

## EXOGENOUS REINFECTION AS A CAUSE OF RECURRENT TUBERCULOSIS AFTER CURATIVE TREATMENT

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### ABSTRACT

**Background** For decades it has been assumed that postprimary tuberculosis is usually caused by reactivation of endogenous infection rather than by a new, exogenous infection.

**Methods** We performed DNA fingerprinting with restriction-fragment-length polymorphism analysis on pairs of isolates of *Mycobacterium tuberculosis* from 16 compliant patients who had a relapse of pulmonary tuberculosis after curative treatment of postprimary tuberculosis. The patients lived in areas of South Africa where tuberculosis is endemic. Medical records were reviewed for clinical data.

**Results** For 12 of the 16 patients, the restriction-fragment-length polymorphism banding patterns for the isolates obtained after the relapse were different from those for the isolates from the initial tuberculous disease. This finding indicates that reinfection was the cause of the recurrence of tuberculosis after curative treatment. Two patients had reinfections with a multidrug-resistant strain. All 15 patients who were tested for the human immunodeficiency virus were seronegative.

**Conclusions** Exogenous reinfection appears to be a major cause of postprimary tuberculosis after a previous cure in an area with a high incidence of this disease. This finding emphasizes the importance of achieving cures and of preventing anyone with infectious tuberculosis from exposing others to the disease. (N Engl J Med 1999;341:1174-9.)

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POSTPRIMARY tuberculosis, which occurs many years after a primary infection, may develop as the result of reactivation of the endogenous, primary infection or as a result of a recent exogenous infection. Models developed by Sutherland and colleagues<sup>1</sup> and more recently by Vynnycky and Fine,<sup>2</sup> based on estimates of the annual risk of infection and the incidence of tuberculosis, have suggested that the relative contribution of exogenous reinfection increases in parallel with the incidence of the disease. However, data for use in evaluating these statistical models have been difficult to obtain. In only a few patients has there been reasonable proof of reinfection by a different organism after known previous infection.

Before the introduction of antituberculous medication, there was little recognition of the distinction between endogenous reactivation and exogenous re-

infection in patients who had multiple episodes of tuberculosis, since untreated established tuberculous lesions may be alternately active and dormant.<sup>3</sup> Effective treatment regimens made possible the sterilization of pulmonary lesions, but it was accepted that subsequent episodes of tuberculosis were almost invariably caused by endogenous reactivation.<sup>4</sup> The complete sterilization of a lesion became possible with improved treatment regimens, especially with the introduction of rifampin, a drug with a potent sterilizing effect. With short-course combination therapy consisting of isoniazid, rifampin, and pyrazinamide, the relapse rate dropped from 21 percent to 1 to 2 percent.<sup>5-7</sup> In this era of effective treatment regimens, the notion that multiple episodes of tuberculosis in one patient are almost always caused by endogenous reactivation may be questioned. It is now possible to characterize the genotype of *Mycobacterium tuberculosis* by DNA fingerprinting, which can show whether a new episode of the disease is caused by infection with the same strain that caused a previous episode or by a different strain.

In this study we used DNA fingerprinting to determine the relative frequency of endogenous reactivation and exogenous reinfection in patients with multiple episodes of postprimary tuberculosis. We aimed to determine the importance of this distinction in terms of the definition of cure, the efficacy of current treatment regimens, and the control of tuberculosis.

### METHODS

All the patients described in this report were treated in two neighboring suburban communities in metropolitan Cape Town, South Africa. These communities have a geographic area of 2.42 km<sup>2</sup> and a population of 34,294, of whom 99.7 percent are of mixed race. The number of reported cases of tuberculosis per year in these two communities is very high (1000 cases per 100,000 population per year).<sup>8</sup> The birth rate is 29.3 per 1000 population, and the infant mortality rate is 38 per 1000 live births. In general, people live in poor socioeconomic conditions, although most live in houses with running water and electricity. Two primary care clinics and an adjacent tertiary care hospital serve the area.

