur in the developing world, and 5% in industrialized countries. World Health Organization officials estimate that about 1,722 million people, or one third of the world population, are infected with *M. tuberculosis* (Cook, 1996).

Although human immunodeficiency virus (HIV) has contributed to the resurgence of tuberculosis, only a fraction of cases worldwide are attributed to coinfection with HIV. For example, in 2000, out of 10.2 million new cases of tuberculosis reported, only 1.4 million, or 13.9%, were attributed to HIV. Thus, independent of the HIV epidemic, tuberculosis is spreading throughout the world at an alarming rate in spite of low treatment costs (Johns Hopkins University, 2002).

In the USA, the number of reported active cases of tuberculosis declined from 1975 to 1985, and has not decreased since then (Johns Hopkins University, 2002). But for most of the developing world, trends are unknown. Tuberculosis has become a silent, unrecognized epidemic in these populations because no one is documenting its emergence, spread, and death toll. The few studies that have been done are cross-sectional without sustained follow-up. Not surprisingly, native communities throughout Central and South America are most severely affected (Chiappino, 1975; Coimbra and Santos, 1994; Conklin, 1994; Fleming-Moran et al., 1991; Meincke-Giesbrecht et al., 1993; Sousa et al., 1997), just as occurred in North America in the early 1900s (Rieder, 1989).

One of the main objectives of the public health sciences and evolutionary medicine is to explain the variation in epidemiological patterns across culturally, socially, and ecologically diverse human groups. Although tuberculosis is becoming a greater menace, and especially among the poor (Farmer et al., 1991) even after controlling for socioeconomic status, some ethnic groups are more affected by the illness than are others (Comstock, 2000). It is widely known that remote, indigenous groups in many areas of the world are highly susceptible to introduced infectious diseases (McNeill, 1976; Ribeiro, 1967). In European populations, approximately 30% of individuals who are exposed to tuberculosis bacilli become infected. Of these, only 10% develop active disease, and 90% remain disease-free for their rest of their lives (Johns Hopkins University, 2002). This, however, is not the case in populations of Amerindians. For example, in the Yukon-Kuskokwim river delta Inuit population of Alaska, more than 0.5% of individuals infected with tuberculosis developed active disease per year over a period of 7 years of observation (1954–1961). Thus a conservative estimate of the risk of active disease in this Inuit population over 60 years is 30%, a rate three times as high as the 10% observed in European populations (Comstock et al., 1967). In some South American indigenous populations, like the Aché of Paraguay, these rates are much higher still (see below).

Because of the absence of longitudinal epidemiological surveillance in isolated regions of the world, data on the causes and consequences of infectious illnesses such as tuberculosis in these populations are extremely sparse. Thus, little is known about differences between the infectious disease epidemiologies of small, more genetically homogenous human groups, and large, genetically diverse human populations.

#### TUBERCULOSIS IN NATIVE POPULATIONS

First and continued contact between small, isolated human populations with few virulent pathogens and larger populations with pathogens that can very quickly become virulent in small populations has probably been a frequent event in human history (McNeill, 1976). A careful examination of the response of small populations to newly introduced diseases should provide insights into selective pressures that influenced the evolution of immune defense phenotypes during much of human history, and at the present time. It should also help us identify ways to prevent future epidemics and deteriorating health in populations already affected.

Pathogens influence the evolution of immune defense genotypes and phenotypes within and among populations, and their effects are uneven across time and space. Virulent pathogens do not emerge at the same time across populations, and when human groups come into contact after long periods of isolation from one another, carriers of once-virulent pathogens in one population may cause the rapid

demise of the other (e.g., measles; see Neel et al., 1970). When naive hosts become exposed to microorganisms that their immune systems are not designed to attack effectively, individuals succumb quickly to them.

For hundreds of years, *Mycobacterium tuberculosis* caused high rates of premature deaths among susceptible Africans and Europeans, while those naturally resistant to this pathogen lived longer lives and passed on their genes (McKinlay and McKinlay, 1977; McKeown, 1988). Therefore, subsequent generations were considerably more resistant to tuberculosis. Along with improved sanitation and diet (Fairchild and Oppenheimer, 1998; Hardy, 1993; McFarlane, 1989; McKeown, 1979; Szreter, 1988), genetic resistance was an important contributor to the slowdown in tuberculosis epidemics prior to Koch's discovery of the pathogen in 1882 and the antimicrobial treatments that followed (McKinlay and McKinlay, 1977; McKeown, 1988).

Over the same time period, in many isolated indigenous groups of the Americas and other parts of the world, tuberculosis had little if any influence on the evolution of immune defense mechanisms. This is particularly true of native populations of lowland South America with group sizes too small (Meliá, 1992; Instituto Nacional de Estadística, 1993) for *M. tuberculosis* to thrive (for a model of group size and tuberculosis transmission in prehistorical populations of North America, see McGrath, 1988). Despite well-publicized findings of the presence of tuberculosis in high-density populations of highland South America (Allison et al., 1973; Salo et al., 1994), there is no evidence of pre-Columbian exposure of lowland groups. In addition, the response to *M. tuberculosis* soon after contact indicates that remote lowland groups are virgin soil to this pathogen (Nutels, 1968).

There are now isolated indigenous communities in many parts of the world that are more susceptible to tuberculosis than are Europeans and Africans because they have had minimal if any exposure to tuberculosis throughout their history. Tuberculosis rates in African, Asian, and European populations have only increased recently due to the HIV epidemic, and increases in crowding and poverty (Cook, 1996).

Among natives of South America who have not yet been affected by HIV, and that do not live in crowded urban areas, high susceptibility to tuberculosis may be ever present (Escobar et al., 2001). In addition to immunological tendencies that may be unique to Amerindians (see below; Sousa et al. 1997), lack of exposure over long periods of time, as well as during early child development, have serious consequences. They cause the rapid demise of these virgin soil populations as they come into contact with carriers of milder, chronic forms of infectious diseases (Neel et al., 1970).

During child development, immunological memory is established more effectively than later in life.

Immunological memory is the immune system's ability to recognize and attack pathogens effectively that the immune system has encountered in the past. This response reflects the growth of clonally expanded populations of antigen-specific lymphocytes to infectious agents and other nonself in individuals throughout their lives. Whether through vaccination or infection, children exposed to pathogens have inapparent, benign reinfections that keep the immune system primed for defense against those same pathogens (Janeway et al., 1999).

This study fully documents the course of a tuberculosis epidemic in an immunologically naive group within fewer than 20 years after first sustained contact with outsiders. Aché (ah-CHAY) natives were probably never exposed to tuberculosis prior to contact. Not surprisingly, the epidemiological characteristics of the disease are quite different from those of populations that have had tuberculosis for centuries.

## METHODS

### The population

The Aché population lives in the tropical forests of the southwestern part of the Eastern Brazilian Highlands, and comprises four major groups. During the 400 years since the first arrival of the Spaniards, the Aché have engaged in hostile relations with outsiders. They relied entirely on hunting and gathering, and did not trade, intermarry, or visit with any of the Guaraní Indian groups. There is also no evidence that they ever experienced amicable relations with any other ethnic population in Paraguay until the 1960s and 1970s, when various cultural groups made contact with outsiders.

Currently the Aché live in five major mission/reservation settlements with a population size of approximately 1,000 individuals. They now have a mixed economy, with some communities almost completely dependent on cultigens, farm animals, and wage labor, while others are still partially dependent on hunting and gathering. This study was done in two communities with a population size of 552 individuals in 1997 located in the buffer zone of the Mbaracayú Biosphere Reserve. The majority of their members belong to the Northern Aché cultural group that lived in isolation until the late 1970s (Hill and Hurtado, 1996).

Although evidence for the pre-Columbian presence of tuberculosis continues to mount (Salo et al., 1994), whether this pathogen would have thrived in the smaller populations of lowland South America is unclear (McGrath, 1988). Before contact in the 1970s, bands had a median of about 50 individuals, with camp composition on single days varying from 3–160 individuals (Hill and Hurtado, 1989). Even though during any given year, a single Aché individual could have interacted with about 500 individuals just prior to contact, the frequency of these interac-

TABLE 1. Operationalization of variables

| Name                   | Type        | Description                                    |
|------------------------|-------------|--|
| Predictors             |             |  |
| Age                    | Continuous  | 0.2–58 years                                   |
| Sex                    | Categorical | Male = 1; female = 0                           |
| Nutritional status     | Continuous  | 2.5–78 kg                                      |
| Wealth                 | Continuous  | 62–950 US dollars                              |
| Level of acculturation | Categorical | Less acculturated = 0; more acculturated = 1   |
| Outcomes               |             |  |
| Active disease         | Categorical | Diagnosed with active disease, 1 = yes, 0 = no |
| Infection status       | Categorical | Positive PPD ( $\geq 5$ mm); 1 = yes, 0 = no   |

tions was probably insufficient to favor host-pathogen coexistence or endemicity (McGrath, 1988).

