Geget (2004) 4 : 61 - 69

Original Article

The Booster Phenomenon in 2-Step Tuberculin Skin Testing in Hemodialysis Patients

Bahia Mostafa, Mona Elattar, Rasha Gamal El-Din and Hossam Masoud*

Departments of Pediatrics and Chest, Faculty of Medicine, Cairo University, Egypt.*

ABSTRACT

Background: Tuberculosis remains a significant health problem for patients receiving long-term hemodialysis (HD). The greater risk of TB is caused by an increase in the likelihood of progression from latent infection to active disease, most likely because of the impaired cell-mediated immunity associated with end-stage renal disease. Consequently routine TB screening of this population is recommended on an annual basis in the dialysis unit. The tuberculin skin test (TST) remains the most useful screening tool.

Objectives: To study the significance and frequency of the booster phenomenon in 2-step tuberculin testing of HD patients.

Methods: Twenty outpatients in the hospital-based hemodialysis center of the Children's Hospital, Cairo University, were screened for tuberculosis with the TST between September and October 2004. To determine the frequency of booster phenomenon, patients with less than 10 mm indurations in the intial TST were given a second test 7 days later. The results were compared with clinical and radiological data.

Results: One of the twenty patients (5%) had a significant tuberculin reaction (≥ 10 mm) on the intial TST. The booster phenomenon was detected in 5 of 19 patients (26.3%) who had a negative reaction (< 10 mm) to the intial test. These results show the significant rates of TST positivity and the booster effect in hemodialysis patients. There was no significant relationship between age, sex, cause of renal failure, hemodialysis duration, serum albumin levels, nor hemoglobin levels with the booster effect. The only significant correlation was detected between serum Ca level and the booster effect ($p = 0.014$).

Conclusions: The 2-step tuberculin testing procedure may be an effective tool to minimize the booster effect, thus allowing accurate monitoring of subsequent tuberculin conversion rates in hemodialysis patients thus detecting patients justified for active treatment of TB.

INTRODUCTION

Patients with end stage renal disease on regular hemodialysis (HD) are at risk to develop tuberculosis (TB) six to 16 times more frequently than other members of the community[1,2]. The greater risk of TB is caused by an increase in the likelihood of progression from latent infection to active disease due to the impaired cellular immunity in chronic renal failure[3]. The high incidence of extra-pulmonary disease may be a significant factor in the delay in diagnosis of TB in these patients. Consequently, routine TB screening of this population is recommended on an annual basis in the dialysis units especially in countries were TB is endemic[4]. The tuberculin skin test (TST) remains the most useful screening tool[5,6], and it is also considered the "gold standard" for latent TB infection[7]. Repeating TST of uninfected persons does not sensitize them to tuberculin. However, delayed-type hypersensitivity to antigens like tuberculin resulting from mycobacterial infection or bacilli Calmettte-Guerin (BCG) vaccination may

gradually wane with years. Although subsequent intial skin testing may be negative for TB, the stimulus of a first test, may boost or increase the size of the reaction to a second test administered one week to one year later and thus may suggest an apparent but false tuberculin conversion[6]. This phenomenon has come to be known as the booster effect. The significance and the frequency of the booster phenomenon in sequential testing of HD patients have not been determined. Therefore, we examined the significance and the frequency of the booster phenomenon in 2-step tuberculin testing of these patients.

AIM OF THE WORK

The purpose of this study was to examine the significance and frequency of the booster phenomenon in 2-step tuberculin skin test in hemodialysis patients. The detection of these booster reactions will decrease the number of apparent - but - false tuberculin conversion.

SUBJECTS AND METHODS

The study was carried out on 20 patients on hemodialysis, from the Nephrology Unit, Children's Hospital, Cairo University. Testing was done between September and October 2004. The study was approved by the ethical committee of the department.

