Table 4—*Frequency of Negative Sputum Smears in AIDS/ARC Patients Compared with a Control Group*

No. of Negative Smears	% AIDS/ARC (No. Evaluable)	% Non-AIDS/ARC Nonrisk Group (No. Evaluable)	Significance*
≥1	78.9 (38)	56.1 (57)	p<0.05
≥2	78.3 (23)	37.8 (45)	p<0.01
≥3	68.4 (19)	27.5 (40)	p<0.01
≥4	58.8 (17)	18.9 (37)	p<0.01
≥5	60.0 (15)	12.9 (31)	p<0.01

*χ^2.

HIV infection and TB had no pulmonary infiltrates seen on pretreatment roentgenograms.[4]

In view of the absence of cavitary disease in most patients with HIV infection, it is not surprising that sputum AFB smears are often negative.[3,4] In our series of 38 patients with AIDS/ARC and culture-proved pulmonary TB, only 45 percent had a positive AFB sputum smear compared with an 81 percent rate among 57 control patients who did not have AIDS/ARC and were outside known high-risk groups (p<0.001). Of the 15 AIDS/ARC patients with numerous sputum samples submitted, 60 percent had ≥5 negative smears compared with only 13 percent of 31 control subjects (p<0.01). In our study the rate of sputum smear positivity was low, even in patients with multilobar involvement or cavitation. The explanation for this observation is unknown. A large number of patients must be evaluated to establish the validity of this finding.

The percentage of patients with positive sputum smears in our patient population, 45 percent (17/38), which consisted principally of IVDAs with AIDS/ARC, is somewhat higher than that of Louie et al,[5] who found 31 percent (5/16) among a mixed group of gay/bisexual men and IVDAs, and somewhat lower than that found by Pitchenik et al,[6] 67 percent (8/12), among predominantly HIV-positive Haitians. The latter study,[6] however, must be interpreted with caution, as there were only 12 patients of whom three were considered by the authors as possibly not infected with HIV. These three patients had roentgenographic and clinical findings (including upper lobe disease, cavities, and tuberculin reactivity) similar to TB in non-HIV-infected patients and had only a weakly or moderately positive ELISA test for HIV antibody. No confirmatory HIV antibody test, such as Western blotting, was done for any of the ELISA-positive specimens in this study.

The 81 percent positivity rate for sputum smears observed in our study among non-AIDS and nonrisk group members is similar to the 74 percent positivity rate reported by Kim et al[7] among 977 patients with pulmonary tuberculosis treated at the Blue Ridge Sanatorium in Charlottesville, Va, between 1974 and 1978. As in our study, Kim et al[7] evaluated numerous sputum samples per patient (minimum of three) and used a concentration technique. Sputum smear positivity in other non-AIDS patient populations has varied widely, with rates as low as 22 percent, and is likely to be directly dependent on the smear technique used, the number of sputum samples examined, the extent of pulmonary involvement, and the presence or absence of cavities.[8-13]

Tuberculosis and HIV infection often coexist in endemic areas for these diseases. Acid-fast smears on sputum specimens are a relatively insensitive diagnostic test for pulmonary tuberculosis in this patient population.

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Microscopy - ZN

A Reevaluation of Sputum Microscopy and Culture in the Diagnosis of Pulmonary Tuberculosis*

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This prospective study was undertaken to determine the interpretation of "scanty-positive" acid-fast bacilli on microscopy and to reevaluate simultaneous microscopy and culture of sputum for the accurate diagnosis of pulmonary tuberculosis (PTB). A total of 2,560 specimens were processed from 727 patients. There were 435 positive specimens (17.0 percent), originating from 139 patients, 10 by microscopy only, 176 by culture only, and 249 on both microscopy and culture. Review of the hospital records showed that 107 patients had PTB, 1 had *Mycobacterium kansasii* colonization, and 31 were thought not to have PTB. Sensitivity and specificity were 53.1 and 99.8 percent for microscopy, 81.5 and 98.4 percent for culture, and 77.6 and 100 percent for microscopy and culture, respectively. Seventy-five microscopy specimens (46 patients) were reported as scanty-positive, of which five (four patients) were deemed false positives, yielding a positive predictive value of 93.3 percent. In those patients with positive sputum microscopy, acid-fast bacilli were detected in one of the first four specimens. Seven isolates (three patients) were mycobacteria other than tubercle (0.27 percent of specimens and 1.6 percent of mycobacteria cultured). Despite the ready availability of laboratory evidence of disease, only 73 percent of cases were diagnosed by ward staff and 36 percent notified by the primary physician. Eleven patients (10.3 percent) died, six of whom had not received diagnoses of PTB before death. Sputum microscopy and culture remains reliable despite Bayesian predictions when applied to a population with a decreasing incidence of tuberculosis.