Before 1996, when all the elements of the World Health Organization (WHO) strategy of directly observed short-course

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**TABLE 1.** DISTRIBUTION OF PATIENTS WITH TUBERCULOSIS FOR WHOM CULTURES WERE AVAILABLE FOR ANALYSIS, ACCORDING TO SOURCE OF INFORMATION.\*

PATIENTS	RFLP DATA BASE		DISTRICT REGISTER	RATE OF CULTURE RECOVERY FOR RFLP†	INCIDENCE OF CULTURE-POSITIVE CASES
	SEPTEMBER 1992 THROUGH MAY 1998	JANUARY 1996 THROUGH MAY 1998	JANUARY 1996 THROUGH MAY 1998		
	no. of patients			percent	no./100,000/yr‡
Total	770§	279	339	82	ND
New patients	461	175	210	83	225
Patients requiring retreatment after previous cure	48¶	16	24	67	26
Others requiring retreatment	261	88	105	84	ND

\*RFLP denotes restriction-fragment-length polymorphism, and ND not determined.

†The rate of recovery of *M. tuberculosis* cultures for RFLP analysis was estimated as the number of patients with results in the RFLP data base from January 1996 through May 1998 divided by the number of patients with episodes in the register for the same period.

‡These rates were calculated only for new patients and patients needing treatment after cure, since other patients needing retreatment do not represent true incident cases.

§This value includes 698 individual cases with cultures plus 72 cultures from 55 patients for whom DNA was available for RFLP for two or more treated episodes.

¶This value includes patients from whom an RFLP analysis was available for an episode requiring treatment after a previous cure. For 16 of these cases, the RFLP result from the first episode was also available, and these patients thus constituted the study population.

treatment (DOTS) were implemented, all patients were treated at one of the primary care clinics by directly observed therapy with three drugs (patients needing treatment for a first episode [new patients]) or four drugs (patients needing treatment for a subsequent episode [returning patients]). Until 1996, there was no systematic surveillance for treatment failure, although for most patients a sputum sample was examined (directly and by culture) between the fourth and sixth months. With its implementation in 1996, the WHO DOTS strategy required an accurate recording of cases in clinic registers, the administration of directly observed therapy (four drugs for new patients and five drugs for returning patients), and surveillance for treatment outcome, including treatment failure. Except for multidrug-resistant infections, there was no surveillance for relapse.

### Patients

Patients included in this study had at least two episodes of postprimary pulmonary tuberculosis within the study period (between September 1992 and May 1998), with cultures from the two most recent successive episodes (referred to as first and second episodes) available for restriction-fragment-length polymorphism (RFLP) analysis and with cure as the outcome of the first episode. Extensive clinical histories of the included patients were obtained and included data on age, sex, medical history, status with regard to infection with the human immunodeficiency virus (HIV), findings on chest radiography, the results of sputum staining and cultures, drug sensitivities, treatment, and outcome. According to WHO criteria, cure was defined as the completion of a course of six to eight months of directly observed combination therapy (with isoniazid, rifampin, and pyrazinamide in a single tablet), compliance (attendance for the course of therapy, with at least 80 percent of prescribed doses taken), and a sputum culture positive for *M. tuberculosis* at diagnosis and at least one negative sputum culture at the end of treatment. All patients who needed treatment for a subsequent episode but who did not meet the criteria for previous cure were excluded from the study.

### *M. tuberculosis* Isolates

Sputum samples were stained and cultured at the laboratory that routinely served the clinics. Drug-susceptibility testing was performed by the indirect-proportion method in accordance with the guidelines of the South African National Tuberculosis Program. In September 1992, in the Cape Town communities described above, we initiated a prospective study in which all cultures positive for *M. tuberculosis* from patients residing in these communities were genotyped by RFLP and a data base of the results was established. To evaluate the representativeness of the patients included in the RFLP data base, they were compared with patients who had positive cultures in the district tuberculosis register for the period from January 1996 through May 1998 with regard to the clinical classification. The percentage of cultures obtained for RFLP analysis was calculated for both new and returning patients. These data were also used to calculate the annual number of cases of culture-positive pulmonary tuberculosis per 100,000 population.