Our dialysis patients had similar social backgrounds and the majority were from the moderate social class. All underwent dialysis for an average of 2 to 3 hours three times a week. Patient charts were reviewed for demographics (age, sex, duration of hemodialysis, cause of renal failure), medical history including prior TB disease and BCG vaccination, meticulous clinical examination, and laboratory values (hemoglobin, total leukocytic count, albumin, Na, K, Ca, pH, BUN, creatinine, and liver function tests). Chest x-ray and tuberculin testing using the Mantoux technique with 0.1 ml (5 tuberculin units) of purified protein derivative (PPD) was intradermally injected into the volar surface of the forearm that did not have the arteriovenous shunt. Areas of skin with scars, lesions, or visible veins were avoided by a minimum of 30 mm of skin. Results were interpreted 48 hours following injection. Tuberculin positivity was defined as an induration of $\geq$ 10 mm. Patients with less than 10 mm indurations in the intial test were given a second test 7 days later to determine the development of the booster phenomenon. The booster phenomenon was defined as positive if induration from the TST-2 was 10 mm or more and measured at least 6 mm more than that for TST-1. The obtained data were then tabulated and statistically analyzed using Pearson correlation test. A p-value of less than 0.05 was accepted as evidence of statistical significance.

RESULTS

Out of 20 patients 5 were females (25%) and 15 were males (75%) (Fig. 1). The age of the studied patients ranged between 4-13 years with a mean of 9 ± 2.15 years. The patients had been undergoing dialysis for an average of 17 ± 11.3 months. A BCG scar was detected in 2 (10%) patients. The etiologic factor for renal failure was obstructive uropathy in 4 (20%),

glomerular disease (GD) in 4 (20%), cystinosis in 2 (10%), and unknown (UNK) in the majority of patients 10 (50%) (Fig. 2).

Intial tuberculin reactivity was classified into the following 4 ranges of induration:

No induration to tuberculin in 7 patients (35%), 1 to 4 mm in 7 (40%), 5 to 9 mm in 5 (25%) and 10 to 15 mm in 1 patient (5%) (Table 2). All the 19 patients with less than 10 mm induration were given a second tuberculin test 7 days later, the induration to tuberculin was classified similarly: No induration to tuberculin was detected in 4 patients (25%), 1 to 4 mm in 4 (20%), 5 to 9 mm in 6 (30%) and 10 to 15 mm in 5 (25%) (Table 2). Thus the booster effect was detected in 5 patients (26.3%) of 19 patients who had a negative reaction to the intial TST. As shown in table 2, the mean size of induration was markedly increased in TST-2 compared with that in TST-1 (2.09 mm versus 6.9 mm, $p < 0.001$).

There was no significant relationship between age, sex (Table 3), cause of renal failure (Table 4), hemodialysis duration, serum albumin levels, liver enzymes, hemoglobin, WBCs levels, serum K or pH levels, blood urea and serum creatinine with the booster effect (Table 1, Figs. 2, 3, 4 & 5). The only significant correlation was found between serum Ca level and the booster effect ($p = 0.014$) (Table 1, Fig. 5).

Table 1: Booster phenomenon in relation to demographic and laboratory data of patients.

	Booster phenomenon +ve		Booster phenomenon -ve		p value
	Mean	± SD	Mean	± SD	
Age	7.8	2.02	9.50	2.56	0.171
Dialysis duration	13	12.04	17.53	11.29	0.484
HB	9.04	1.62	8.97	1.52	0.965
WBCs	6.9	1.61	7.36	1.93	0.662
BUN	90.80	11.26	73.53	18.88	0.088
Creatinine	6.60	2.15	6.39	1.45	0.694
Na	133	5.03	134	2.96	0.539
K	5.84	.72	5.02	1.00	0.113
Ca	9.86	0.58	8.8	0.75	0.014*
pH	5.80	2.11	6.27	1.86	0.694
Albumin	4.14	0.42	4.06	0.52	0.493
ALT	72.4	79.52	46.73	34.31	0.930
AST	41.4	45.71	41.00	35.04	0.861

Table 2: Comparison of the change between TST-1 and TST-2*.

Size of induration to tuberculin (mm)	TST-1	TST-2
0	7	4
1-4	7	4
5-9	5	6
≥ 10	0	5
Mean induration (mm)	2.09	6.9

* 19 patients with induration less than 10 mm to the intial TST had a second tuberculin test 7 days later, $p < 0.001$.

Table 3: Sex effect on booster phenomenon.

	Booster phenomenon +ve		Booster phenomenon -ve		p value
	No.	%	No.	%	
Male	5	100	10	66.7	0.266
Female	0	0	5	33.3	

Table 4: Cause of renal failure in relation to booster phenomenon.