During a 20-year-long study of demography and life history (Hill and Hurtado, 1996), tuberculosis emerged as a major source of mortality and morbidity in Aché communities requiring urgent medical relief interventions and documentation by anthropologists and international, local, and national health officials. According to informants, the sources of tuberculosis infection in Aché communities were Avá Guaraní indigenous neighbors (contacted by Europeans in the 16th century) with active disease (Reed, 1995). Because the Aché live in an area that is fairly remote without adequate laboratory facilities, the authors had to rely on observational data and tuberculin skin test responsiveness (purified protein derivative test; PPD) to estimate the incidence of the disease and to describe other aspects of the epidemic.

#### Demographic and epidemiologic data

As part of ongoing, longitudinal studies of Aché communities, informants were weighed and interviewed annually or biannually from 1980–1999 about any changes in health status they may have experienced or observed. Individuals were weighed on mechanical weigh scales that were routinely calibrated to a known weight to ensure accuracy. Field sessions varied in length between 2 weeks and 14 months. Methods used to assign ages and to estimate the monetary worth of Western possessions owned by an individual or his or her parents, or “wealth,” are described elsewhere (Hill and Hurtado, 1996). Age was estimated for each individual by assigning relative ages using a population-wide relative age list (Hill and Hurtado, 1996, p. 120–123). “Wealth” was estimated by calculating the value of all personal property in a sample of 67 couples in 1995 (Hill and Hurtado, 1996, p. 303). In this study, children’s wealth was operationalized as the average of the wealth of their two biological parents.

The two communities of Aché in this study differ by level of acculturation. Because one of the communities is located on a main rural road, nonnatives visit the community frequently. Consequently, its members are more acculturated, engage in more wage labor, and speak their native language less. In contrast, the Aché who reside in the second commu-

nity, located 5 km away from main rural roads, are less acculturated, interact with nonnatives infrequently, rarely engage in wage labor, and speak pure Aché more frequently. Based on these criteria, these communities were coded as “more acculturated” and “less acculturated,” respectively, for purposes of statistical analysis (see Table 1).

Since contact, the Aché have relied on missionaries, anthropologists, and local, national, and international health professionals to learn about Western treatments and the Western terminology that describes the symptoms and causes of their illnesses. Patients or their more educated relatives or friends often keep copies of medical records after making visits to hospitals and clinics, or remember in great detail when, how, and why they were treated, and if left untreated, what symptoms ailed them and over what period of time. In addition, healthcare workers keep records of community-based medical interventions, and these are excellent sources of epidemiological data. Over a 12-month period from June 1997–June 1998, one of us (A.M.H.) interviewed multiple individuals in Aché communities, health centers, and rural clinics to verify information on active tuberculosis disease status provided by Aché informants. In addition, we kept records of PPD results during community-wide screenings. Moreover, from 1997–1998, A.M.H. worked for the National Commission of Tuberculosis Control of Paraguay (NCTB) in order to help train healthcare workers and to provide assistance with transport of health personnel and delivery of tuberculosis medication to remote Aché communities. Thus, for this study, the authors relied on three major sources of epidemiological data: interviews with informants in their native language, clinical records (PPD results and physicians’ diagnoses), and reviews of community health records.

In 1992, several doctors working for the Japanese International Cooperation Agency (JICA) diagnosed cases of active tuberculosis in two Aché communities of the Mbaracayú region. Between 1990–1992, several other cases had been diagnosed in major towns and cities of eastern Paraguay during visits to hospitals and clinics made possible by missionaries, anthropologists, or more acculturated Aché. According to Aché informants, it was not possible to diagnose all cases based on sputum smear analysis. This is because the Aché have considerable difficulty ex-

pectorating sputum, perhaps because they are usually dehydrated. The effects of dehydration on sputum production were also reported for the Tarahumara natives of Mexico (Vigil, 2000). In addition, bronchoscopy or gastric aspirations are not viable diagnostic options under difficult field conditions, and because the sensitivity of smear examinations is only 65%, many patients must be diagnosed on the basis of clinical signs and symptoms and radiology (Galeano Jiménez, 1995). Lastly, JICA doctors were unable to collect sputum from patients on 3 consecutive days as is recommended by international health agencies (Enarson et al., 1993) because the Aché frequently leave permanent settlements to go on forest treks or because they begin work in their fields at dawn. Consequently, single samples of sputum were used to diagnose some cases, while others required a combination of X-rays, contact histories, and clinical symptoms.

According to community records, a team working for the JICA collected single sputum samples from 12 Aché who had been diagnosed with tuberculosis 1 year earlier. All these samples tested negative for mycobacteria, suggesting that these 12 individuals were cured. Five years later, several new cases of tuberculosis were diagnosed based on X-rays, correlative clinical symptoms, and contact histories with the assistance of medical volunteers, missionaries, and anthropologists at various hospitals and clinics.

#### Skin tests and BCG vaccination

In 1992, Proyecto Guaraní, a nongovernmental health organization of Paraguay, administered tuberculin skin tests (2 tuberculin units of PPD) supplied by the Ministry of Health of the Government of Paraguay to 190 individuals in two communities of Mbaracayú. Proyecto Guaraní staff and Aché healthcare workers then measured the diameter of induration, using the "ballpoint" method 72 hr after inoculation (Sokal, 1975). In addition to PPD wheal size, project staff noted in community records those who had been immunized with BCG. Several years later, in 1997, local health professionals, volunteer medical personnel, and Aché healthcare workers, supervised by staff from the Ministry of Health, used the same protocols in the same two communities to screen for tuberculosis infection on a larger sample of 427 individuals. Data on BCG vaccinations were not collected in 1997.

It is unlikely that data collectors failed to classify children into the right immunization status categories. This is because the healthcare professionals involved checked for BCG scars in order to verify immunization records. They also checked BCG scars when parents had lost copies of their children's immunization records. Even in immunocompromised populations, absence of scarring after vaccination is a rare event (Morbidity and Mortality Weekly Report, 1991).

#### Treatment

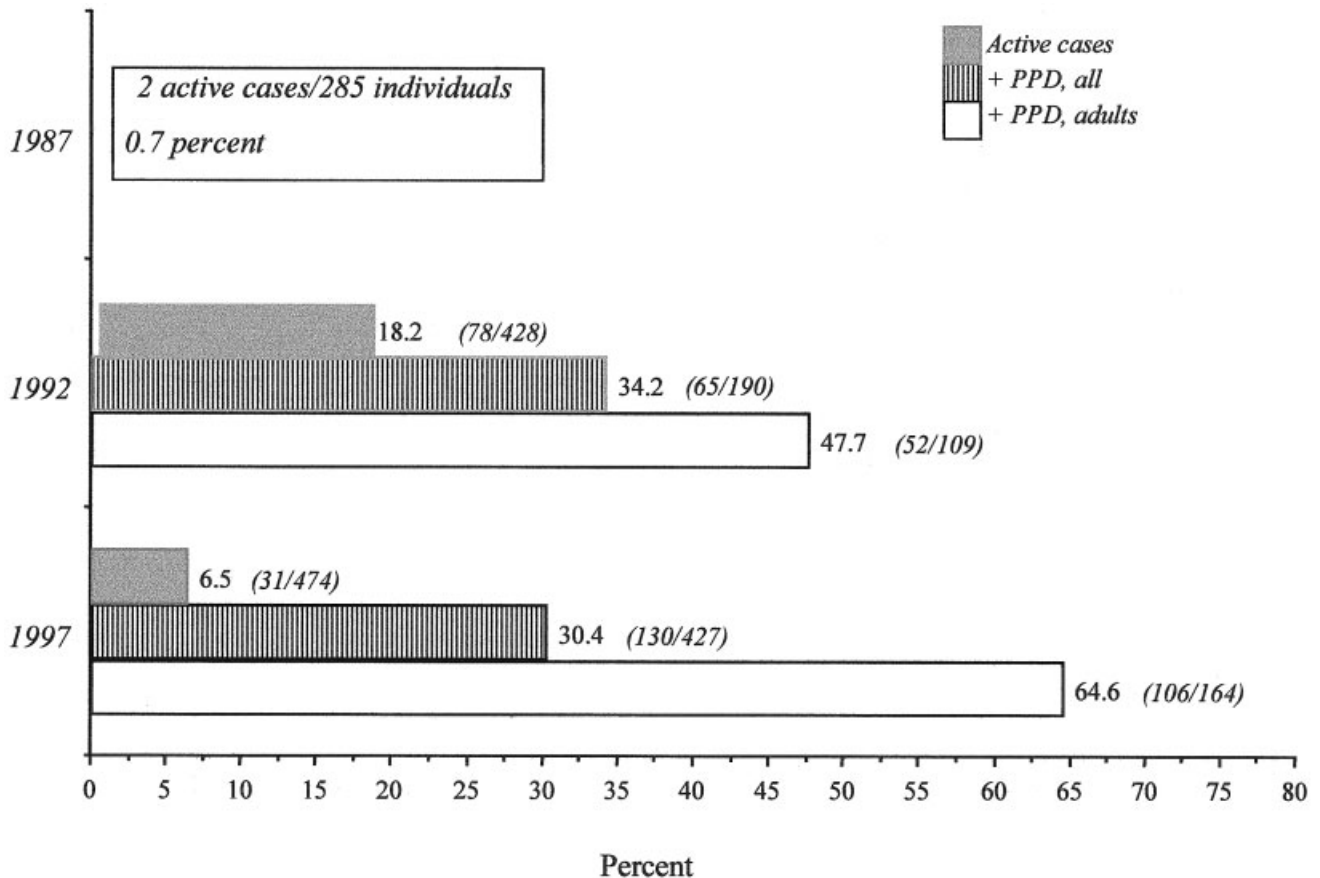
Aché with active tuberculosis were first treated with *Isoprodian* in 1992. A single tablet of *Isoprodian* contains isoniazid, prothionamide, dapson, and rifampicin. It is manufactured by a German pharmaceutical company, and has been widely used in Paraguay since 1984 (Kleeberg, 1987). The World Health Organization and the International Union Against Tuberculosis and Lung Diseases do not recommend *Isoprodian* because this combination drug has never been tested in clinical trials, even though it appears to be effective in the treatment of leprosy and tuberculosis (Sighart et al., 1982).

