Course.—It was specifically reported in several instances that recovery followed withdrawal of the drug, and it was presumed that this occurred within a few weeks. Most of these instances were associated with depression of a single blood cell type. On the other hand, of the 75 patients known to be alive with persistent evidence of the dyscrasia despite cessation of the drug, 20 (27%) were alive 100 to 299 days after onset, and 11 (14%) were alive 300 or more days after onset. Recoveries have sometimes been noted after relatively long periods of disease.

Death is known to have occurred in 186 cases, 95% from complications of the dyscrasia. Performance of an autopsy was noted for 24% of these cases; however, details of this examination were not usually reported.

Therapeutic measures directed against the marrow depression were usually not reported, and no attempt was made to evaluate these.

PROGNOSIS

Detailed studies on prognosis have been submitted for publication elsewhere (W. R. Best). The most important clinical findings are that improved survival is associated with fewer cell-types depressed, shorter delays in onset, larger daily doses, and occurrence in Negroes.

COMMENT

Yunis and Bloomberg have reviewed various types of evidence bearing on the pathogenesis of those hematologic reactions to chloramphenicol which occur in rare cases at commonly employed dosage levels. They found no convincing evidence to support an autoimmune process, and the current data cannot be construed as adding such. Abnormal susceptibility due to some biochemical abnormality seems more likely, but the exact nature of such a disorder remains to be determined.

Yunis and Bloomberg suggest that a defect in localization, metabolism, or excretion of chloramphenicol, or an enzymatic or other biochemical deficiency involving a metabolic pathway that becomes essential in the presence of this drug, could account for these reactions. One suspects that there is an underlying hereditary difference between individuals who do and those who do not develop this reaction to chloramphenicol. The occurrence of dyscrasias in both members of a set of identical twins is one of the most interesting findings in the Registry relative to the genetic question. It is reasonable to suppose that many close relatives of Registry patients have received courses of chloramphenicol comparable to those of corresponding affected family members, and that a high percentage, if not all instances of multiple cases in a single family would have been called to the attention of the Registry. Yet, so far as we have been able to determine, the only instance in the Registry or the medical literature in which more than one member of a family has developed such a dyscrasia is this particular one involving the relatively rare sib combination of identical twins. One could reasonably expect several nontwin sibling pairs in the total experience to date if this susceptibility to chloramphenicol required a homozygous state relative to a single recessive gene. Simultaneous exposure to some unusual environmental factor or the fact that the only known sibling pair developing this defect share an identical genetic constitution strongly suggests that an unusual combination of genetic factors must be present in a homozygous form before this abnormal susceptibility becomes manifest.

Unusual racial or ethnic patterns of occurrence or course would be consistent with genetic disorders, but would not provide conclusive evidence thereof. Considering the racial composition and patterns of medical care of populations about whom the Registry is most likely to receive reports, one has no compelling reason to suspect that members of one race are more likely to develop this reaction, given a similar drug exposure, than are those of another. However, a striking difference in clinical course seems to be related to race in this series. Nonwhite patients tend to have a much more benign course than whites, a trend not previously noted.

Unusual patterns of occurrence relative to age or sex, if not otherwise explained, would tend to implicate developmental, degenerative, or hormonal factors as being of at least secondary importance. Females accounted for 54% of cases surveyed by Yunis and Bloomberg and 62% in the current report.

Some of the age-sex patterns noted can reasonably be assumed to reflect differences in occurrence rate for various diseases for which chloramphenicol is