Isolates of *M. tuberculosis* were genotyped by RFLP according to an internationally standardized method,<sup>9</sup> and the results were analyzed with GelCompar software (version 4.0, Applied Maths BVBA, Kortrijk, Belgium). For the RFLP data base, the extent of accumulated laboratory error was calculated by comparing successive DNA fingerprints for serial isolates collected during the first two months of treatment, according to the following formula: laboratory error rate equals the number of isolates with DNA fingerprints that failed to match the DNA fingerprints of the subsequent isolate, divided by the total number of serial isolates analyzed. To exclude the possibility of mixed infection, DNA was isolated from the entire culture, and all RFLP patterns were carefully analyzed to identify any background bands reflecting different strains. Analysis of the complete RFLP data base identified only five isolates with background bands. These isolates were excluded from further analysis.

The isolates included in this study were analyzed as follows. Genomic DNA was digested with *Pvu*II or *Hin*I, electrophoretically fractionated, and transferred to Hybond-N<sup>+</sup> membranes

(Amersham, Buckinghamshire, United Kingdom). The *Pvu*II digests were hybridized with an IS6110 3' probe (complementary to the IS6110 domain between nucleotides 631 and 875) that had been labeled by enhanced chemiluminescence. The *Hinf*I digests were hybridized with a <sup>32</sup>P-labeled MTB484(1) probe.<sup>10</sup> The respective RFLP patterns were visualized by autoradiography. The IS6110 3' DNA fingerprints from each patient's isolates were compared with those in the complete RFLP data base (with data gathered from September 1992 through May 1998) by means of the clustering formula known as the "unweighted pair-group method using arithmetic averages" and the Dice coefficient to determine whether the isolates belonged to a cluster (suggesting infection by recent transmission) or were unique (suggesting reactivation of a latent infection) within the communities studied.

A patient whose isolates of *M. tuberculosis* from the first and second episodes of postprimary tuberculosis were identical on RFLP analysis with each DNA probe was considered to have tuberculosis due to reactivation of endogenous infection. A patient whose isolates from the first and second episodes of postprimary tuberculosis were different was considered to have tuberculosis due to a new, exogenous infection.

## RESULTS

The rate of reported cases of culture-positive pulmonary tuberculosis from January 1996 through May 1998 was estimated to be very high (225 cases per 100,000 population per year for new cases and 251 per 100,000 per year for all true incident cases) (Table 1).

During the study period (September 1992 through May 1998), DNA from cultures of *M. tuberculosis* was available for at least one RFLP analysis for 698 patients. For the period from January 1996 (when reliable information became available for case notification as a result of the implementation of the DOTS strategy) through May 1998, the average rate of recovery of cultures of *M. tuberculosis* for RFLP analysis was estimated to be 82 percent (83 percent for new patients, 67 percent for patients needing retreatment after cure, and 84 percent for other patients needing retreatment) (Table 1). DNA from at least one episode was available for RFLP analysis for 48 patients considered to have tuberculosis requiring retreatment after cure. However, in only 16 of these 48 patients were the results of the RFLP analysis for two episodes available, and these 16 patients thus met the requirements for inclusion in the study: two episodes of postprimary pulmonary tuberculosis within the study period and cure as the outcome of the first of those two episodes.

The median age of these 16 patients was 35 years; 9 were women and 7 were men (Table 2). The median interval between cure and subsequent diagnosis (isolation of a subsequent culture-positive specimen) was 25.5 months. Fifteen patients (94 percent) were tested for HIV infection, and all 15 tested negative. None of the patients had a medical history of diabetes, end-stage renal disease, or cancer or had been treated with immunosuppressive drugs. Chest radiographs revealed evidence of cavitory disease in 11 patients during the first episode of tuberculosis and in 12 during the second episode of tuberculosis.

