troduce further subdivisions (TT/BT, BT/BB). However, even these subdivisions could not replace a thorough, detailed clinical description of the lesions in the individual patient. Hence I feel that there is need for these subdivisions.

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The Effect on Pregnant Mice of 0.05% B1912 Fed in the Diet

To the Editor:

Morrison and Marley stated, in a Letter to the Editor ([2]), that B1912, like clofazimine (B663), interacted with DNA's with "upfield red shifts" at 482 nm. The degree of this shift was found to be 4 to 5.7 times greater for B1912 than for B663. While it was not stated as such, apparently the extent of this shift for B1912, as opposed to B663, necessitated an expression of precaution as to the "implications of the data for testing of B1912 in human volunteers." The precaution was inferred on the basis that B1912 vs. DNA interaction, indicated by the upfield red shift, was assumed to be accountable for the strong antimitotic effects seen in tissue culture in the authors' laboratory. The antimitotic effects were not described in the letter nor was there any reference to the B663 effect in tissue culture under similar conditions.

Some time later, the same authors made a similar report to the Twelfth Joint Leprosy Research Conference, U.S.–Japan Cooperative Medical Science Program. The abstract of this presentation ([3]) clarified the antimitotic effects by offering the suggestion that "B1912 acts as a metaphase inhibitor producing lethal effects in rapidly dividing cells" at concentrations that could be attained in human serum. This effect was termed "nucleotoxicity," and the authors stated this property to be consistent with the formation of stable complexes between B1912 and human DNA, as indicated in their earlier data. Nucleotoxicity was confirmed by their finding that complete interrruption of pregnancy occurred in pregnant mice fed 0.05% B1912 in the diet for five days during mid pregnancy. No details were presented to document or describe these results, but fetal death, resorption and at least one abortion was mentioned. Again, the authors offered a precaution that a considerable amount of preclinical testing will be required before B1912 can be safely tested in human volunteers.

Apparently most leprosy workers feel that, since B663 is available, there is little need for urgency in the evaluation of its analog, B1912. However, Barry, *et al.* ([1]), after comparing B663 and B1912 reported that there were differences between these compounds in growth-inhibitory activity against certain mycobacteria. Differences were also observed in the "*in vivo*" tissue distribution of the two compounds. They concluded that B1912 had potential as a potent compound for leprosy and tuberculosis. For this reason, we felt that the claims of Morrison and Marley merited further investigation.

We decided to investigate the report that B1912 induced abortion in laboratory mice. Three successive attempts were made to repeat this observation using our NAMRU (Naval Medical Research Unit) inbred strain of mice.

In the first attempt, five pairs of mice were fed 0.05% B1912 in the diet from the date of pairing until parturition. All five females delivered a total of 41 weanlings (17 males, 24 females). All birth processes and offspring were normal except for an obvious red discoloration of parents, offspring, and fetal tissue. This discoloration disappeared in 6 to 8 weeks and all weanlings matured into normal adults.

In the second trial, three pairs of mice were fed 0.05% B1912 in their diet starting 2 weeks after pairing. Two additional pairings were maintained as controls, without B1912, under otherwise identical circumstances. All females were routinely weighed during the course of the observations. All five females produced healthy lit-

ters, the only difference between B1912 and the control litters was in the red discoloration of the B1912 weanlings. There were no significant weight differences between the groups during gestation. The respective litter sizes were 5 and 5 for control vs. 7, 6, and 5 for B1912 mothers.

In the third trial, thirteen pairs of mice were mated. Administration of B1912, 0.05% in the diet, was commenced for each pair on the day that the females' weight was observed to be obviously elevated above her previous normal daily weight fluctuation. The drug was then continued until parturition. Using this guideline, three pairs of mice received B1912 for 4 days and seven pairs of mice received B1912 from 5 to 9 days. Three pairs received no drug because a weight elevation was never observed. Of these three, one pair produced seven normal weanlings and the remaining two pair did not give obvious birth. No abortion was evident and autopsy, after sacrifice, of the non-delivering females showed no evidence of pregnancy. The 10 B1912 mothers produced a total of 60 red but healthy offspring with litter sizes ranging from 2 to 8.

In the course of these three trials, eighteen pregnant mice were fed 0.05% B1912 in their diet for a minimum time of at least 4 days up to a maximum time that covered the entire gestation period. All B1912 treated females had normal births. A total of 119 offspring was delivered. All were stained red but were otherwise normal. The B1912 discoloration of mother and weanling disappeared in 6 to 8 weeks after the drug was discontinued, and all offspring matured normally. Accordingly, B1912 nucleotoxicity, demonstrated by drug induced abortion, as reported by Morrison and Marley, was not observed.

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Abortifacient Activity of B1912

To the Editor:

A brief comment on the failure of Reich and de la Cruz to demonstrate B1912 abortifacient activity in mice is as follows. Differences are apparent between the Baltimore and Cebu experiments involving methodology, experimental design, and mouse strain reproductive capacity. While complete details of the Baltimore experiments will be published elsewhere, the following differences are cited.

Dietary dose calculations used by Morrison and Marley refer to B1912 at 0.05% (w/w) of moisture-free mouse diet (Ralston Purina Company, powdered chow #5001) in which the B1912 was blended in a micronized powder form to accelerate absorption.

The Baltimore experiments indicate that a critical time point during embryogenesis was present in order to demonstrate abortifacient activity. The results of Reich and de la Cruz show that they have either missed this time point (Experiment 2) or have pre-induced metabolism to confer protection against the embryotoxic metabolites of B1912 (Experiment 1). We agree with the lack of B1912 effects when added during the weight-gain period (Experiment 3).