Cause of renal failure	Booster phenomenon +ve		Booster phenomenon -ve	
	No.	%	No.	%
GD	0	0	4	26.7
Unknown	2	40	8	53.3
Cystinosis	0	0	2	13.3
Obstructive	3	60	1	6.7

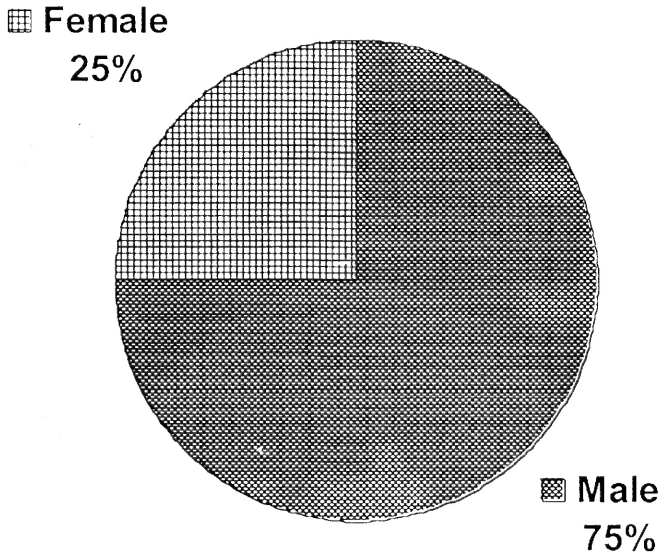

Fig. 1: Sex distribution among studied cases.

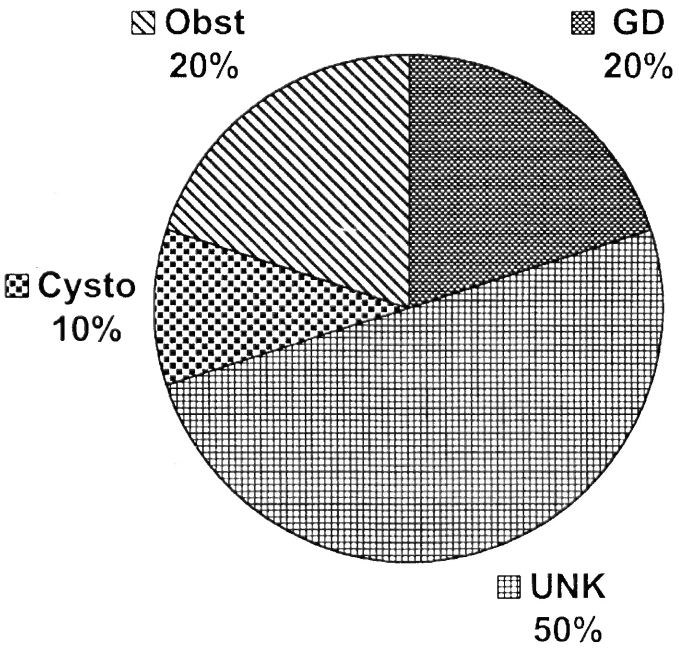

Fig. 2: Causes of renal failure among studied cases.

