

## CHAPTER V

### REVIEW OF LITERATURE

A ten-year literature search for articles on drug resistance among pulmonary tuberculous patients and risk factors/predictors was done using Compact Cambridge, Medline, 1991. Index Medicus issues from January to August, 1992 were also reviewed. Topics for the search were divided into: (1) PTB (2) antituberculosis drugs (3) drug resistance (4) risk factors/ predictors. Selected topics were photocopied from available journals. References used in the selected articles deemed useful for the study were also obtained. Articles which were not available in Thailand were obtained from the Philippines, Japan and the United States.

The published articles mostly dealt on prevalence of drug resistance and emergence of resistant strains on the different anti-tuberculosis medicines included in the culture and sensitivity medium. They were descriptive exploratory in nature.

An article useful in the research was the study on host determinants of susceptibility to *Mycobacterium tuberculosis* by Sifford and Bates. In the paper, the authors claimed that acquired resistance is mediated via macrophages and controlled by T-helper cells. Therefore, concurrent

disease states and use of immunosuppressive agents decrease one's capability of developing immunity to the tubercle bacilli.<sup>(25)</sup>

A considerable number of papers were retrospective; two papers were prospective studies. The retrospective articles were exploratory and dealt on prevalence of resistance to the anti-tuberculosis drug; single, 2-drug or more drugs. The prospective researches aimed to identify epidemiologic factors for drug resistance. In all the papers, what was outstanding was the higher prevalence of drug resistance among patients who were previously treated for tuberculosis. However, none of the authors specified whether the patients evaluated took adequate therapy at the prescribed time or they were cases of treatment failure or non-compliant patients.

Shennan on his work on African subjects in Malawi defined "previous treatment" as any treatment for tuberculosis given at anytime prior to admission to any 3 main Malawi Hospitals which were his study settings. There were 39/75 (52%) treated patients with cultures resistant to at least one drug compared to 44 out of 234 (19%) of untreated cases. All seven patients (9%) with resistance to isoniazid, para-aminosalicylic acid, and streptomycin gave history of previous treatment.<sup>(18)</sup>

Aitken made a prospective study in the United States to assess the ability of risk factors to predict presence of

drug-resistant organisms in tuberculous patients. In his research, 13% of the patients (101/766) were drug-resistant cases. Of the 101 patients, 60% were Asians. Thus, he concluded the need to routinely test Asian immigrants with tuberculosis for drug resistance. He observed the poor ability of the risk factors (alcoholism, previous antituberculosis treatment, history of adverse reaction and patient unreliability) to separate the 40 (40%) non-Asians with drug resistant disease from the group of 513 non-Asians with drug-sensitive microorganisms. Because he had high false positive rate, he believed that the risk factors were insensitive and so believed that the presence of drug-resistant disease in non-Asian patients can not be predicted.<sup>(15)</sup>

On the other hand, Peter Barnes also conducted his study in California on epidemiologic factors that predicted drug resistance by using his patients as subjects<sup>(26)</sup>. From his patients with culture positive tuberculosis, he observed a higher rate of drug resistance among those with prior treatment (presumably secondary drug resistance) SDR than those without previous therapy (presumably primary drug resistance) PDR. It was 26% for SDR vs 13% for PDR. A striking difference was noted if the country of origin of the subjects was taken into account. Forty two percent (42%) of patients who came from areas with high incidence of tuberculosis manifested drug resistance while only 13% of patients coming from low incidence areas developed resist-

ance. He also observed that the rate of drug resistance among patients who have never been treated for tuberculosis but came from areas with high TB incidence rate was higher : 23% vs 6.5% (low incidence areas). Age was another factor evaluated by Barnes. There were higher resistance rates in patients under 30 years of age who came from high incidence areas. However, no statistical significance was demonstrated when compared to the rate in older patients. It would have been better if patients below 15 years old were included and evaluated. Suspicion that primary drug resistance maybe more frequent in the very young is aroused.

Barnes did not provide information about his subjects' treatment history especially those who developed secondary drug resistance. The differences between the high incidence area patients may have been clarified if he considered whether they had been adequately or erratically treated, were treatment failure cases or had relapsed while under therapy or not. His paper did not say whether the factors he found to predict drug resistance were used to select the treatment regimen he gave his patients or not or whether this affected the treatment outcome. He gave no recommendation on what strategy should be adapted to avoid inadequate therapy in patients at greater risk for drug resistance.