All cases treated in 1992 were prescribed *Isoprodian* for a period of 12 months. Most Aché were expected to travel many miles to rural clinics, although at times, Proyecto Guaraní personnel delivered the medication to patients. Because rural roads are often flooded and because most Aché do not have the necessary income to pay for transportation, many patients did not take *Isoprodian* consistently.

In contrast, cases diagnosed in 1997 were treated by the National Commission of Tuberculosis Control of Paraguay (NCTB), with logistical help provided by the Director of the Mbaracayú Reserve, Alberto Yanosky, and A.M.H. The NCTB follows a treatment protocol sanctioned by the Pan American Health Organization (PAHO) which requires that patients take once a day for a period of 2 months one Rifampicin/Isoniazid combination tablet and one Pyrazinamide tablet, and one Rifampicin/Isoniazid combination tablet per day for 4 months thereafter. Adults also take one tablet of Etambutol per day for the first 2 months of treatment (Pan American Health Organization, 1986). A.M.H. and Aché healthcare workers monitored medication intake, depending on the willingness of the patient to take the medication regularly or the willingness of family members to monitor their relatives' compliance to the treatment protocol. In some cases, A.M.H. or healthcare workers counted the number of pills left after a week's treatment. In other cases, they administered medications to the patient daily. When pills were lost or damaged, they were replaced with a fresh supply immediately.

#### Data analyses

Data on age, sex, infection status, active disease, weight, level of acculturation of the community, wealth of parent, or own wealth were entered into Excel spreadsheets, and transferred into the PC SAS statistical program for logistic regression analyses, and into Cricket Graph II, MacIntosh program, for graphing. Variables were operationalized as shown in Table 1. We chose logistic regression procedures because they allow us to model the effects of continuous or categorical variables on categorical outcomes (i.e., 1, disease present; 0, disease absent). Logistic regressions also allow us to estimate odds ratios, or the relative increase in risk as a function of



**Fig. 1.** Number and percent of active cases and positive PPD in Aché communities in 1987, 1992, and 1997. Numbers without parentheses indicate percentages. Numbers in parentheses indicate number of cases diagnosed over a 5-year interval (numerator) divided by number of individuals at risk of the event (denominator), i.e., individuals who had never experienced the event. For example, in 1997, 474 Aché who had not been diagnosed with active tuberculosis ever in their lives were at risk of the event between 1993–1997. Thirty-one individuals were diagnosed with active tuberculosis over that period. In 1997, out of 427 individuals who were given a PPD skin test, 130 had a positive reaction, i.e., 30.4% of those tested. Note that in 1992, only 190 individuals had a PPD test, a subset of the total population.

a given exposure (i.e., male vs. female). Thus, we are able to interpret parameter estimates in terms of easy-to-understand probabilities. The interpretation of an odds ratio is as follows. When the parameter estimate is positive, then individuals exposed to a given factor are  $n$  times more likely to develop active tuberculosis disease or to become infected with *M. tuberculosis* over some time period.

## RESULTS

### The epidemic

Over the course of 10 years, the Aché learned very quickly about tuberculosis as they watched friends and relatives either die or become very ill. In 1986, they had seen a 31-year-old woman die of pulmonary tuberculosis, and had watched a 60-year-old man grow increasingly weaker and thinner as symptoms of active pulmonary disease became more severe. In 1993, a 47-year-old woman died of tuberculosis in the same community. Her death was followed in 1995 by that of a 59-year-old and a 71-year-old man, and finally in 1996 by 2 young women who were only

26 and 31 years of age. These 6 patients died either because they were diagnosed and treated too late, or because they refused to take *Isoprodian*.

In 1992, doctors working for the JICA diagnosed 62 cases of active tuberculosis, while 16 other cases were diagnosed at hospitals and clinics in various towns and cities of eastern Paraguay, for a total of 78 cases. The lifetime prevalence rate of active tuberculosis at that time was minimally 18.2% (78 cases out of 429 individuals at risk) (Fig. 1), i.e., a cumulative incidence rate of 3.7% per year over a period of 5 years (1987–1992). By 1997, 6 individuals with active tuberculosis had died, a case fatality rate of 7.7%. The treatment failure rate among those patients treated in 1992 with *Isoprodian* was 34.6% (27 of 78 individuals). These 27 patients remained disease-free for several years, but had to be treated again with medications recommended by PAHO when they developed anew the clinical signs and symptoms of severe pulmonary tuberculosis. According to Aché informants, all had failed to take medication on a daily basis, and many missed entire

months at a time. It is not possible to determine whether treatment failure is due to noncompliance or to the use of *Isoprodian*, or both. Overall, what is clear is that without the use of antimicrobial agents, up to 18% of the Aché population would have died of tuberculosis within the first decade of exposure.

In 1997, 31 new active cases of tuberculosis were diagnosed (6.5%, or 31 of 474 individuals who had never been diagnosed with tuberculosis). According to these population figures, the tuberculosis epidemic reached a peak in 1992, followed by a reduction in the number of new cases (Fig. 1).

The rate of extrapulmonary tuberculosis was only 1.8%, mainly two cases of mal de Potts out of 109 cases diagnosed between 1992–1997. This is probably an underestimate of the true rate, since in non-immunocompromised individuals, extrapulmonary tuberculosis is diagnosed in about 15% of cases in some European populations (Thornton, 1995; Escobar et al., 2001), and in 9% of new cases diagnosed in Paraguay in 1999 (MSPBS, 1999). Paraguayan rural clinics and most urban hospitals are ill-equipped to diagnose adequately extrapulmonary cases of tuberculosis. Thus, it is possible that extrapulmonary tuberculosis caused some deaths during the period of observation (see Discussion).

The temporal pattern of tuberculosis infection and active disease is confounded by the age distribution of individuals who were administered tuberculin tests in 1992 and 1997. In 1992, 34.2% of individuals (65 out of 190) tested positive, while in 1997, 30.4% (130 out of 427) tested positive. Because the Aché tend to be unresponsive to PPD (see below), 5 mm instead of 10 mm was used as the criterion for assigning a positive result (Hopewell and Chaisson, 2000). As noted for active disease, rates of infection appear to be decreasing when individuals of all ages are considered. This is due to the fact that more children were tested in 1997 than in 1992, and that children tend to test negative on skin tests more frequently than do adults (Steiner et al., 1979). In fact, when only adults ( $\geq 20$  years) are considered, infection rates increased from 47.7% (52 of 109) in 1992 to 64.6% (106 of 164) in 1997 (Fig. 1). Thus, over the sample period, infection rates increased among adults, while active disease rates decreased when all age groups are combined.

Curiously, among the Aché, infants and children from birth to 5 years of age are least affected by tuberculosis, even though the opposite trend is usually observed among immunologically naive populations such as the Chippewa at the turn of the Century (Indian Health Service, 1930). The youngest victims among the Aché were two 4-year-old children. All other children diagnosed with active tuberculosis were over 6 years of age. As occurs elsewhere, older Aché children and adolescents have lower rates of active disease than do adults. The probability of having been diagnosed with active tuberculosis increases throughout the life course (Fig. 2).

