Simplified isoniazid acetylator phenotyping

To the Editor:

In the article "Inactivation of isoniazid by Canadian Eskimos and Indians" (*Can Med Assoc J* 106: 331, 1972) Drs. Jeanes, Schaefer and Eidus draw welcome attention to the growing need for simple and reliable methods of isoniazid acetylator phenotyping. It is now well established that, under controlled conditions of isoniazid administration and urine collection, measurement of the ratio of acetylated to free isoniazid in the urine provides the basis for such a method.[1, 2]

The technique of phenotyping that was developed in our laboratory utilizes this principle.[3] It is based on the observation that individuals who are in a steady state in respect of isoniazid excrete the acetylated and free drug in a ratio that is approximately constant. It avoids venipuncture by using orally-administered isoniazid in a simple dosage regimen that results in an approach to steady-state conditions. Properly performed, it gives unambiguous results.

Dr. Eidus and his colleagues comment that the isoniazid dose used in our method is small and therefore produces drug concentrations in the urine that are too low. This criticism is difficult to understand. The method used to measure acetylisoniazid is a semiquantitative modification of the very reliable technique, introduced by Dr. Eidus and his co-workers to detect this metabolite, with the object of determining whether or not patients are taking isoniazid.[4, 5] The dose we use is that normally given to tuberculosis patients, for whom that test was devised. We have analysed 242 morning urine specimens from 152 individuals who had received three spaced oral 100-mg. doses of isoniazid on the previous day. In no case was the concentration of acetylisoniazid below 20 μg./ml., and in 234 specimens (96%) it was 40 μg/ml. or more. Our test for free isoniazid measures down to 2 μg./ml.; for purposes of calculation concentrations below this value are scored as 1 μg./ml. Thus, in the least favourable case when only 20 μg. of acetylisoniazid and no detectable free isoniazid are present, the inactivation index (termed by us the A:I ratio) is 20 and as such identifies a rapid inactivator.[1, 3] This extreme situation was encountered in only one individual, whose morning urine volume was regularly more than one litre.

Dr. Eidus and his colleagues also comment that the semiquantitative analytical methods used by us are "not suitable". Their results show that 6-8 hours after isoniazid administration the inactivation indices of rapid and slow acetylators already differ by a factor of 3 or more, and that the difference is still increasing. Our studies indicate that the steady-state A:I ratios of rapid and slow acetylators differ by a factor of approximately 10. As has been shown,[1] even inexperienced observers can readily detect such a difference with our methods.

In the most recent application of our technique, steady-state A:I ratios (inactivation indices) of 120 Ethiopians were measured using a "kit" transported in one suitcase from the Medical School at Dalhousie to Ethiopia.[6] The only local physical facilities required were water and electricity, the latter to run a small centrifuge and a mixer, both of which could be supplied from a portable generator. In that study our methods were slightly modified to increase the speed and precision of the analyses. I shall be pleased to supply details to interested persons in advance of publication.

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References

1. RUSSELL DW: Simple method for determining isoniazid acetylator phenotype. *Br Med J* 3: 324-325, 1970
2. EIDUS L, HARNANASINGH AMT, JESSAMINE AG: Urine test for phenotyping isoniazid inactivators. *Am Rev Resp Dis* 104: 587, 591, 1971
3. MASON E, RUSSELL DW: Isoniazid acetylation rates (phenotypes) of patients being treated for tuberculosis. *Bull Wld Hlth Org*, in press
4. EIDUS L, HAMILTON EJ: A new method for the determination of N-acetylisoniazid in urine of ambulatory patients. *Am Rev Resp Dis* 89: 587-588, 1964
5. VENKATARAMAN P, EIDUS L, TRIPATHY SP: Method for estimation of acetylisoniazid in urine. *Tubercle* (Lond.) 49: 210-216, 1968
6. RUSSELL SL, RUSSELL DW: Isoniazid acetylator phenotyping of Amharas in Ethiopia. *Afr J Med Sci*, in press

To the Editor:

Dr. Jeanes, Dr. Schaefer and myself appreciate the comments of Dr. Russell. We were particularly interested to read of his isoniazid phenotyping program in Ethiopia.

At present it is accepted by a number of investigators that isoniazid inactivator phenotypes can be determined in urine by estimation of the ratio between the excreted acetylisoniazid and free INH. This ratio is