(Chest 1989; 95:1193-97)

Pulmonary tuberculosis (PTB) remains the major health problem in developing countries. This also applies to [redacted] Africa, which has a wide gradation of health care facilities.[1] The presumptive diagnosis of active disease depends on the demonstration of acid-fast bacilli by microscopy, with definitive diagnosis by subsequent culture of *Mycobacterium tuberculosis*.[2] Both techniques may be subject to false positive and false negative error. A decreasing reliability of acid-fast bacilli on smear as a screening test for culture-positive pulmonary disease has been predicted as the prevalence of tuberculosis declines (Bayes' theorem). Studies in the United States, India, and Singapore have borne out this statistical prediction.[3-5] In view of this, the interpretation of "scanty-positive" specimens has become contentious. This study was instituted at Hillbrow Hospital, Johannesburg, to determine the interpretation of scanty-positive microscopy results and the sensitivity and specificity of Ziehl-Neelsen staining and mycobacterial culture in a black urban population, since a decline has been reported[6] in the overall prevalence in South Africa of patients notified of having tuberculosis. Microbiologic investigations were performed prospectively on all specimens submitted for mycobacterial study over a 100-day period, and the results were correlated with clinical data.

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Material and Methods

A prospective study was undertaken at the Hillbrow Hospital during the 100-day period April 15 to July 25, 1986. The mycobacterial results of sputum specimens of adequate volume and quality that were submitted to the diagnostic laboratories of the South African Institute for Medical Research were studied. Specimens were collected and submitted by ward staff according to routine practice. Sputum specimens submitted for bacterial culture were also analyzed for mycobacteria by the laboratory.

All technical preparations were carried out in a Bio-hazard vertical laminar flow cabinet, Model WVBR8 (Fibatron Filter Co), which was fitted with prefilters and a high-efficiency particle air filter. Approximately 2 ml of the specimen was transferred to a sterile, 10-ml, cork-stoppered glass test tube and the remainder refrigerated. Laboratory tests were made on [redacted]

Smears for [redacted] Staining and Microscopy Preparation

Clean unused glass slides stored in rectified spirits were air dried on a slide board. Sufficient material was removed from the glass test tube using a sterile wire loop and transferred to the glass slide. When the smear had dried sufficiently, it was methanol fixed. Slides were individually transferred to a special staining rack and were always kept apart to prevent cross-contamination. A 1 percent solution of carbolfuchsin was poured onto the slides and heated on a Bunsen burner until steam rose. The stain was left in contact with the smear for 10 min; then the stain was washed off the slide

RM 5991

by a gentle stream of filtered water, used for all washing steps. The slide was then flooded for 2 min with a 20 percent aqueous sulphuric acid solution. This additional procedure is thought to promote in the decolorization of weakly acid-fast bacteria that are likely to be nonpathogenic. After washing off the first decolorizing agent, the slide was flooded with an aliquot of a mixture of 1 ml of concentrated hydrochloric acid and 99 ml of rectified spirits for 5 min. This decolorizing mixture was then washed off and the smear counterstained with a 0.1 percent aqueous methylene blue solution for 60 s, and after gentle washing the slide was air dried.

The smear was examined by a trained microscopist for [redacted] positive smears were confirmed by a senior trained microscopist. Results were reported as: negative; a scanty number with fewer than 5/slide; a scanty number with 5 or more/slide; a moderate number of acid-fast bacilli (1 to 10/field); numerous acid-fast bacilli morphologically resembling *M tuberculosis* (more than 10/field).

