ISONIAZID RESISTANCE IN MURINE LEPROSY [1]

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Several workers have reported a marked suppressive effect by isoniazid in murine leprosy as compared with that shown by the sulfones, but there is now little doubt that isoniazid has no such spectacular effect in the human disease. That this is disappointing needs no emphasis, since the drug is cheap, of low toxicity, and easily administered. The question is raised whether isoniazid fails merely because *Mycobacterum leprae* is insensitive to isoniazid or because the organisms, like *M. tuberculosis*, become rapidly resistant to the drug. These differences are of course important because, if its failure is due to resistance, a choice of drugs used in combination might prevent this resistance from developing.

In a paper published early this year (1) we showed by counting the number of *M. leprae murium* present in spleen and liver smears from mice infected intravenously 180 days previously and treated continuously with isoniazid, that the treatment had almost completely suppressed the multiplication of the organisms. Incidentally, in the same experiment streptomycin had a very definite effect; the thiosemicarbazone, TB-1/698, had some effect; but the sulfones had little effect.

We have continued these experiments, and it is now apparent that the beneficial effect of isoniazid is only temporary, and that this is due to the development of resistant organisms. In these further experiments we continued the treatment with isoniazid indefinitely, and in about one year the animals died (untreated animals die in approximately 150 days) and the spleen, liver and skin were found to contain myriads of organisms, similar in number to those present in untreated mice.

That the loss of suppressive action by isoniazid was due to the development of resistance on the part of the organisms was shown by the failure of isoniazid to give any protection to further mice infected with spleen suspensions from the originally treated animals. Also—and this is important—a similar

[1] Read at the VI International Congress of Leprology, Madrid, October 1953.

passage made with the few organisms present in the animals of the original experiment, killed after 180 days of treatment, showed that these organisms, too, were resistant.

Although isoniazid is almost specifically active against mycobacteria, the sensitivity of different species varies. For instance, the strains of *M. avium* that we have examined required 50 μg isoniazid per ml. to be inhibited, and this concentration is not usually attained with the present therapeutic doses. It could therefore be argued that *M. leprae* is also somewhat insensitive. However, we regard our observations with its close relation, *M. leprae murium,* as strongly suggesting that isoniazid is failing in man because of rapid development of resistant strains. (In mice they developed in less than six months.)

In consequence, we feel that a plea should be made for the adoption of a similar attitude for using isoniazid in leprosy as has been adopted for its use in tuberculosis; that is, that it be used only in conjunction with other known antileprosy drugs.

We would like to add, in conclusion, that we are conducting in mice experiments designed to help in deciding the best combinations of drugs.

ABSTRACTO

Los autores han informado previamente, que en ratoncillos infectados por vía intravenosa con *M. leprae murium,* y tratados con isoniazid continuamente por 180 días, hubo una supresión casi total en la multiplicación de los microorganismos. Ahora se ha descubierto, sinembargo, que si el tratamiento se continúa indefinidamente éstos animales mueren antes de un año con tantos bacilos en los órganos como los animales testigos. Que éste desarrollo se dehe a la adquisición de resistencia a la droga por el bacilo, lo comprobó el hecho que cuando la infección fué transferida a otros animales, el tratamiento con isoniazid fue totalmente inefectivo. Además, nuevos ratoncillos con los pocos bacilos obtenidos de los animales sacrificados a los 180 días, tampoco fueron beneficiados con el tratamiento, demostrando que resistencia a la droga ya se había desarrollado. Diferentes mycobacterias varían en su sensitividad a la isoniazid, y los malos resultados en casos de lepra humana tratados con ésta droga pueden ser dehidos a falta de sensitividad de parte de *M. leprae,* pero los autores creen que la dificultad es más probable que sea el desarrollo de resistencia a la droga, y la isoniazid debe usarse solamente con otras drogas antileprosas.

REFERENCE

1. BARNETT, M. and BUSHBY, S. R. M. The activity of isonicotinic acid hydrazide in murine leprosy. Leprosy Rev. **24** (1953) 19-26.