Not surprisingly, the number of infected cases is usually greater than the number of active cases in any given interval. In the sample of PPD measurements taken in 1997, by age 20, close to 50% of individuals in each subsequent 5-year interval until age 40 tested positive for tuberculosis. After age 40, this probability declines (Fig. 3), although the risk of active tuberculosis reaches its peak after this age (Fig. 2). Interestingly, females tend to test positive at a higher rate than do males in all intervals except between 35–40 years of age (Fig. 3), even though females are not more likely to be diagnosed as active cases (Fig. 2) than are males. These differences are not statistically significant (logistic regression,  $P = 0.215$ ).

### Previous BCG vaccination

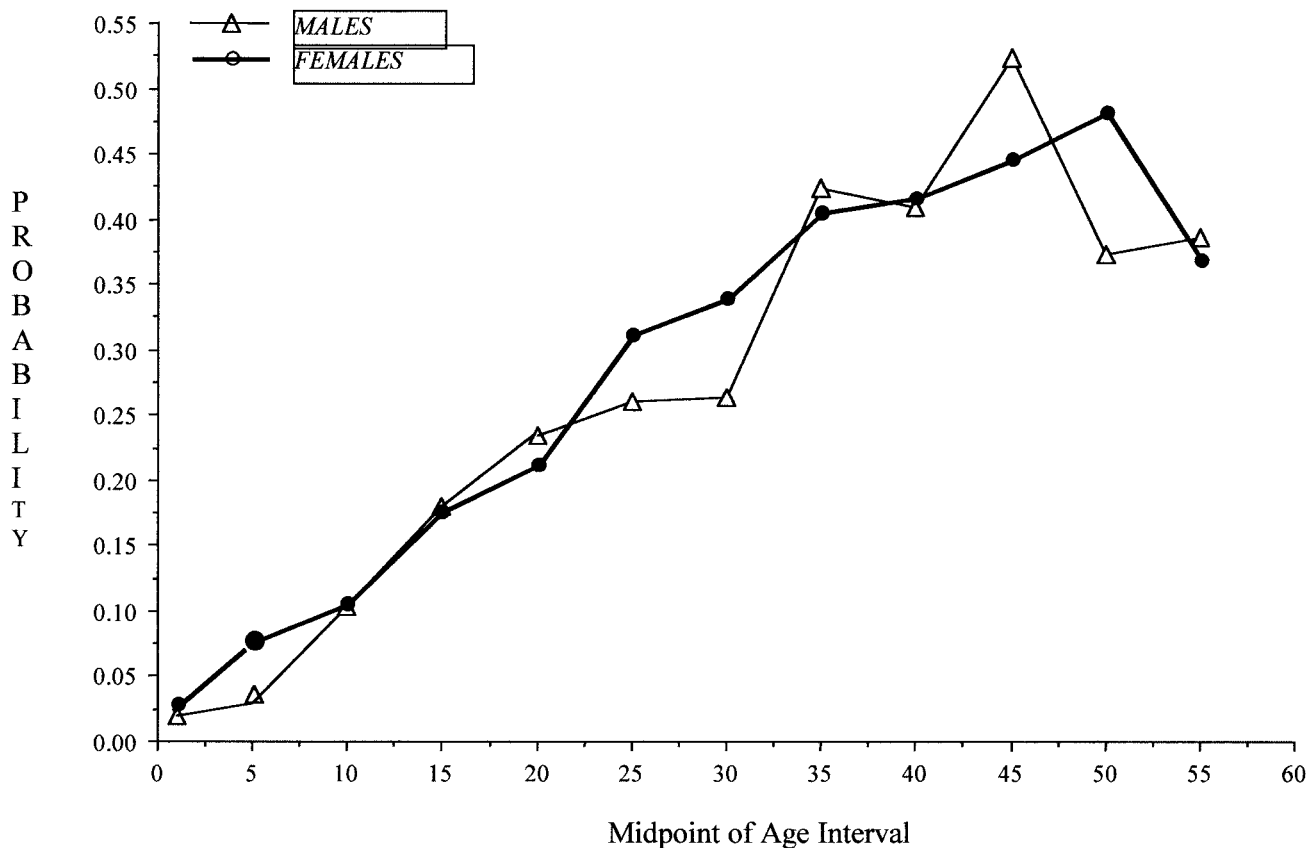
In 1997, only individuals under 20 years of age had received BCG vaccinations, and all were administered during the first 3 years of life. This is because in Paraguay, all infants receive BCG vaccination along with other routine immunizations. There are no national tuberculosis vaccination programs for adults.

The principle of immunological memory and previous studies show that individuals who are vaccinated with BCG have positive PPD test results through much of their lives (Menzies et al., 1992). Thus, all Aché vaccinated with BCG are expected to have a positive PPD test result, but this did not turn out to be the case. A higher fraction of young individuals who were immunized with BCG (93.3%) had *negative responses* than did those who were not immunized (68.3%) (Fig. 4), and this difference is statistically significant (odds ratio =  $1.36 \pm 0.112$ ,  $P = 0.0412$ ).

Curiously, even though BCG vaccination is not associated with a positive PPD test result, it may play some role in progression to active disease, although the results are inconclusive. Of 199 individuals under 20 years of age who were given skin tests in 1992, only 60 (29.7%) had been immunized with BCG. Of the 60 individuals who were immunized with BCG, only 2 (3%) developed active disease, while of the 139 who were not immunized, 18 (13%) developed active disease. Even though young individuals who had never been immunized were 3.1 times more likely to develop active disease, *this increased risk is not statistically significant* (SE of odds ratio =  $\pm 2.83$ ,  $P = 0.36$ ).

### Correlates of disease and infection

**Nutritional status.** Surprisingly, among the Aché, the better-nourished are more at risk of active disease and infection than are others. Multiple logistic regression analyses show a positive association between weight and the risk of developing active disease in 1998 after controlling for the effects of age, age-squared, sex, wealth, and level acculturation (Table 2). Similarly, in 1992 and 1998, we found a positive correlation between weight and the



**Fig. 2.** Probability of ever having been diagnosed with active tuberculosis (lifetime prevalence) among Aché males and females plotted by midpoint of age intervals.

probability of having a positive PPD, but the relationship is not statistically significant (Table 2).

**Wealth.** Wealthier individuals were also more likely to test positive for tuberculosis in 1998 than did others after controlling for confounders, although the relationship is not statistically significant. At the same time, we did not find an association between wealth and infection in 1992, or between wealth and active disease.

**Acculturation.** Individuals residing in the more acculturated community were at higher risk of active disease in 1992 and 1998. However, the relationship is only borderline-significant in the 1992 sample. In addition, members of the more acculturated community were also at higher risk of having a positive PPD in 1992.