Mycobacterial Culture

Immediately after the removal of sputum for smear preparation, 2 ml of a 4 percent aqueous sodium hydroxide solution was added to the remaining 2 ml of sputum in the glass test tube, which was then agitated for 15 min in a water bath at 37°C to mix, digest, and decontaminate the specimen. Thereafter, the test tube was centrifuged for 25 min at 2,000 g. The supernatant was discarded and the sediment was inoculated with a sterile wire loop directly onto buffered modified Lowenstein-Jensen medium so that neutralization was not required. The modified Lowenstein-Jensen medium consisted of 28.5 g KH_2PO_4 (Merck); 15 g Na_2HPO_4 (Merck); 0.75 g $MgSO_4 \cdot 7H_2O$ (Merck); 30 ml glycerol (Analar); 1,500 ml sterile distilled water; 25 ml 2 percent malachite green (Merck); 2,500 ml aseptically prepared beaten eggs; 150 mg crystalline sodium benzylpenicillin (Novopen) in 1 ml sterile distilled water. Two slopes with glycerol to enhance the growth of *M tuberculosis* and one slope containing pyruvate to enhance the growth of *M bovis* were inoculated. (Modified Lowenstein-Jensen medium with glycerol replaced by 30 ml of a 700 ml 2N NaOH and 100 ml 0.418 percent sodium pyruvate [Merck] solution titrated to a pH between 7.0 and 7.3). The slopes were incubated at 37°C and read at weekly intervals. If contaminating bacteria were seen after incubation for 1 week, a repeated decontamination procedure was carried out, using 4 ml of [redacted] nt aqueous sodium hydroxide on the remaining original sputum, which had been refrigerated. When sufficient growth appeared, identification procedures were performed and a rough colony count reported: − negative; positive with the actual colony count for counts fewer than 20 colonies; + for colony counts 20 to 99; + + for 100 to 200 colonies; + + + for approximately 500 colonies; and + + + + for confluent growth.

Mycobacterial Identification

A smear was prepared by transferring some of the growth to a clean, unused glass slide with a sterile wire loop. The specimen was fixed in methanol as a laboratory safety precaution. The smear was dried, then Ziehl-Neelsen stained. When both the macroscopic and microscopic appearance suggested *M tuberculosis*, an abridged identification procedure was done. If, however, mycobacteria other than tubercle bacilli (MOTT) were suspected, a comprehensive range of tests required for identification of the major pathogenic species was performed.

The abridged identification procedure was performed by transferring 1 mg of growth using a sterile loop into a bijou bottle containing 1 ml of 0.01% aqueous Tween 80 and several small glass beads. The contents of the bottle was mixed on a vortex shaker to break up and emulsify the growth. Two modified Lowenstein-Jensen slopes containing glycerol were inoculated with mycobacterial suspension. One was incubated at 25°C and the other at 37°C, and they were read after four days' incubation to detect rapidly growing MOTT bacilli. After incubation for two to four weeks, probable *M tuberculosis* strains showed no growth on the 25°C slope and approximately 500 colonies on the 37°C slope. If positive by the niacin test,[7] the organism was identified as *M tuberculosis* and assigned to the MOTT group as negative.

[redacted]

This information was used to categorize individual sputum culture results as: true positive (patient has PTB and sputum result positive); false positive (patient thought not to have PTB but sputum result positive), and false negative (patient has PTB but sputum result negative). Laboratory results were defined as true negative if both sputum microscopy and culture were negative. The records of these patients were not reviewed, since they could not have been retrospectively categorized on chart review alone as having PTB. None of these patients had a positive culture from nonsputum sources, *ie*, lung biopsy, bronchoscopy brushing or washings, urine, spinal fluid, pleural fluid, or bone marrow biopsy. Further, none had been notified as having PTB on clinical grounds nor had been referred to the pulmonary consultations service, which would have been the case if PTB was suspected but could not be documented. Clinical prediction rules were calculated from this categorization.

