APPENDIX

Appendix I. Articles From Various Sources re Drug Chloromycetin (Chloramphenicol)

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Chloramphenicol-Induced Bone-Marrow Aplasia

Although chloramphenicol continues to be the leading single cause of drug-induced aplastic anemia, little progress has been made in elucidating the mechanism of its toxic effect. The reversible erythroid depression occurring concurrently with chloramphenicol therapy is a pharmacologic effect.[1] Although there is clearly a relation between this type of toxicity and dosage, there is none between dosage and reversibility. The occurrence of bone-marrow aplasia is only an occasional subject receiving chloramphenicol, coupled with the lack of a dose-effect relation, almost certainly indicates an individual susceptibility.

In sensitive bacteria chloramphenicol in small concentrations causes complete inhibition of protein synthesis. There is good evidence that this action is exerted through stereospecific binding of the drug to the 50–S ribosomal subunit, thereby inhibiting, in an as yet undefined manner, the formation of the peptide bond.[2] The drug does not seem to interfere with the function of messenger RNA (mRNA).[2] In mammalian cells in vitro on the other hand, concentrations many times the usual therapeutic levels are needed to inhibit protein synthesis significantly. Recently, Weisberger et al.[3] reported profound inhibition of mRNA-induced protein synthesis in a cell-free system from rabbit reticulocytes by small concentrations of chloramphenicol, reversed by increasing the concentration of messenger. They concluded that chloramphenicol inhibits protein synthesis in mammalian cells by interfereing with the binding of mRNA to ribosomes. However, other investigators are unable to corroborate these findings.[4] In similar systems about 20 per cent inhibition of amino acid incorporation into ribosomes can be demonstrated at therapeutic drug concentrations. This slight inhibition is unrelated to the concentration of messenger in the system. Furthermore, chloramphenicol does not bind to reticulocyte ribosomes, nor does it interfere with the ribosomal binding of mRNA.[4] The problem of whether hematologic toxicity from chloramphenicol is related to its effect on protein synthesis cannot be resolved at present. It is entirely possible that the reversible erythroid depression from the drug is related to its small inhibitory effect on protein synthesis as observed in vitro. The length of exposure may render this small effect significant in the overall metabolism of the erythroid cell.

Bone-marrow aplasia from chloramphenicol is more difficult to explain. Here some specific biochemical susceptibility is the most likely underlying factor. The demonstration that chloramphenicol inhibits the uptake of ^{14}C formate into nucleic acids of bone-marrow cells from patients who have recovered from chloramphenicol-induced aplastic anemia supports this hypothesis.[1] However, further studies in similar cases are needed to determine the significance of these findings.

Several observations in patients with chloramphenicol-induced aplastic anemia suggest that this drug exerts its action at the stem-cell level. Thus, the latent period between drug administration and the onset of anemia, the characteristic pancytopenia and the long duration of the aplasia after the drug has been discontinued are all compatible with an injury to a precursor pool common to all 3 cell lines. The persistence of aplasia long after discontinuation of the drug indicates either that chloramphenicol has a lethal effect on these cells or that, by affecting the genetic pattern of the stem ceil, it causes the

Note.—Numbered footnotes at end of article, p. 2654.