For 12 of the 16 patients, the RFLP patterns of the strains of *M. tuberculosis* responsible for the disease differed between the two episodes, indicating exogenous reinfection (Table 2 and Fig. 1). For the other four patients, the RFLP patterns of the *M. tuberculosis* strains were identical for the two episodes, indicating endogenous reactivation. Of the 16 patients, 4 had drug-resistant tuberculosis during the second episode (Table 2), which in 2 patients was caused by exogenous reinfection with a multidrug-resistant strain and in the other 2 patients (both resistant to only isoniazid) was caused by endogenous reactivation. In one of the latter two patients, drug-susceptibility testing performed during the first episode identified a fully drug-sensitive organism. However, during an episode before the two described in this study, resistance to isoniazid had been diagnosed. During the episode after cure, drug resistance was proved in only one of five cultures obtained, indicating that the resistance to isoniazid was borderline. In the other patient, no drug-susceptibility testing was performed on the isolate from the first episode.

Because exogenous reinfection most likely results from close contact with an adult who has active infection, isolates from the 12 patients with reinfection were studied in relation to the complete RFLP data base for the two communities (covering September 1992 through May 1998 and including 698 patients). It was found that 11 of the 12 isolates obtained during the second episode of tuberculosis from patients who had exogenous reinfection belonged to a cluster of strains present in the communities; for the remaining isolate no matching strain was identified in the data base.

Of the four patients with tuberculosis due to reactivation, two were older than the median age and two younger. The interval from cure to reactivation was longer than the median interval in one patient and less than the median in the other three. All four patients were infected with a strain that belonged to a cluster circulating in the community during their respective disease-free intervals.

## DISCUSSION

Using DNA fingerprinting, we found evidence that exogenous reinfection can have a dominant role in the pathogenesis of postprimary tuberculosis in adults in an area with a high incidence of the disease.<sup>1,2,11</sup> To our knowledge, there have been only two other reports of RFLP analysis of isolates from patients with repeated episodes of tuberculosis who were living in a high-incidence area.<sup>12,13</sup> These studies suggested that under conditions of endemic disease, the rate of endogenous reactivation far exceeds the rate of exogenous reinfection. However, these reports do not include a definition of cure or detailed information on the patients' drug regimens, compliance, or immune status. Furthermore, 15 patients (34 per-

**TABLE 2.** EPIDEMIOLOGIC AND CLINICAL CHARACTERISTICS OF 16 PATIENTS WITH POSTPRIMARY PULMONARY TUBERCULOSIS AFTER PREVIOUS CURE.\*

PATIENT NO.	AGE (YR)/SEX	INTERVAL BETWEEN EPISODES†	NEGATIVE SMEAR, SINGLE POSITIVE CULTURE		EXOGENOUS REINFECTION
			PREVIOUS EPISODE	SUBSEQUENT EPISODE	
		mo			
1	25/F	28	Yes	No	Yes
2	29/M	26	Yes	No	Yes
3	34/F	38	Yes	No	Yes
4	42/M	32	No	No	Yes
5	36/M	19	Yes	No	No (reactivation)
6	40/M	8	No	No	Yes
7	47/F	7	No	Yes	Yes
8	50/M	21	No	No	Yes
9	45/M	12	No	Yes	Yes
10	30/F	35	No	No	Yes
11	39/F	31	No	No	No (reactivation)
12	30/F	52	Yes	No	Yes
13	28/F	35	Yes	No	Yes
14	54/M	25	No	No	Yes
15	24/F	13	No	No	No (reactivation)
16‡	33/F	11	No	No	No (reactivation)

\*For Patients 1 through 14, RFLP patterns are shown in Figure 1. For Patients 13 and 14, the subsequent episode was diagnosed as multidrug-resistant tuberculosis; for Patients 15 and 16, the subsequent episode was diagnosed as tuberculosis resistant only to isoniazid.

