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N-Acetyltransferase2 **Genotype Correlated with Isoniazid Acetylation in Japanese Tuberculous Patients.**

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Isoniazid (INH) is metabolized by polymorphic N-acetyltransferase2 (NAT2). In the present study, the relationship between the NAT2 genotype and the INH acetylator phenotype was examined in Japanese tuberculous patients and compared with healthy subjects. Subjects were classified according to the genotyping into NAT2*5B (allele4), NAT2*6A (allele3) and NAT2*7B (allele2), using the PCR-RFLP method. Twelve healthy subjects and 7 tuberculous patients participated in the INH acetylator phenotyping study, in which each subject was administered an oral dose of INH, followed by urine sampling for 24 h. Urinary concentrations of INH and N-acetylisoniazid (AcINH) were measured by the HPLC method. The urinary recoveries of INH (% of dose) in healthy subjects in relation to NAT2 genotyping were as follows: 6.4+/-2.2 in the homozygotes for the wild-type allele, 10.7+/-2.2 in the compound heterozygotes for the mutant allele, and 38.6+/-6.4 in the homozygotes for the mutant allele. In the patients study, the findings in the corresponding three groups were 4.0+/-1.7, 8.8 and 18.3+/-9.3. Although no significant difference was found because of the lower systemic exposure of INH in patients compared with healthy subjects, there were differences in the disposition kinetics of INH between subjects with and without mutations in the NAT2 gene, and these findings were observed not only in healthy subjects but also in patients who had comedicated drugs and hepatic dysfunctions. The findings indicated that the metabolism of INH by NAT2 is clearly impaired in subjects with

mutations in the NAT2 gene, and thus genotyping for three NAT2 point mutations was adequate to predict the metabolism of INH in Japanese tuberculous patients as well as healthy subjects. NAT2 genotyping could become a useful alternative to TDM for INH.