#### Ethnic differences in response to TB exposure

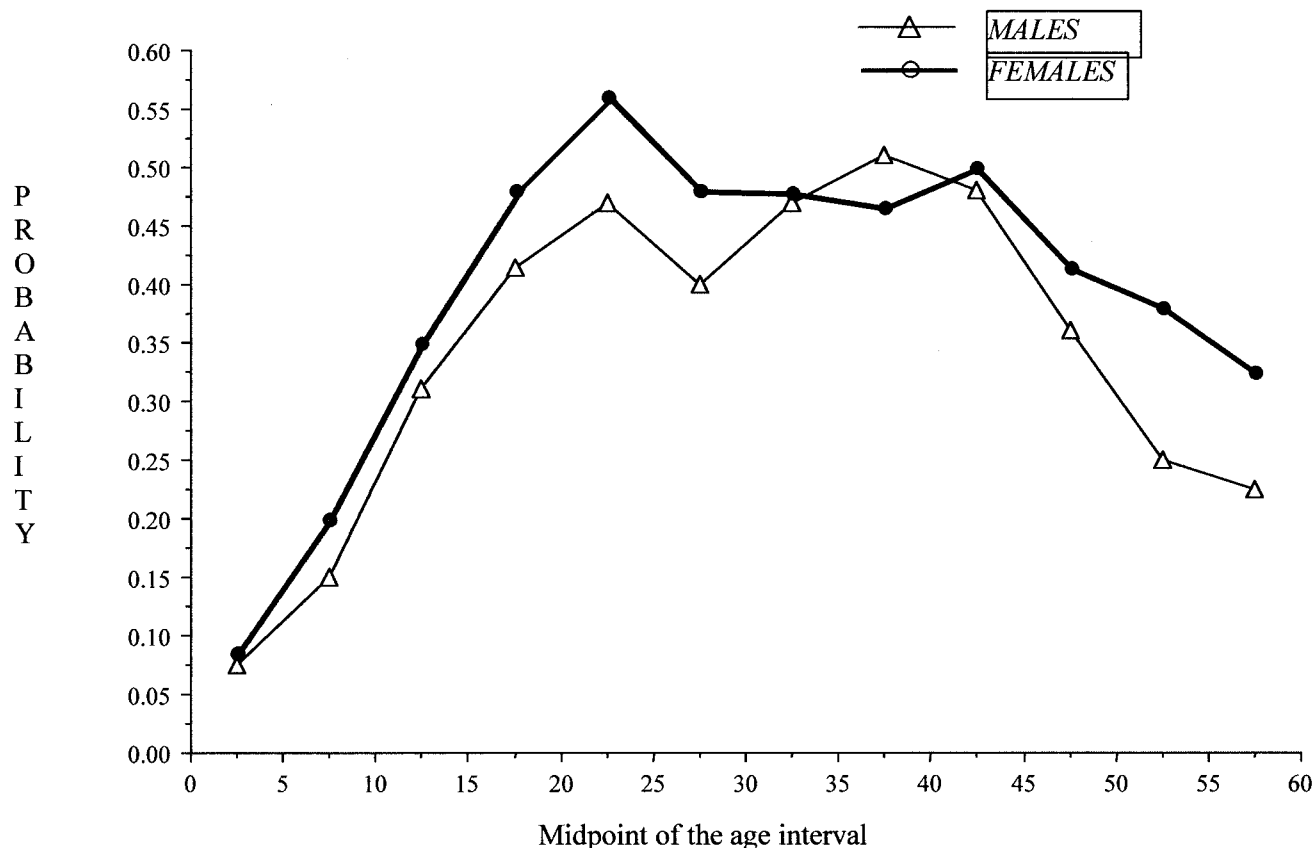
A closer look at responsiveness to tuberculin challenge (i.e., whether or not an individual has a positive reaction to PPD injection) provides insights into the uniqueness of South American Indian immune responses. Given that an individual has been exposed to tuberculosis, poor responsiveness to tuberculin challenge indicates that the host's response to *M. tuberculosis* is ineffective. The negative tuberculin reaction rate observed among the Aché is slightly

lower (68.3%) than the rate reported for the Yanomamö of Brazil (76%) (see Fig. 5 and Sousa et al., 1997) and the Chippewa of Wisconsin (Indian Health Service, 1930) in the 1930s (73%).

Because these population statistics may include individuals who may not be at risk of infection, it is useful to examine rates of responsiveness among individuals who have had active disease. Based on the principle of immunological memory (Janeway et al., 1999), those with active disease at any point in their lives should always test positive for tuberculosis infection. However, among the Aché and the Yanomamö, we find that 39% of individuals who currently have, or who had active disease in the past, had negative reactions in response to PPD injection, whereas only 12% of Brazilian descendants of Europeans and Africans with active disease had negative reactions (Fig. 6). In addition, while 59% of nonindigenous Brazilians have wheal sizes over 15 mm, only 33% of the Aché and 24% of the Yanomamö have wheal sizes this large. This suggests that the Amerindian immune response to tuberculosis may be different from that of populations of African or European descent.

#### DISCUSSION

This is the first study to document longitudinally the inception and course of a tuberculosis epidemic



**Fig. 3.** Probability that Aché males or females tested positive ( $\geq 5$  mm) on PPD tests administered in 1992 or 1997, plotted by midpoint of age intervals.

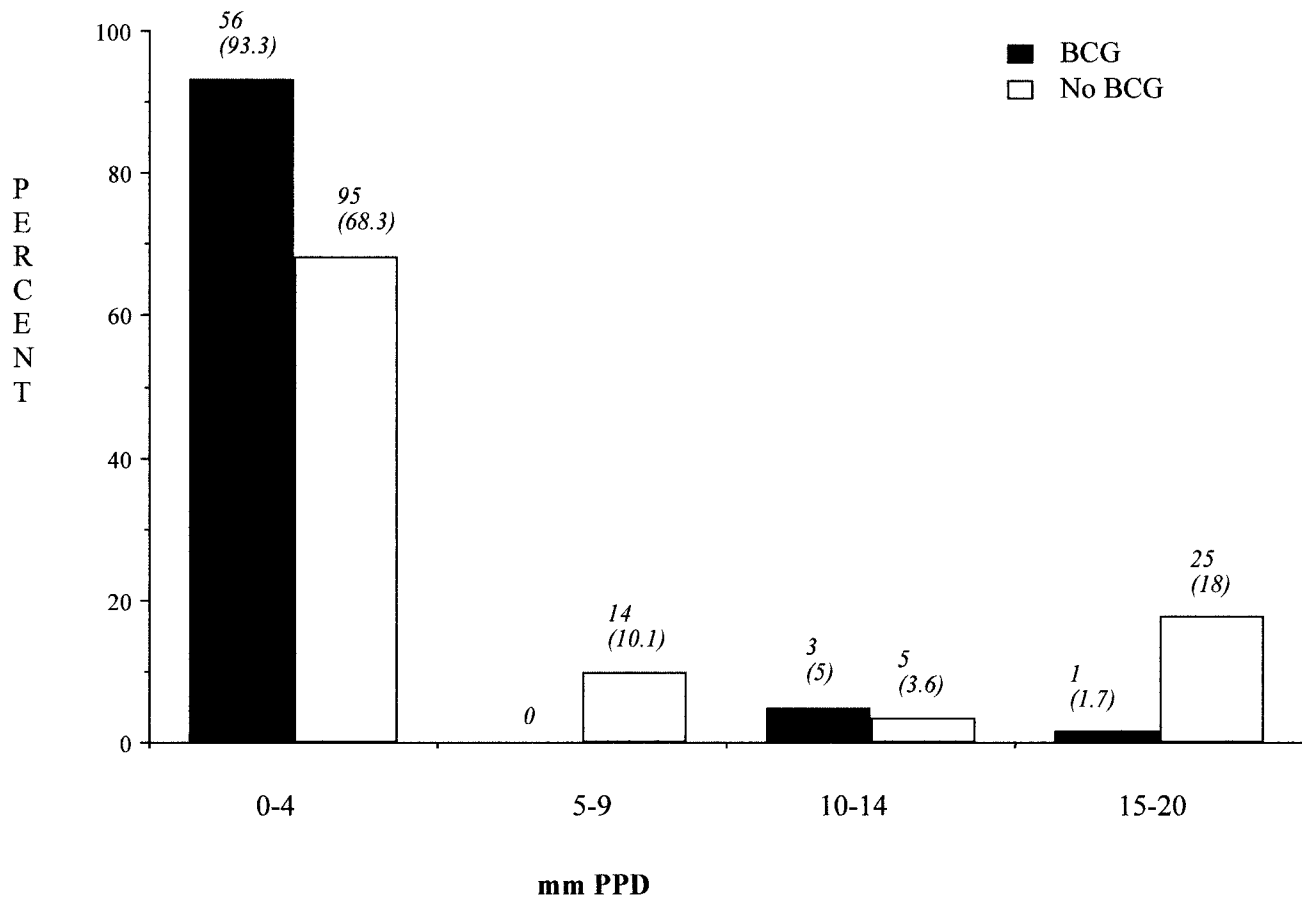
in an immunologically naive group of lowland South American natives. Rates of tuberculosis infection and disease reached epidemic proportions during the 1990s in two Aché communities of Mbaracayú. In fewer than 15 years after first contact, 18% of the population had been diagnosed with active tuberculosis. This rate is almost twice as high as the 10% rate of active disease that is expected among individuals of European descent *later in life, and many years after initial infection*. In addition, during the initial 5 years of the epidemic from 1987–1992, the annual cumulative incidence rate of active tuberculosis of 3.7% (3,700 per 100,000 individuals) observed among the Aché was *20-fold higher* than that observed in the country of Paraguay in 1999 (826 cases for a population of 4,585,652, or 180 active cases of tuberculosis per 100,000) (MSBPS, 1999). The rate observed among the Aché is also almost 10-fold higher than that observed in 1993 in indigenous areas of the Paraguayan Chaco, where tuberculosis has been a public health menace for decades (400 cases per 100,000) (Galeano Jiménez, 1995). The true difference between rates observed among the Aché and regional or national rates is probably lower. This is because surveillance of tuberculosis cases in native groups (population size, 49,487 in 1992; Meliá, 1997, p. 92) is inadequate, and these groups have the highest rates of tuberculosis in the

country (Galeano Jiménez, 1995; Meincke-Giesbrecht et al., 1993).

Similar patterns were documented in Brazil. In the State of Rondonia, the difference in tuberculosis rates is 10-fold. The annual incidence of active tuberculosis among natives is 1% per year (1,000 per 100,000 individuals), while the annual incidence rate for nonnatives is only 0.1% (100 per 100,000 individuals) (Escobar et al., 2001).