†This interval is the time between the cure of the previous episode and the diagnosis of the subsequent episode.

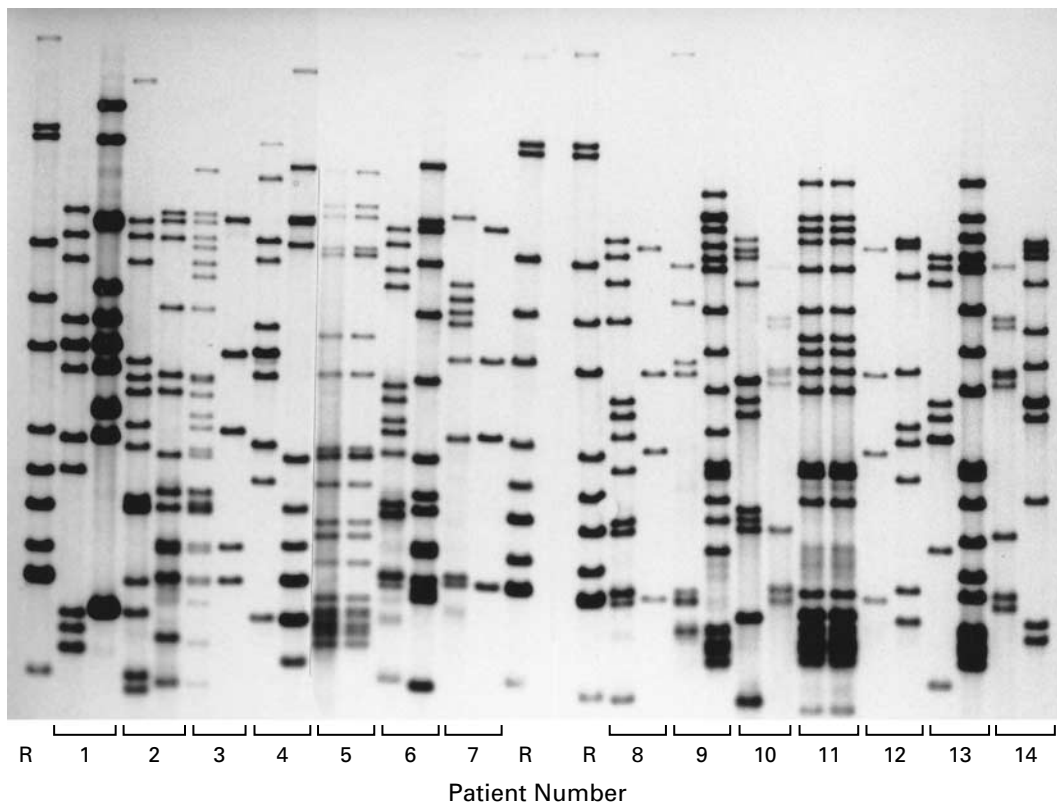
‡Patient 16 was not tested for HIV infection.

cent)<sup>12</sup> and 40 patients (49 percent)<sup>13</sup> were excluded because only a single culture was positive and the possibility of laboratory contamination was raised. If they had not been excluded, 90 percent of these patients would have been classified as having disease due to exogenous reinfection. Their exclusion might therefore have biased the results toward the importance of endogenous reactivation.

In our study, the rate of recovery of cultures of *M. tuberculosis* for RFLP analysis was lower for patients needing retreatment after cure than for other patients. The reason for this difference is not clear; it was not the result of any deliberate policy. The results of the study must, however, be viewed with caution because of the possibility of some unintentional bias. Nevertheless, there is no reason to suppose that strains from cases due to reinfection would be preferentially recovered as compared with those from cases due to reactivation, a condition necessary for such a bias.

