CORRESPONDENCE

This department is provided for the publication of informal communications which are of interest because they are informative or stimulating, and for the discussion of controversial matters.

BLUISH DISCOLORATION IN LEPROMATOUS LESIONS DURING TREATMENT WITH AMODIAQUIN

To the Editor:

Dr. László Kátó has kindly permitted me to read in advance of publication the paper entitled "Reticulo-endothelial response in murine leprosy" by him and Béla Gözsy. This paper seems to me to have more than theoretical interest, although its immediate value is to emphasize the need for further study of the role of the capillary endothelium in human leprosy and in mycobacterial infections of animals.

Dr. Kátó tells me that the idea for his experiments originated in a conversation with me during which I described the occurrence of blueness in lepromatous lesions following treatment with amodiaquin (Camoquin, Parke, Davis and Co.). This happened during the fourth series of clinical evaluation studies of the Leonard Wood Memorial and the Department of Health of the Philippines. In this series, four therapies were used, viz., (1) a thiourea, (2) amodiaquin (0.2 gm. daily), (3) a higher dose of 4, 4'-diaminodiphenyl sulfone (DDS) and (4) a lower dose of DDS. The scheme was a double-blind one and the group receiving amodiaquin was called B/K. All drugs were given by mouth. The experiment was conducted in duplicate—at the Central Luzon Sanitarium near Manila and at the Eversley Childs Sanitarium at Cebu—there being about 55 patients in each of the four groups at each place.

Therapy was commenced at Eversley Childs on June 3, 1957. On August 7—that is, at the beginning of the 10th week of treatment—Dr. Jose G. Tolentino, the Memorial's research leprologist, reported that patients in the B/K group "are observed to acquire bluish discoloration of the skin, especially of the face." The color was actually rather bluish-green, and it appeared to have an affinity for areas of infiltration. About September 1 all patients in the experiment were inspected and also 55 newly admitted patients. Moderate or marked blueness was noted in 55 per cent of the amodiaquin group. Two patients on the thiourea and one of the new admissions also showed some bluish-tinted areas on the skin. Examination in the 16th week showed no essential changes in this situation.

Treatment at Central Luzon was commenced June 17. When the patients were examined in the 16th week of treatment by Dr. Juan V. Fernandez, the Memorial's junior leprologist, he classified 48 per cent of those of the B/K group as showing blueness of a moderate or marked degree, but none of those of the other groups. During the 19th week, Dr. R. S. Guinto, the Memorial's epidemiologist, examined the Central Luzon patients independently and included 58 per cent in the moderately or markedly blue class. In February 1958, in the 32nd week of treatment, Dr. Jose N. Rodriguez, the Memorial's consultant, made a careful reexamination of 194 ambulatory patients at Central Luzon, in random order and not by group. Of 49 in the B/K group, 26 showed blueness in the lesions, in some cases deeply marked. Of 146 other patients, only one showed a lesion with a bluish tinge. Treatment was continued, and in October 1958, when observed by the writer, blueness was conspicuous in many of the B/K patients at both institutions.

There were no untoward signs of any kind other than the blueness. Urine findings remained normal. Gain in weight and other signs of improvement were as good in the B/K as in other groups in the early months of therapy.

Patients of each therapy group were given two kinds of tablets, one a placebo and the other the drug under study. In the case of B/K, the B tablet was the yellow amodiaquin and the K one, the placebo, was light blue in color. Consequently the blueness was at first attributed to the blue tablet. On checking with the manufacturer, however, it was found that another placebo tablet, green in color, given to another group, contained nearly 70 times as much blue dye as did tablet K. Nevertheless, no patient of that group at either institution showed blue lesions.

On November 5, 1957, Dr. Tolentino placed 5 newly-admitted lepromatous patients on amodiaquin alone, and 5 others on the light-blue tablet K. In the 7th week of treatment, 4 of the former were examined and all showed blueness; 3 of those on K were examined and none was blue. Blueness took more than three months to disappear after discontinuance of amodiaquin.

Dr. Y. T. Chang, the Memorial's associate pharmacologist, working at the National Institutes of Health, Bethesda, Md., placed 20 apparently healthy white mice on the blue (placebo) compound and 20 on the blue compound plus amodiaquin—both in the diet. On autopsy, after 3 months' treatment, none of either group showed gross evidence of blueness in the skin or in any of the organs.

Dr. Frank B. Johnson and his associates at the Armed Forces Institute of Pathology, Washington, D. C., made histochemical studies on 9 biopsy specimens from patients of Group B/K, Central Luzon. In one there was observed a strong reaction for iron due to a brown granular pigment, presumably hemosiderin, and in two others traces of a simi-

lar pigment were found. Dr. Johnson thought that these brown granules might account for the bluish-black lesions. The source might have been local hemorrhage or increased permeability of the blood vessels in the lesions. No iron-positive pigment was found in 15 sections of lepromatous lesions from the A.F.I.P. files.

The phenomenon remains unexplained. It is possible that in lepromatous lesions there is an increase in the permeability of the capillaries. Amodiaquin is not known to have caused blueness in any other disease or in healthy persons. It has not been tried, to my knowledge, in tuberculoid leprosy. Localization of methylene blue in leprous lesions was observed by Montel twenty-five years ago. In 1954 the same author described (THE JOURNAL **22**: 403-408) cases with both lepromatous and tuberculoid lesions, "the former uncolored by methylene blue the latter intensely stained by it"—to quote from Wade's editorial comment in the same issue. In 1956 Convit *et al* (THE JOURNAL **24**: 375-381) commented that the lesions of borderline cases retain methylene blue in direct proportion to the amount of lepromatous granuloma they contain. Simple passage of amodiaquin into the tissues, with chemical change to a bluish compound, does not seem to be the explanation in our patients and further study is indicated.

Leonard Wood Memorial
Washington, D. C.

JAMES A. DOULL, M.D.
Medical Director