



Shortly after its introduction, at least one observer, Smadel,³ called attention to the nitrobenzene radical in the drug and warned of its possible toxic effects on blood-forming apparatus. Early reports indicating possible toxic hematologic reactions of Chloromycetin were largely minimized, especially since in the great majority of the cases in which the drug was used, no ill effects were noted. Furthermore, it was not clear in some of the cases whether Chloromycetin was the sole responsible agent. Recently, however, we have been apprised of a rapidly increasing number of cases from all parts of the country,⁴ and we ourselves have observed a striking instance of hypoplastic anemia following the long term administration of Chloromycetin for mild acne of the face. Although it is likely that a number of cases are in the process of publication⁵ there has been as yet only one article⁶ in 1952 dealing with aplastic anemia following prolonged administration of the drug. Many of the cases have been shown to be irreversible and therefore fatal. Although most of the reports are still in the status of "personal communications," there seems to be no question as to their authenticity or their relationship on a circumstantial basis to chloramphenicol administration. It appears from the various reports that severe myelotoxic reactions have followed both the lengthy administration of the drug and its intermittent use.

It seems increasingly clear that a real danger exists in the uncritical use of this drug by the medical profession. A recent pamphlet⁷ recognizes this possibility but places the emphasis upon the very large number of cases and the millions of administrations in which no harmful effects have apparently been observed. There can be no doubt regarding the relatively small proportion of severe hematologic reaction, thus indicating a possible allergic susceptibility on the part of some. However, to the luckless individual who develops pancytopenia, the 10-percentage figure means very little.

In the instance of a valuable drug with potential toxic effects, the ultimate safety of the patient must transcend all other considerations. With the use of Chloromycetin the physician is assuming an admittedly small but nevertheless "calculated risk," and should, therefore, be on the watch for possible hematologic reactions, particularly during long term administration.

Chloromycetin appears to offer a potential hazard to the bone marrow, at least in some individuals, and it would, therefore, seem wise to use it only for short term administration and when there is a clear and impelling need for this particular medication. Its indiscriminate use for trivial infections and as a household remedy must be deplored.

It is unfortunate that no good method has yet been devised to measure in advance the tendency of new drugs to cause hematologic reactions. Certainly in the case of chloramphenicol, careful animal and human studies on the metabolic disposition and toxicity of the drug gave no hint that it might induce severe bone marrow reactions. Much thus remains to be done in the important field of drug sensitivity particularly as it relates to the bone marrow and blood.

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EXHIBIT B

During a recent trip to the Far East where aplastic anemia appears to be unduly prevalent (perhaps because the use of chloramphenicol is relatively uninhibited), it was evident that the incidence of PNH was also unduly high. Thus, in Manila, the Philippines, Dr. Allen Caviles of the Philippines General Hos-

³ Smadel, J. E.: *Am. J. Med.* 7: 671, 1949.

⁴ The U.S. Food and Drug Administration has collected about 40 cases (with 9 deaths) in which severe hematologic reactions occurred following use of chloramphenicol.

⁵ Smiley, R. K., Cartwright, G. E. and Wintrobe, M. M.: *J.A.M.A.* In press.

⁶ Wilson, L. E., Harris, M. S., Henstell, H. H., Witherbee, O. O. and Kahn, Julius: *J.A.M.A.* 149: 231, 1952.

⁷ Chloromycetin from the Hematologist's Point of View, Detroit, Parke, Davis, 1952.