In our study, we did not exclude patients with only a single positive culture, for the following rea-

sons. It has been shown that tuberculous lesions can yield an isolated positive culture.<sup>14</sup> There was no evidence of false positive cultures: all the patients received a diagnosis of active tuberculosis for both episodes on the basis of positive sputum-test results, the findings on chest radiographs, and the clinical history. The complete RFLP data base was analyzed to assess the extent of laboratory contamination, and the rate of accumulated error was found to be only 3.4 percent (17 discordant results among 499 serial isolates). On the basis of this error rate, it is possible that results for 1 isolate (3.4 percent of 32 isolates) may have been erroneous. Therefore, we believe that it is unlikely that the classification of disease as due to exogenous reinfection reflects extensive laboratory error, such as error due to cross-contamination or mixed infection at the first episode. This argument is further supported by the observation that in 11 of the 12 cases of exogenous reinfection, the strain responsible for reinfection was identified as one of a cluster of strains present in the communities. Only one isolate was retrieved from a patient with reinfec-



**Figure 1.** Restriction-Fragment–Length Polymorphism Patterns of 14 Pairs of Isolates of *M. tuberculosis* from Patients with Recurrence of Tuberculosis after Cure.

Lanes 1 to 14 show serial isolates from Patients 1 to 14, respectively. Lanes labeled R correspond to control cultures (strain MTB 14323).

tion for whom there was no matching isolate in the entire data base. This patient appears to have been reinfected outside the communities or by an undetected source within the communities.

All four patients who were found to have disease due to reactivation were infected with individual strains that belonged to a cluster circulating within the communities during these patients' respective disease-free intervals. The molecular definition of exogenous reinfection used in this study excludes the possibility of exogenous reinfection with the same strain. Therefore, it is possible that some of the patients considered to have reactivation actually had new, exogenous infection with the same strain. Our results may thus underestimate the extent of exogenous reinfection.

It has generally been believed that reinfection is more difficult to confirm than primary infection, because of the immune response to *M. tuberculosis* antigens that develops after primary infection. There are no empirical data on the changes in the level of immunity over time, but it is assumed that in immunocompetent persons, reinfection is rare during the

first two to five years after a first infection.<sup>2</sup> In our study, cases of reactivation tended to occur soon after the previous episode was cured, but many of the cases due to reinfection also occurred early after a previous cure. It has been shown in persons infected with HIV that reinfection can occur not only years after a previous infection (or episode of disease) but even during treatment for active tuberculosis.<sup>15</sup> In our study, in which all the patients tested for HIV infection were negative, reinfection occurred as little as seven and eight months after a previous cure. These results suggest that in immunocompetent persons living in an area where tuberculosis is endemic, reinfection and progression to active disease may occur at any time after treatment has been discontinued.

In patients previously treated and cured, a subsequent episode would be expected to represent endogenous reactivation. We found that exogenous reinfection has a predominant role in this population of patients, who have multiple episodes of active tuberculosis. In areas with a high incidence of tuberculosis, exogenous reinfection might also be a cause of the first episode of postprimary tuberculosis, since

the immunity that develops after primary infection followed by a period of latency cannot be expected to confer more protection against exogenous reinfection than the immunity that develops after an episode of active disease.

The controversy with regard to endogenous as opposed to exogenous pathogenesis of tuberculosis is of importance in the planning of clinical trials and national tuberculosis-control programs. If, in areas with a high incidence of the disease, postprimary episodes of pulmonary tuberculosis after previous cure result predominantly from exogenous reinfection, as indicated by our results, the effectiveness of a drug regimen cannot be evaluated on the basis of the relapse rate without the additional information provided by RFLP analysis of bacterial isolates. In the evaluation of national tuberculosis-control programs for areas in which the disease is endemic, RFLP analysis can prove the effectiveness of the currently used treatment regimens. "Cure" in a patient who later has another episode of tuberculosis is not necessarily an incorrect concept. The more likely possibility is that he or she has a new infection after the cure. The emphasis should thus be placed on achieving cure in patients and on prompt case detection to prevent reexposure to sources of active tuberculosis.

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