The patient's clinical course was recorded, and it was noted whether the ward staff had diagnosed and notified public health service.

Results

During the three-month period, 2,560 sputum specimens, which originated from 727 patients at Hillbrow Hospital, were processed for evidence of mycobacterial infection. A total of [redacted] specimens were positive for [redacted], representing 17.0 percent of all specimens processed. Ten specimens were positive on microscopy alone, 176 on culture alone, and 249 on both microscopy and culture. These originated from 139 patients. The [redacted] (Table 1). Specimens defined as true

Table 1—*Number of Sputum Specimens Submitted per Patient*

No. of specimens	No. of Patients	% of Specimens	Cumulative Percentage
1	236	9.2	9.2
2	132	10.3	19.5
3	84	9.8	29.4
4	73	11.4	40.8
5	54	10.5	51.3
6	47	11.0	62.3
7	30	8.2	70.5
8	25	7.8	78.4
9	12	4.2	82.6
10	12	4.7	87.3
11	11	4.7	92.0
12	7	3.3	95.3
13	3	1.5	96.8
15	4	2.3	99.1
22	1	0.9	100.0

Table 2—*Clinical Prediction Rules for Microscopy and/or Culture of Sputum for Tuberculosis*

	Microscopy	Culture	Microscopy and Culture
True positive	255	392	249
False positive	4	33	0
True negative	2,076	2,046	2,239
False negative	225	89	72
Sensitivity, %	53.1	81.5	77.6
Specificity, %	99.8	98.4	100.0
Positive predictive value, %	98.5	92.2	100.0
Negative predictive value, %	90.2	95.8	96.9
False positive rate, %	0.2	1.6	0
False negative rate, %	86.9	20.9	28.9
False positive diagnosis rate, %	1.5	7.8	0
False negative diagnosis rate, %	9.8	0.04	3.1

negative totaled 2,022. A range of one to 21 specimens was submitted (median, five) from such negative subjects. Two or more negative specimens were submitted in 89.1 percent of instances.

Following the review of hospital records, 107 patients were thought to have PTB, 31 had no evidence of PTB, and one patient had colonization by *M kansasii*. Microscopy and culture were analyzed in the light of this categorization to obtain clinical prediction rules. Microscopy alone had a sensitivity of 53.1 percent and specificity of 99.8 percent; culture had a sensitivity of 81.5 percent and specificity of 98.4 percent; and microscopy together with culture had a sensitivity of 77.6 percent and specificity of 100 percent (Table 2).

Scanty-positive acid-fast bacilli were seen on 75 smears. These were obtained from 46 patients, 42 of whom were thought to have PTB on review. *M tuberculosis* was cultured from all except ten scanty-positive specimens. Analysis of clinical records showed that five of these ten specimens originated from three patients who were thought to have active PTB. Two of these patients had numerous other microscopy and culture positive specimens. The third had three scanty-positive specimens, and it is uncertain why culture was negative. Five specimens (four patients) were deemed to be "false positive microscopy." From clinical prediction rules, a scanty-positive smear provides a false positive diagnosis rate of 6.7 percent and positive predictive value of 93.3 percent.

Analysis of microscopy data for [redacted] deemed to have active PTB showed that [redacted] bacilli (range, one to 12 specimens submitted) and that the remainder were [redacted] (Table 3).

[redacted]

The cumulative percentage of culture-positive *M tuberculosis* rises with the number of specimens sent, with all cases detected within eight specimens

Table 3—*Number of Sputum Specimens Submitted Before Acid-fast Bacilli Were Detected by Microscopy from Patients with Tuberculosis or MOTT Disease*

Specimen No.	No. of Patients	Cumulative Percentage
1	58	53.7
2	7	60.2
3	4	63.9
4	2	65.7
Total	71	
Not detected by microscopy	37	34.3
Total	108	100.0

(Table 4). One patient had five specimens sent, all of which failed to culture *M tuberculosis*, but three smears revealed acid-fast bacilli.