### Susceptibility

Clearly, the Aché of Paraguay are extremely susceptible to pathogens such as *M. tuberculosis*. As was found in other studies (Miranda, 1985), more acculturated Aché who have stronger economic and social ties to Paraguayan peasants are at higher risk of tuberculosis infection and disease than are less acculturated Aché. In addition, susceptibility to disease once exposed is extraordinary. At contact, virgin-soil respiratory diseases that were never adequately diagnosed killed about 37% of the Aché population within 2 years (Hill and Hurtado, 1996). Because deaths occurred within weeks or months of exposure, and within days of onset of illness, it is unlikely that the pathogenic agent that caused these contact-related respiratory illnesses was *M. tuberculosis*. However, we can only guess that if individuals who were susceptible to acute respiratory infec-



**Fig. 4.** Percent (indicated in parentheses) individuals between birth and age 20 years grouped by BCG immunization status and size of PPD induration. Numbers without parentheses indicate number of individuals in each group.

**TABLE 2.** Correlates of active disease and infection status

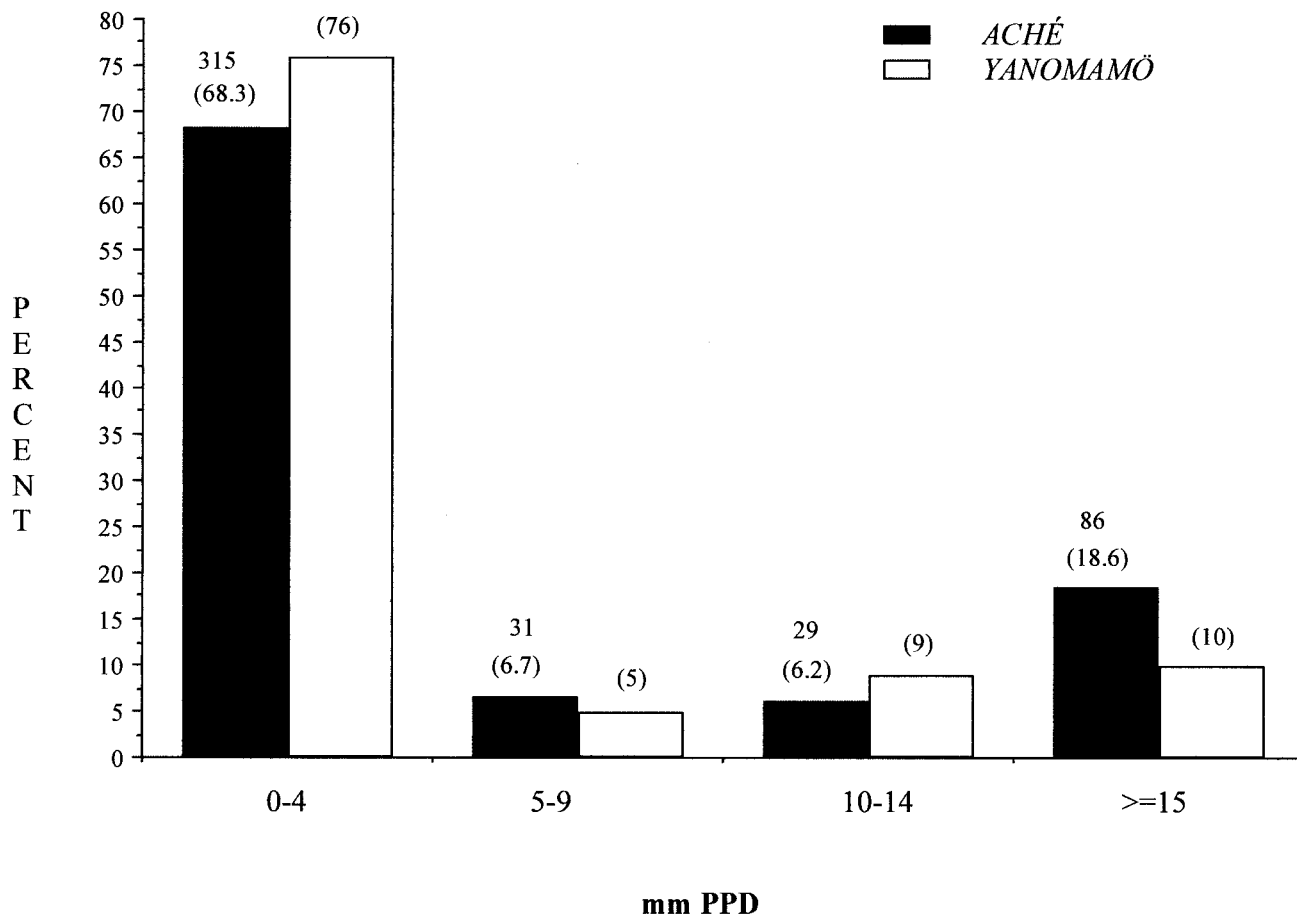
| Predictors  | Partial parameter estimates, codd's ratio $\pm$ standard error |   |   |   |
|---|--|---|---|---|
|   | Active case  |   | Positive PPD                            |   |
|   | 1992   | 1998                                    | 1992                                    | 1998                                    |
| Acculturation 1, more acculturated; 0, less acculturated) | 1.24 $\pm$ 1.13 $P = 0.0673$<br>n = 457                        | 1.76 $\pm$ 1.17 $P = 0.0003$<br>n = 562 | 1.77 $\pm$ 1.27 $P = 0.0173$<br>n = 190 | n.s.                                    |
| Weight (continuous)                                       | n.s.   | 1.07 $\pm$ 1.03 $P = 0.0236$<br>n = 392 | 1.03 $\pm$ 1.02 $P = 0.1362$<br>n = 130 | 1.02 $\pm$ 1.01 $P = 0.1435$<br>n = 319 |
| Wealth (continuous)                                       | n.s.   | n.s.                                    | n.s.                                    | 1.00 $\pm$ 1.00 $P = 0.0726$<br>n = 267 |

<sup>1</sup> Partial estimates from multiple regressions that control for effects of acculturation, age, age-squared, and sex. Because relationship between age and outcome variables is nonlinear, age-squared was added to regressions.

tions were more likely to be susceptible to tuberculosis, a survivor bias would occur, and would affect the interpretation of our findings. If this bias were present, then the true rate of tuberculosis would have been much higher, had previous respiratory epidemics failed to kill so many Aché at contact.

The observed rate is nevertheless extraordinarily high. In fewer than 20 years after contact, tuberculosis could have taken the lives of close to 20% of the population, most of them adults of reproductive age. Medical interventions prevented what could have

been an even higher death rate during the early stages of the epidemic, and saved many lives among those afflicted with tuberculosis several years later. The case fatality rate among persons with active disease would have probably been much higher without medical intervention (47.4%; 31 recurrent cases, plus 6 deaths divided by 78 cases diagnosed in 1992) than that observed (7.7%) if recurrent cases of tuberculosis among those on initial and intermittent treatment with *Isoprodiol* had not been promptly treated a second time with rifampicin, isoniazid, pirazinamide, or etambutol.