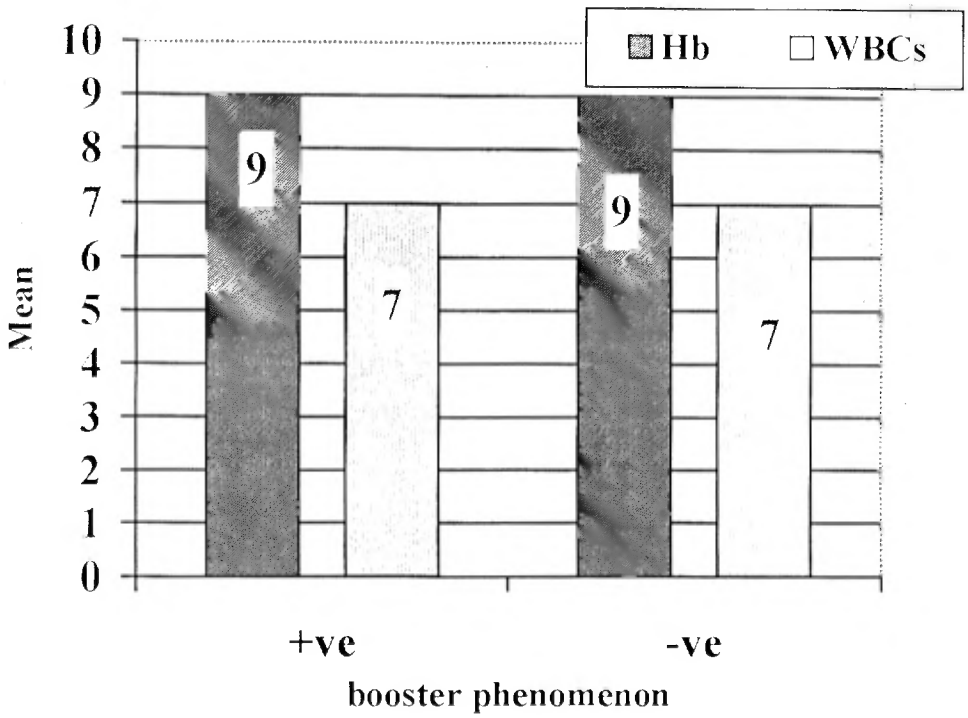

Fig. 3: Hb and WBCs levels of studied cases in relation to booster phenomenon.

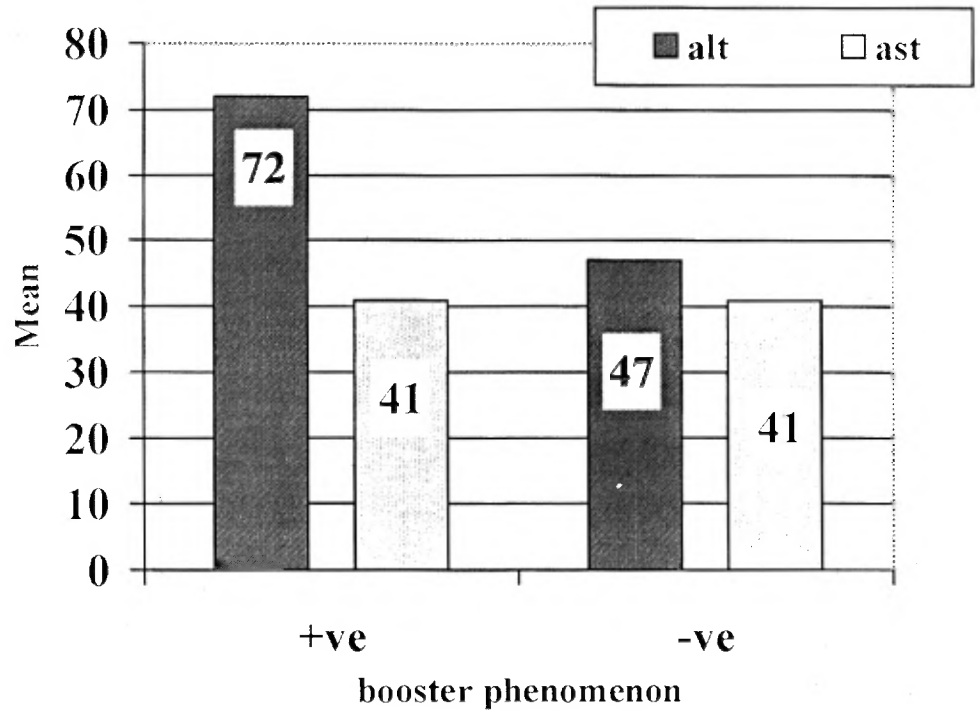

Fig. 4: Liver enzymes of studied cases in relation to booster phenomenon.