Seven of the isolates were shown to be MOTT bacilli and represented 0.27 percent of all specimens submitted and 1.6 percent of cultures. None were seen on microscopy. These had been obtained from three patients. Five specimens of *M kansasii* were produced by an asymptomatic patient who was judged to have colonization of a lung destroyed by previous PTB. *M fortuitum* obtained in a single specimen from another patient was thought to represent a contaminant. A MOTT that was not fully identified due to contamination of the primary culture by interfering bacteria was thought to represent a casual mycobacterium. No mixed MOTT and *M tuberculosis* cultures were obtained.

The diagnosis of active PTB was not made by the ward staff in 27 percent of these patients. Notification of patients with active PTB is required by law, but only 36 percent had been notified. Eleven of the patients with active disease died (10.3 percent), and only five of these had been diagnosed before death. One patient who died undiagnosed, due to a delay in obtaining the laboratory results, had four sputum specimens that were positive for acid-fast bacilli. Only two of the patients who died from tuberculosis were notified.

The 31 patients who on review were thought not to have PTB included two patients with a single specimen

Table 4—*Number of Sputum Specimens Submitted Before M tuberculosis was Cultured from Patients with Tuberculosis*

Specimen No.	No. of Patients	Cumulative Percentage
1	89	83.2
2	10	92.5
3	2	94.4
4	2	96.3
5	1	97.2
6	1	98.1
8	1	99.1
Not grown	1	0.9
Total	107	100.0

that grew MOTT and other microscopy- and culture-negative specimens. Three patients had single specimens read as "scanty-positive" microscopy that were negative on culture (one also having another negative specimen). We excluded nine patients with a single colony on culture, six of whom also had other negative specimens, and seven patients with fewer than ten colonies on culture, all of whom also had numerous other negative specimens. Of the remaining ten patients, four had + colonies on culture but at least two other completely negative specimens. Two patients had + colonies on culture in single specimens, and their pneumonia responded completely to antibiotic therapy. One patient had a single specimen submitted which was microscopically negative but had + + + colonies. He died of massive GI bleeding and had no evidence of chest disease. Only two of these patients had more than one culture-positive specimen (all with fewer than ten colonies) but they respectively had another three and 12 completely negative specimens. The remaining patient had two scanty-positive specimens, which were culture negative and a microscopy-negative specimen which grew six colonies. Her lobar pneumonia cleared completely with therapy. Clinically, eight of these 31 patients had normal chest x-ray films and fewer than ten colonies on culture, ten had lobar pneumonia that cleared completely with antibiotic treatment, one had a hydatid cyst, one hilar adenopathy only and MOTT-contaminated sputum, and one had tubo-ovarian abscess (no chest x-ray film available). While nine of the 31 patients had chest x-ray films compatible with PTB, they all had fewer than ten colonies cultured from a single specimen and numerous other culture-negative specimens together with a clinical course unlike tuberculosis. None of these 31 patients had been considered by ward staff to have PTB.

Discussion

Tuberculosis remains a significant health problem, particularly in the Third World.[1] The diagnosis rests on the detection of appropriately staining organisms and/or culture of *M tuberculosis*,[2] and the reliability of laboratory results must be constantly evaluated.

Sputum samples were positive by microscopy and/or culture in 17.0 percent of specimens. PTB was thought to be present in 107 of 727 patients who provided specimens (14.7 percent). It is in the range of 10 percent to 20 percent prevalence that false positive smears become important.[4] Unlike studies in the United States, India, and Singapore, which have borne out Bayesian predictions,[3-5,9,10] our study shows the continued reliability of Ziehl-Neelsen staining and microscopy.

e 2).