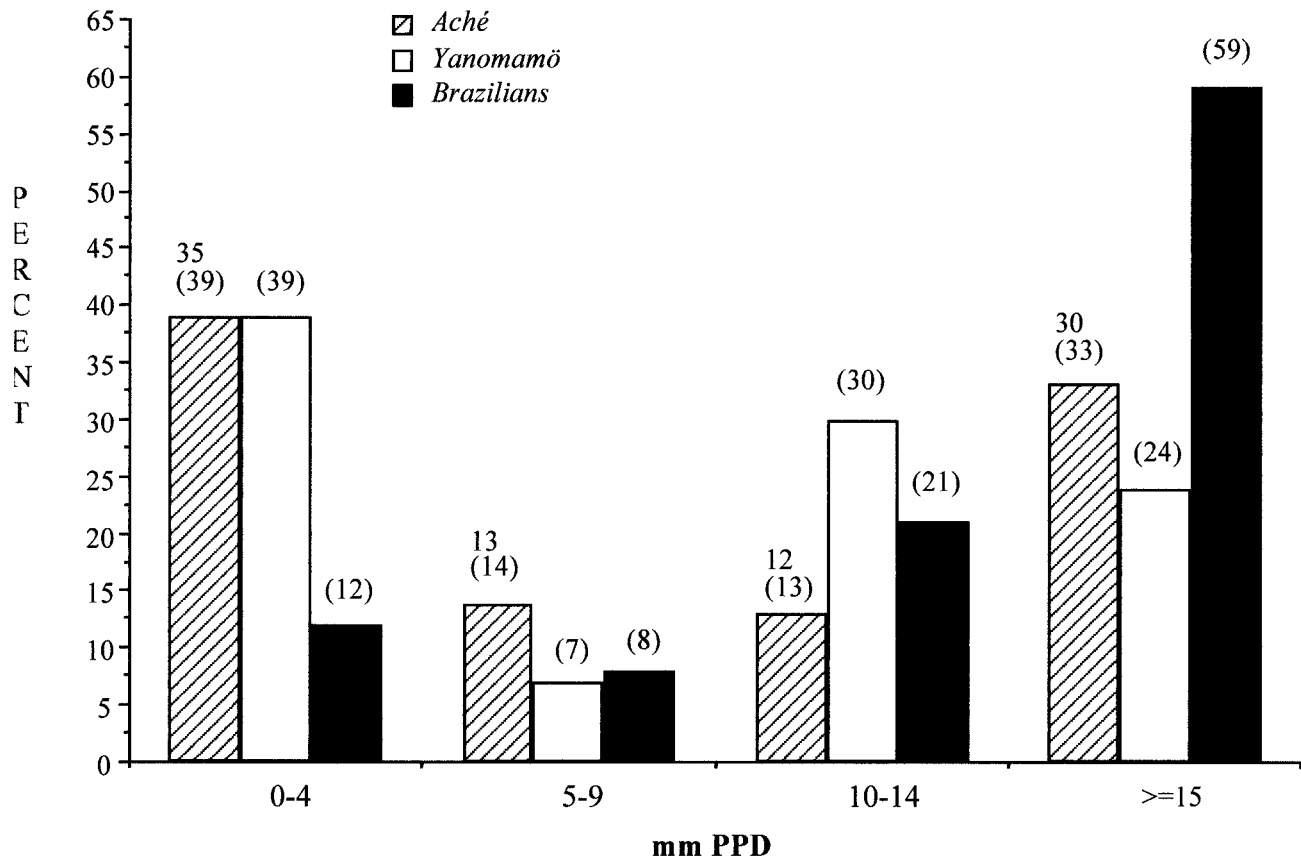
**Fig. 5.** Percent (indicated in parentheses) of Aché and Yanomamö individuals grouped by size of PPD induration. Numbers without parentheses indicate number of individuals in each group in Aché sample. Source of Yanomamö values is Sousa et al. (1997).

High susceptibility to tuberculosis is probably common in most South American Native communities. The median percentage of positive responses to tuberculin tests among adults of indigenous South American communities that have not been vaccinated with BCG at the time of the studies is 18.5% (range, 0–71;  $n = 24$  communities; Salzano and Callagheri-Jacques, 1988, Table 5.3), a lower rate than that observed among the Aché (64.6%). However, several communities in the sample have rates close to those documented in this study, mainly the Ona and Yámana (62%), the Alacaluf (50%), the Oajana (42%), and the Aymara (46%). These studies took place from the 1940s until the 1960s. If public health agencies have not intervened in these communities, rates of infection are likely to be much higher today.

In addition, unlike populations of European descent (Zopf, 1992, p. 164), but not unlike other native South American populations (Escobar et al., 2001, p. 288), Aché females are just as likely to have active disease as are males. But curiously, in most age intervals, females tend to be more responsive to tuberculin challenge than are males, even though males are just as likely to develop active disease. However, the differences are not statistically signif-

icant. In addition, and quite unexpectedly, the wealthy and better-nourished are more at risk of disease and infection than are others, and children immunized with BCG are *less* responsive to tuberculin challenge than are other children. Previous studies and the principle of immunological memory suggest that most children who have been vaccinated with BCG should have positive PPD test results (Menzies et al., 1992). But unexpectedly, analyses show a statistically significant negative correlation between BCG immunization and responsiveness to tuberculin challenge. To our knowledge, this trend has not been observed elsewhere.

Lastly, very few cases of extrapulmonary tuberculosis have been identified among the Aché. This is probably due in part to the observational methods used in this study, which are inadequate for detecting these types of cases. In addition, since children tend to be at higher risk of extrapulmonary tuberculosis, and some Aché children in the sample were vaccinated with BCG, it is possible that the vaccine provided protection. However, only 30% of individuals between birth and 20 years of age had been vaccinated with BCG. Fourteen Aché adults and 27 infants and children died between 1986–1998 of



**Fig. 6.** Percent (indicated in parentheses) Aché, Yanomamö, and nonindigenous Brazilians with active tuberculosis grouped by size of PPD induration. Numbers without parentheses indicate number of individuals in each group in Aché sample. Source of Yanomamö and nonindigenous Brazilian values is Sousa et al. (1997).

health conditions that were never diagnosed, and some of these deaths could have been cases of extrapulmonary tuberculosis. Possibly, some undiagnosed deaths in the younger age groups were caused by extrapulmonary tuberculosis. Thus, inadequate methods and BCG vaccination in the younger age groups may account for the finding that the Aché appear to experience low rates of extrapulmonary tuberculosis, even though they are very susceptible to pulmonary tuberculosis. It is important to note, however, that Nutels et al. (1967), who also reported low rates of extrapulmonary tuberculosis, found that the clinico-radiological and epidemiological aspects of tuberculosis epidemics among the Suiá and Txukahamae of Brazil were similar to those in populations previously exposed to the bacilli. This suggests that factors other than immunosuppression may be essential to understanding the high rates of active pulmonary tuberculosis among natives. Among individuals immunosuppressed by human immunodeficiency virus, 70% of patients developed extrapulmonary tuberculosis (Braun et al., 1990).

#### Th2 dominance

The observed ethnic differences in immune responsiveness by Aché and Yanomamö Amerindians

vs. populations composed of European and African descendants may be due in part to a high prevalence of diminished cell-mediated immunity, high rates of antibody production, and Th2-mediated activation among indigenous peoples (Sousa et al., 1997). Such Th2 immune responses compete with Th1-mediated defenses that are more effective against infectious diseases such as tuberculosis and malaria than are Th2 responses (Beyers et al., 1998). An important aspect of Th2 responses is overproduction of immunoglobulin E (IgE) (Janeway et al., 1999). South American Indians produce IgE at some of the highest levels ever reported anywhere in the world and yet they do not experience asthma, allergies, or the more severe manifestation of atopy, lethal anaphylaxis, that individuals with high IgE levels in other populations generally experience (Hurtado et al., 1999). Thus, researchers have been baffled by the finding that indigenous persons with extraordinarily high IgE levels are healthy and active members of their groups (Kaplan et al., 1980).

These observations raise several intriguing questions. BCG vaccination dampens positive responses to PPD skin tests among the Aché. Does Th2 dominance play a role in the lack of positive responses to PPD challenge among individuals vaccinated with

BCG? A lack of response to PPD challenge suggests no prior recognition by the immune system of the pathogen *M. tuberculosis*, but we know that these individuals were exposed because they received BCG vaccination. Other results suggest that some sort of recognition and containment of the pathogen must have taken place among those vaccinated with BCG. This is because these individuals were less likely to develop active disease than others who were not vaccinated. Although the test was not statistically significant, the magnitude of the effect, an odds ratio of 3.1, is considerable. This suggests that the pathogen was recognized, contained, but somehow not detected by cells that would then also respond to PPD challenge at a later point in time. Could BCG exert its efficacy through an immunological pathway that is different from those of Caucasian populations, and if so, what role does Th2 dominance play? In Africa, where populations also tend to have a skewed Th2 response, as many as 30% of healthy children vaccinated with BCG had negative PPD tests (Morbidity and Mortality Weekly Report, 1991). However, in the Aché sample, 93.3% of healthy infants and children who had been vaccinated with BCG had a negative response. Taken together, these observations point to intriguing ethnic differences responses to immunological challenges, with natives showing extreme levels of unresponsiveness.

### Homozygosity

Interactions between environmental and genetic factors probably give rise to this unique indigenous immune defense profile. An important environmental stimulus of Th2 responses is helminthic infection, which is endemic and ubiquitous among them (Salzano and Callagheri-Jacques, 1988; Hurtado et al., 1997). However, nonindigenous populations with helminthic infection rates as high as those observed among South American Indians do not overproduce IgE to the same extent (Lynch et al., 1993). This raises the possibility that genotypic effects, in interaction with helminthic infections, help shape the indigenous immune profile. On average, when compared to other populations, indigenous peoples have much less heterogeneity in highly polymorphic loci that control the immune system, the class I and II histocompatibility antigens (MHC), and the immunoglobulin allotype genes (Black, 1994). The Aché population studied here was shown to have low heterozygosity at some loci relative to African and European populations (Mingroni-Netto et al., 2001). Low genetic diversity is in turn associated with higher rates of illnesses in nonindigenous populations (Carrington et al., 1999; McNicholl et al., 2000). However, relationships between low genetic diversity and Th2 predominance, and interaction effects between genetic diversity and helminthic infection on Th2 predominance, have yet to be investigated (Gorman et al., 1997; Xu et al., 2000).