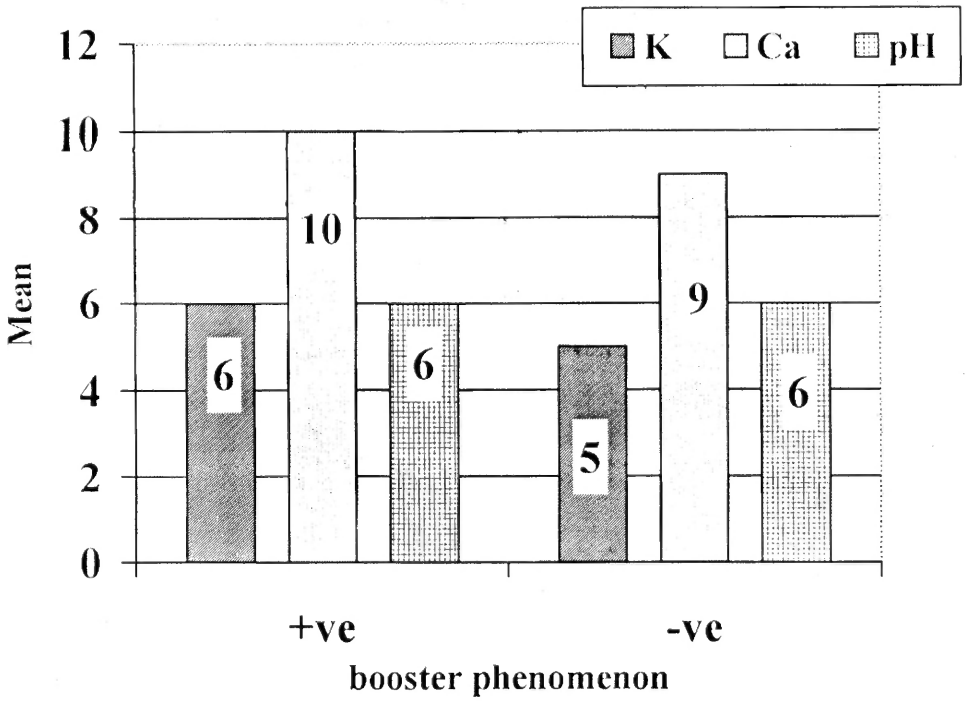

Fig. 5: Serum K, Ca and pH levels of studied cases in relation to booster phenomenon.

DISCUSSION

Tuberculosis remains a significant health problem for patients receiving long-term hemodialysis (HD)[8]. Because of the immunity depression, patients with chronic renal failure undergoing hemodialysis are at increased risk for developing infections, Mycobacterium tuberculosis (MTb) in particular[9]. Patients receiving hemodialysis (HD) are at risk to develop tuberculosis (TB) six to 16 times more frequently than other members of the community[1,2]. For that reason, there has been an increased awareness of the need to vigorously promote TB control measures, including screening and the use of prophylactic therapy for TB infection to prevent the development of active disease in high risk children on hemodialysis[10].

Periodic use of TST is valuable for the surveillance of patients at risk for developing TB. The test is neither 100% sensitive nor 100% specific because of cross-reactivity of other mycobacterial antigens, faulty techniques of application and reading, or immunologic abnormalities and nutritional status of the host. Despite these difficulties, the TST is an important method for detecting MTb infection[5,6].

In our study we found a 5% rate of TST positivity in the 20 patients undergoing dialysis who were tested with the intial TST. This finding was much lower than those of Woeltje et al., Smirnoff et al., and Akcay et al., who have shown the high prevalence of tuberculin positivity (16%-46%-35.8%). However, these results should not be extrapolated to all patients receiving HD. Each country should give their patients the TST to ascertain TB infection rates specific to their populations[9].

The booster effect is defined as an initially negative TST in a patient whose delayed-type sensitivity reaction has

diminished with time but whose results from a subsequent test are boosted to a positive reaction by the test itself[12]. The current concept of the booster phenomenon is made on the basis of waning of delayed-type sensitivity and its recall by the minor stimulus of a skin test. The detection of these booster reactions will decrease the number of false skin tests[13]. We identified rates of the booster phenomenon in the HD patients tested. Of nineteen patients in our study whose intial TST was negative for TB, 26.3% had a positive tuberculin reaction on the second test. This finding was slightly lower than that of Akacy et al., who reported a rate of booster phenomenon of 29.4%.

We detect the booster phenomenon in 5 of 19 patients (26.3%). However there are several limitations to our study. First, the small size of this study. Second, some of our patients had a history of BCG vaccine. BCG vaccination is the most common factor for tuberculin reactivity and the development of booster phenomenon[14,15].

The 2-step tuberculin testing is an essential means of distinguishing new TB infection from the booster phenomenon, according to the recommendations of the Advisory Council for the Elimination of Tuberculosis[5]. When TST of HD patients is repeated periodically, an intial 2-step approach can reduce the likelihood that a boosted reaction will be misinterpreted as a recent infection[8,16]. If the first TST result is negative for TB, a second test should be administered 1 week later. A positive result on the second test probably indicates boosting from a past infection or prior BCG vaccination. If the second result is negative for TB, the patient is probably not infected or is anergic; however, a positive reaction to subsequent tests would indicate a true TST conversion[8,17-19].