Absolute frequency of false-positive smears

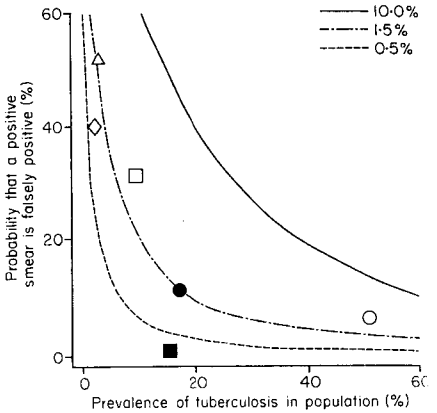

FIGURE 1. The relation of disease prevalence to the probability that a positive smear is false positive. The symbols represent the percentage of false positive smears relative to total positive smears as calculated by ■ present study, △ Boyd and Marr,[4] ◇ Narain et al, □ Truant et al,[9] ○ Chan et al,[10] • Blair et al.[11] According to predictions present study should have fallen on 1.5 percent line. (Redrawn from Boyd and Marr[4] with permission.)

The smear to culture positivity ratio was 66 percent, the highest reported (reported range, 22 to 67 percent).[3-5,9] This is of major public health importance, because there must be approximately 10^4/ml organisms in sputum for tubercle bacilli to be seen by microscopic examination,[2] and the smear-positive group is responsible for the majority of new cases.[1] This suggests that the majority of our cases are highly infective and are less likely to be missed in prevalence studies based on sputum microscopy alone compared with other studies.

The finding of scanty-positive (four or fewer) bacilli on smear microscopy has been stated to be due to artifact and should not be the basis of diagnosis.[12] In this study, however, the positive predictive value of scanty-positive smears (91.3 percent) remains excellent. In a patient, PTB should be di

The cumulative percentage positivity obtained with successive specimens in our study was better than that reported by Blair et al.[11] four should be submitted for a favorable cost/benefit ratio. Our definition of true negativity may have led to the underestimation of false negativity; however, for 89.1 percent of these specimens two or more sets had been submitted (median, five specimens). We did not review the clinical records of these patients, since even a highly suggestive clinical picture could not be confirmed as a definite case of PTB in the absence of bacteriologic proof, which we know was unavailable. These patients were, however, not referred to the pulmonary service for diagnosis, which would have been the case if PTB was suspected, and none had bronchoscopic examination.

are included in this study. Twelve false positive culture specimens from 11 patients, which yielded one colony only, should therefore be excluded. The remaining 21 false positive cultures included only eight specimens with more than 20 colonies, which more accurately reflects the culture false positivity and is similar to microscopy false positivity. Possible sources of error include transfer of bacilli from positive to negative specimens in the laboratory and clerical errors. Transfer of bacilli between specimens is related more to the quality of the technician than to the detail of the technical methods in the laboratory, and constant quality control in the laboratory is essential to reduce this source of error.[13] From a clinical and public health standpoint, however, it is prudent to consider all positives as true positive until proved otherwise. Tracheal or nasopharyngeal tuberculosis can account for positive microscopy and culture results, but is not addressed in this study of PTB.

MOTT bacilli do not constitute a significant proportion of mycobacteria in southern Africa (0.11 to 12 percent),[14-16] when compared with those pertaining to worldwide studies (0.5 to 48 percent).[17] MOTT accounted for 0.6 percent of cultures in our laboratory, a fraction of our laboratory but only false negativity findings.

Unfortunately, our study revealed that despite the positive results obtained in the laboratory, the diagnosis of tuberculosis was not made by the physicians caring for the patients in 27 percent of cases, primarily owing to an excessive workload and the lack of follow-up of available microscopy and, especially, culture results. Patients were located by follow-up by primary health care nurse and public health service after laboratory notification of the case. Particularly worrisome is that 11 patients died without the diagnosis of tuberculosis being considered by ward staff. This is similar to US studies in which undue delays in initiating therapy occurred[18] or where the diagnosis was only made by autopsy.[19]

Up to 15 specimens were submitted from patients when multiple positive microscopy results had already been obtained. We recommend that when three microscopy positive smears have been obtained, the patient should be notified and treated, since no patient deemed not to have PTB had more than two microscopy positive smears.

Notification of positive cases of PTB by physicians was abysmal in our series, and a similar problem may exist internationally. Laboratory notification was complete, but delayed diagnoses and infective cases were discharged from the hospital without treatment which has significant public health implications. The timely and rational clinical application of the results of laboratory investigations, which remain extremely reliable despite Bayesian predictions, can only result in a decrease in a major Third World health problem.

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