### Intergroup interactions

Intergroup interactions can exert important selective pressures in small populations in many ways. Of 129 groups that were contacted in Brazil in the early 1900s, 47 were already extinct by 1957 (36%) (Ribeiro, 1967, p. 92). Clearly, although interactions with outsiders can be devastating (McNeill, 1976), they do not always cause the extinction of small groups. Throughout human history, contact between populations has resulted in economic and social interactions that can range from beneficial to extremely detrimental to small human groups. First, social domination negatively impacts on economic and nutritional well-being, and it can induce stress which ultimately compromises the immune system (Cohen et al., 1991; Glaser et al., 1985, Syme and Balfour, Glaser et al., 2000).

Second, intergroup interaction can include a great deal of medical assistance or none at all. In recent contact situations, some small populations have been more fortunate than others, and have received both effective health assistance as well as buffering of some of the direct effects of social domination. Not surprisingly, such groups thrive demographically compared to the typical native experience (Early and Peters, 2000). At present, most South American indigenous groups receive some tuberculosis treatment from public health officials, but this help is for the most part very unpredictable. Because the national tuberculosis programs of Paraguay are poorly equipped and understaffed, cases are serendipitously identified and treated, creating ideal conditions for the emergence of multiple drug-resistant strains of *M. tuberculosis* (Farmer et al., 2000). In spite of the findings reported here, and discussed at length with Paraguayan health officials, the Ministry of Health has failed to institute systematic surveillance of tuberculosis cases in Aché and other native communities over the past 7 years. Therefore, due to inadequate governmental help, the quality of life and success of native lineages will be determined by naturally occurring immune resistance as occurred in Europe for hundreds of years, and in native populations of North America during the early 1900s (Rieder, 1989).

### Behavioral noncompliance

Noncompliance, or failure to adhere to tuberculosis medication protocols, is another important selective force. As occurs in many other populations (Farmer et al., 1991), even when the Aché receive assistance with tuberculosis medications, many individuals refuse to take medications regularly. In order to prevent the emergence of drug-resistant tuberculosis, medication intake was monitored carefully with the help of Aché healthcare workers in 1997–1998. A high treatment failure rate (34.6%) among patients treated with *Isoprodian* in 1992 without direct observed treatment (Farmer et al.,

2000) suggests that poor compliance was quite prevalent in this population. Informants report that those Aché who obtained or received medications for tuberculosis in a timely manner did not take *Isoprodian* daily, and sometimes skipped weeks at a time. Most Aché are now well aware that medical advances provide novel ways to improve health. However, while some Aché individuals engage in the aggressive pursuit of timely diagnoses and treatment, others do not, even though all Aché have had similar exposure to outsiders and Western education. If these behavioral decisions are a heritable component, compliant individuals are more likely to have healthy lives and to reproduce in turn than others who fail to comply. Those who fail to comply are at high risk of developing multiple drug-resistant tuberculosis.

It is well-documented that when patients' medication intake is not adequately monitored, the higher are the rates of acquired drug resistance. In addition, as the proportion of poorly treated patients in the community increases, the risk of transmission of resistant bacilli to family members also increases (Chaulet and Hershfield, 2000). For example, in Korea, the prevalence of resistant strains among patients with active tuberculosis fell from 27% to 6% from 1965 to 1995, as better treatment programs became more widely used (Hong et al., 1998). Thus, those protected from disease through behavioral choice, by choosing to comply to medication protocols, are similar to those protected by naturally occurring immune defenses, except that they are buffered from disease by a behavioral rather than an immunological mechanism. At present, and for as long as adequate healthcare is not made available, these mechanisms will continue to exert important selective pressures on native subpopulations that have no access to tuberculosis medications, and those that have some but not enough.

The diversity of immune responses that have resulted from the coevolutionary race between hosts and pathogens across initially distant populations now creates dynamic and complex epidemiological problems that plague once-remote South American Indian communities. In order to develop better treatment and disease-prevention strategies for these immunologically naive populations, we need to begin to unravel some of this complexity with programs that combine careful research with reliable medical assistance, and with programs that prevent exposure to yet more lethal pathogens such as HIV. Given the infection rates of tuberculosis among the Aché, their lack of resistance to pathogens novel to them, and the synergism between HIV and *M. tuberculosis*, if HIV appears, the population is likely to go extinct in a very short period of time. Aché susceptibility to tuberculosis infection is extreme by modern world standards, as it is likely to be to many other infectious agents. We suggest that this may be due to a combination of four factors: TH2 domi-

nance; low heterozygosity of loci involved in disease resistance; negative intergroup interactions by a conquering dominant society; and behavioral non-compliance to treatment regimes.

## CONCLUSIONS

This study suggests that to be effective, programs for native populations must use the following criteria. First, education on prevention and intervention needs to be the core of all public health and medical work in native communities. This helps to ensure that its members will report problems as soon as they arise, and that they will invest in health at the community and individual levels (Gyarfas, 1992; Weinehall et al., 2001). Given how quickly infectious pathogens can spread, there needs to be ongoing epidemiological surveillance at the local and community levels. As soon as the first cases are reported, public health agencies must act quickly, particularly in more acculturated communities that act as entries of epidemics into more remote and less accessible villages. Second, there need to be ongoing educational programs in place that teach individuals of all ages about the signs, symptoms, lethal outcomes, and prevention of illnesses such as AIDS that could quickly cause the extinction of native groups.

Third, programs must include well-planned, culturally appropriate, direct-observed treatment (DOT) protocols (Weis et al., 1994) in order to eliminate the problems of distrust caused by negative intergroup relations and poor compliance to medication protocols. DOT programs were developed to maximize the chance that people with tuberculosis complete treatment. They usually involve a trained healthcare worker who observes every dose of medication that a patient takes (Fujiwara et al., 2000).

Fourth, international agencies and governments should fund long-term national research programs that investigate prevention and treatment strategies best suited for native biology, taking into account:

- The efficacy and effectiveness of universal BCG vaccination in native groups as compared to other populations;

- The role of PPDs as a diagnostic tool in native populations with high numbers of false-negative test results;

- The prophylactic value and cost-effectiveness of drug treatments in highly susceptible native groups. In industrialized countries, persons with positive PPD tests are protected from active disease for life through prophylactic treatment with a combination drug, Isoniazid, for 6 months (Wang, 1999). This option is not available to peoples of developing countries (Comstock, 2000);

- The effects of macroparasite eradication on Th1 immune responses, and on resistance to tuberculosis in turn; and Alternative laboratory techniques to

detect active pulmonary disease. Polymerase chain reaction techniques can be used to detect *M. tuberculosis* in easy-to-collect cheek saliva and mucus in native patients who have difficulty producing sputum. It is also convenient to use when patients live in homesteads or villages too far from clinics for the collection of sputum 3 days in a row, and as soon as patients wake up.

In summary, in order to decrease the length of drug-sensitive tuberculosis epidemics and the emergence of drug resistance, within the next decade, international health agencies, in partnership with governments, will need to institutionalize programs that take into account the biological and cultural characteristics of indigenous groups. If international agencies fail to hold national ministries of health and governments accountable for this institutionalization, *M. tuberculosis* will continue to sap the lives, and the quality of life, of South American natives, just as it did 100 years earlier in North America (Rieder, 1989).

#### ACKNOWLEDGMENTS

We thank Alberto Yanosky (Fundación Moisés Bertoni), Calderoli Vargas (National Commission of Tuberculosis Control of Paraguay), Tim McCall (McLennan County Medical Education and Research Foundation), John McCall (University of Tennessee), John Wickman (Memphis Health Department), and Calderoli Vargas (National Tuberculosis Control Program, Paraguay) for providing logistical support. We are also grateful to Carlos Tykuanagi, Margarita Mbywagi, Iginio Cherygi, and other Aché friends, Anne Stone and Alicia Wilbur (Department of Anthropology, University of New Mexico), Inés Hurtado (Instituto Venezolano de Investigaciones Científicas), Dolly Smith (Puesto de Salud, Ygatimí, Paraguay), Lucy Aquino (World Wildlife Fund, Paraguay), Alberto Villalba (ILDES, Paraguay), Jonathan Padwe (Department of Environmental Studies, Yale University), and Beth Ratiagan, Julia Bauer, and Julie Griffin (Department of Anthropology, University of New Mexico) for assistance with various aspects of treatment and research. This research was made possible by a grant from the National Science Foundation to K.R.H. and A.M.H. entitled "Ecological Studies of Aché Foragers," and medical assistance funds were provided by the Avina Foundation. We are very indebted to the anonymous reviewers whose extensive comments helped us strengthen our main points.

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