Both Shennan and Costello in their separate work in Africa and America respectively, noted increasing resistance

rate with increasing duration of previous therapy. In Costello's study, the linear relationship between length of therapy and resistance rate was significant ( $r = 0.82$ ,  $p < 0.05$ ). This finding was only true for INH - resistant organisms. For previous streptomycin monotherapy, the correlation did not achieve significance ( $r = 0.70$ ,  $0.05 < p < 0.10$ ). However, the number of persons who received streptomycin was small.<sup>(22)</sup>

In the United Kingdom, a retrospective descriptive study conducted by D.Wosornu et al demonstrated high INH-resistance rate among individuals who never had been treated for tuberculosis. Apparently, histories of treatment, compliance and outcome were fully recorded. The investigators believed that previous inadequate or erratic treatment could not explain the high incidence (57%) of isoniazid resistance. Therefore, two social factors common to the drug resistant group were assessed: current or recent accommodation in a night shelter or hostel for the homeless and alcohol consumption. From this study, isoniazid resistance was alarming among male, homeless and alcoholics. These group of people seemed to be a susceptible population among whom re-infection and cross-infection could easily occur.<sup>(27)</sup> No statistical analysis was done to prove any correlation between the social factors noted and drug resistance.<sup>(27)</sup>

A retrospective epidemiological analysis carried out by Howell, Kelly and Clancy in Ireland showed predominance of tuberculosis among male subjects, smokers and alcohol

users. Primary drug resistance occurred in 0.9% of the patients .<sup>(28)</sup>

Riley, Arathoon and Loverde in a community-based research at Sta. Clara County, California noted that isolates from Asian immigrants had the highest frequency of resistance (33 to 45%) and Southeast Asian immigrants had a drug resistant tuberculosis case not greater than 30/100,000 population per year. Patients who had cavitary lung disease and those who had previous history of tuberculosis, drug resistant pulmonary TB was 3.5 times as likely to occur.

To recapitulate the findings by the different investigators, they are simplified as follows:

TABLE 5. FACTORS THAT INCREASED DRUG RESISTANCE RATES

AUTHOR(S)	FACTORS
Riley, Arathoon, Loverde	Asian immigrants Cavitary lung disease Previous history of TB
P. Barnes	Previous anti-TB therapy Country of origin Duration of residence in USA
D. Wosornu, McIntyre, Watt	Males Homeless Alcoholics
O.T. Cheung	Previous drug treatment Immigrants > 5 years Recent immigrants
Suwanogool, Smith, Smith Eng	Alcoholics Patients with chronic obstructive pulmonary disease Diabetics
Aitken	Asians
Shennan	Previous anti-TB therapy Duration of prior treatment
Costello	Previous anti-TB therapy Duration of previous therapy

## CRITICAL APPRAISAL OF THE JOURNALS REVIEWED

### I. Research Design:

AUTHOR	DESIGN
A. Shennan	- Cross-sectional descriptive study
B. Aitken	- Cohort
C. Barnes	- Cohort
D. Costello, et al	- Retrospective exploratory
E. Wosornu, et al	- Retrospective descriptive
F. Howell, et al	- Retrospective descriptive
G. Riley, et al	- Cross-sectional design

### II. Criteria for Causation

Only the researches made by Aitken and Barnes attempted to identify valid risk factors for drug resistance, hence only these will be evaluated according to the criteria. The rest were simply descriptive studies.

A. Is there evidence from true experiments in humans?

None of the papers reviewed satisfies this criterion. Although an experimental design has the greatest strength in terms of study design, for this particular objective, such a design is unethical and not feasible.



B. Is the association strong?

The findings by both authors as regards drug resistance and immigrants (Asians or country of origin) show some degree of association.

C. Is the association consistent from study to study?

Barnes in his prospective study was able to demonstrate a high incidence of drug resistant tuberculosis among his patients who had previous treatment for the disease. Such was the observation made by 3 other investigators who made a retrospective descriptive study on prevalence of drug resistance.

Likewise, the country of origin (immigrants-Asians) was consistently a source for increased drug resistance rates in all the studies.

D. Is the temporal relationship correct?

A definite temporal sequence has not been established clearly by both papers regarding the factors analyzed and drug resistance.

E. Is there a dose-response gradient ?

Again, this criterion was not accomplished in the research. Barnes in his observation of high resistance rate among patients previously treated did not attempt to show any relationship between the length of therapy the patient

underwent through and increasing rate of resistance. Aitken also failed to demonstrate this relationship.

F. Does the association make epidemiologic sense ?

The association between drug resistant tuberculosis and the individual's country of origin certainly makes epidemiologic sense, demonstrated by Barnes and Aitken.

G. Is the association specific?

Drug resistance and risk factors or predictors mentioned have not shown specificity of effect.

H. Is the association analogous to a previously proven causal association?

Since only two papers so far tried to prove any causal association between certain factors and drug resistant tuberculosis, comparing these papers, only the country of origin as a factor for development of drug resistance is common to both.