Letters to the Editor

Chemotherapy for Tuberculosis

While commenting on the Recommendations by the American Thoracic Society (ATS) regarding treatment of tuberculosis and tuberculosis infection in children, Dr. Singh(l) has virtually 'endorsed', instead of critically analyzing, the recommendations by ATS that 4-drug regimen is desirable in our pediatric patients due to the initial INH resistance of more than 4% in Indian population (around 10-12% by WHO unpublished data). Such a generalized statement in the absence of any clinical trial justifying use of 4 drug over 2 or 3 drug regimens in children as a population, irrespective of the type of disease, may reflect different connotation to the readers and result in advocating or suggesting routine use of 4-drug regimen in children.

It is very important to realize that recommendations made by the ATS are applicable to adult and child patient populations of USA and Canada based upon and taking into consideration several factors like geographic variations, racial factors, low-prevalence countries, high-risk groups within a low-prevalence population, socio-economic status, accessibility to health care system, association with HIV and AIDS, *etc.* Further, the higher dose-range recommendations of INH and rifampicin at 10-20 mg/kg in daily regimens are presumably empirical and not based upon the current research data for providing evidence that these higher doses are more clinically efficacious than those of 5 mg/kg of INH and 10 mg/kg of rifampicin as recommended by WHO and International Union Against Tuberculosis and Lung Disease, for global use. Developing countries, as has been advocated by WHO, should evolve and formulate strategies as per the needs, feasibility and cost-effectiveness of the treatment modalities tested in the individual country and not merely adopting recommendations formulated by and for the developed countries.

I wish to emphasize that the prevalence of primary INH resistance in India was reported to be 10.6% in 1976(2) and around 10 to 12% now (WHO unpublished data)(l), remaining more or less same by these imprecise available epidemiological data. Despite this prevalence of primary INH resistance, (>4%), there has not been a single clinical trial or even report in children in India indicating failure of the generally followed 2-drug (6HR) or 3-drug (2HRZ, 4HR) short-course regimens attributable entirely to this resistance necessitating use of 4-drug regimen, barring individual cases with severe disease or unsatisfactory response.

On the contrary, randomized case- control and other studies(3-5) have shown that 2-drug and 3-drug regimens, of both continuous (daily) and intermittent frequency, have proven clinical efficacy in Indian children with tuberculosis irrespective of the extent of prevalence of primary INH resistance (not precisely estimated for India) in the adult community with tuberculosis. The use of 4 or 5 drug regimens should be confined to the severe forms like TBM and miliary disease. This has been shown in the trial in Thai children with tuberculous meningitis where a 6-month 4-drug regimen 2SHRZ, 4HR proved more efficacious than other regimens of 9 or 12 months duration(6). Furthermore, a recent study(7) has clearly established that directly observed therapy (DOT) for *Mycobacterium tuberculosis* infection leads to significant reductions in the frequency of primary and acquired drug resistance, as well as the relapses even with multi-drug resistant organisms. Thus, it is the drug-compliance and not necessarily, the inclusion of additional drug(s) that gives favorable response to therapy on a community basis. Interestingly, INH resistance is often

accompanied by greatly diminished virulence of *M. tuberculosis(8).*

Paradoxically, fully drug-sensitive *M. tuberculosis* bacilli have the ability to survive in the cells and tissues of patients despite the adequate and regular administration of such drugs and indeed, most bacteriological relapses after adequately supervised modern short-course chemotherapy are due to drug-sensitive organisms(2).

These observations, though contradictory to each other, clearly point towards the importance of adopting clinically tested and proven recommendations rather than observations based on theoretical or hypothetical considerations. Therefore, the desirability of adopting a 4-drug regimen as recommended by ATS is totally unwarranted in Indian circumstances as of now. Besides, the bacillary load in tuberculous disease and infection is far less in children than adult patients and type of disease in children (primary, progressive or disseminated) is very different from that in the adults (the secondary or 'adult-type'-cavitary or massive infiltrative pulmonary disease). The need to provide uniform guidelines in this direction for Indian population is indeed timely, and in my opinion, the Indian Academy of Pediatrics should be the torch-bearer in this context.

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Reply

Dr. Seth has raised relevant issues which required a detailed discussion and were beyond the purview of a comment on a 'Selected Summary'. The impact of the prevalence of primary drug resistance in the community on the efficacy of initial drug regimes has been studied largely in adults(l). Childhood tuberculosis, which reflects the persistence of infection among the adult cases, is also likely to be affected by the resistance pattern in the adult contacts. The country has recently witnessed an increase in the number of drug resistant cases due to a variety of rea-