In conclusion, these results show the significant rates of TST positivity and the booster effect in hemodialysis patients. The 2-step tuberculin testing procedure may be an effective tool to minimize the booster effect, thus allowing accurate monitoring of subsequent tuberculin conversion rates detecting patients justified for active treatment. Further investigations are required to ascertain the true significance of this boosted reaction among hemodialysis patients.

REFERENCES

1. **Woeltje, K.; Mathew, A.; Rothstein, M.; Seiler, S. and Fraser, V. (1998):** Tuberculosis infection and anergy in hemodialysis patients. Am. J. Kidney Dis.; 31: 848-852.
2. **Imon, T.; Paul, S.; Wartenberg, D. and Tokars, J. (1999):** Tuberculosis in hemodialysis patients in New Jersey: a statewide study. Infect. Control Hosp. Epidemiol.; 20: 607-609.
3. **Cohen, G.; Hagg-Weber, M. and Horl, W. (1997):** Immune dysfunction in uremia. Kidney Int.; 52 (suppl 62): 579-582.
4. **Murhty, B. and Pereira, B. (1997):** A 1990s perspective of hepatitis C, human immunodeficiency virus, and tuberculosis infection in dialysis patients. Semin. Nephrol.; 17: 346-63.
5. **Centers for Disease Control and prevention (1995):** Screening for tuberculosis and tuberculosis infection in high-risk population. Mor. Mortal Wkly Rep. M.M.W.R.; 44 (RR-11).
6. **Centers for Disease Control and prevention (2000):** Targeted tuberculin testing and

treatment of latent tuberculosis infection. Mor. Mortal Wkly. Rep. M.M.W.R.; 49 (RR-6).

7. **Reichman, L. (1998):** A scandalous incompetence. Continued Chest; 113: 1153-4.
8. **Akcay, A.; Erdem, Y.; Altun, B.; Usalan, C.; Agca, E.; Yasavul, U.; Turgan, C. and Caglar, S. (2003):** The booster phenomenon in patients receiving long term hemodialysis. Am. J. Infect. Control; 31 (6): 371-4.
9. **Poduval, R. and Hammes, M. (2003):** Tuberculosis screening in dialysis patients - is the tuberculin test effective? Clin. Nephrol.; 59 (6): 436-40.
10. **Enarson, D. (2004):** Use of the tuberculine skin test in children. Pediatr. Respir. Rev.; 5 Suppl A: S135-7.
11. **Smirnoff, M.; Patt, C.; Seckler, B. and Adler, J. (1998):** Tuberculin and anergy skin testing of patients receiving long-term hemodialysis Chest; 114 (3): 947-8.
12. **Wauters, A.; Peetermans, W.; van den Brande, P.; De Moor, B.; Evenepoel, P.; Keuleers, H.; Kuypers, D.; Stas, K.; Vanwalleghem, J.; Vanrenterghem, Y. and Maes, B. (2004):** The value of tuberculin skin testing in hemodialysis patients. Nephrol. Dial. Transplant.; 19 (2): 433-8.
13. **Menzies, D. (1999):** Interpretation of repeated tuberculin tests. Am. J. Respir. Crit. Care Med.; 159: 15-21.
14. **Menzies, D. (2000):** What does tuberculin reactivity after bacille Calmette-Guerin vaccination tell us? Clin. Infect. Dis.; 3 (supp l3): s71-74.
15. **Wang, L.; Turner, M.; Elwood, R.; Schulzer, M. and FitzGerald, J. (2002):** A meta-analysis of the effect of Bacille Camette Guerin vaccination on tuberculin skin test measurements. Thorax.; 57: 804-809.
16. **Kursat, S. and Ozgur, B. (2001):** Increased incidence of tuberculosis in hemodialysis patients. Am. J. Nephrol.; 21: 490-3.
17. **Korztes, A. and Gafter, U. (1999):** Tuberculosis prophylaxis for the chronically dialysed patient – yes or no? Nephro. Dial. Transplant.; 14: 2857-2859.
18. **Rose, D. (2000):** Benefits of screening for latent Mycobacterium tuberculosis infection. Arch. Intern. Med.; 160: 1513-1521.
19. **Jasmer, R.; Nahid, P. and Hopewell, P. (2002):** Latent tuberculosis infection .N. Engl. J. Med.; 347: 1860-1866.