varying conditions under which these measurements were obtained detract from their significance.

Discussion

Well-controlled studies for determining abnormal symptoms, signs, and laboratory tests associated with drug therapy take spontaneous occurrence into account and tend to eliminate the biasing factor of clinical expectation. The disadvantages of our technique are that the ranges of drug dosage are arbitrary during the critical early part of therapy and that the technique of observation of patients varies greatly. The dosage schedule in this study was therapeutically efficacious, simulating usual clinical conditions. Differences between observers should have been equally distributed among the 6 treatment groups, not constituting a major biasing factor.

Consideration of the occurrence of abnormal signs and symptoms in the 6 treatment groups led to three possible conclusions: (1) Their occurrence with phenothiazine derivatives has been greatly overestimated. (2) Phenobarbital produces more side effects than is ordinarily believed. (3) Many phenomena represent spontaneous fluctuations in schizophrenic patients or manifestations of the illness itself. Of these, the last has probably not been stressed enough. Examples of the first possibility were the relatively infrequent occurrence of extrapyramidal syndromes (less than 10 per cent), seizures, and skin eruptions in patients treated with phenothiazine derivatives. Examples of the second and third possibilities were the occurrence of depression, anxiety, agitation, akathisia, and autonomic nervous system side effects during therapy with phenobarbital. The abnormal behavioral symptoms were probably manifestations of schizophrenia rather than drug effects.

Leukocytosis, leukopenia, and eosinophilia are known to be consequences of treatment with phenothiazine derivatives.[3,8,12] However, each hematologic abnormality was present in control counts and just as frequent during treatment with phenobarbital as with the other drugs. The development of leukopenia during drug therapy is especially important. Twenty-five of the 36 patients in this study with leukopenia (absolute neutrophil counts

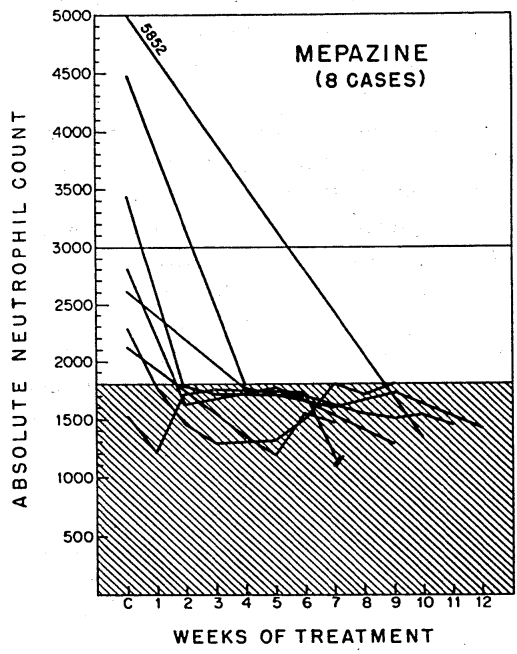

Fig. 4.

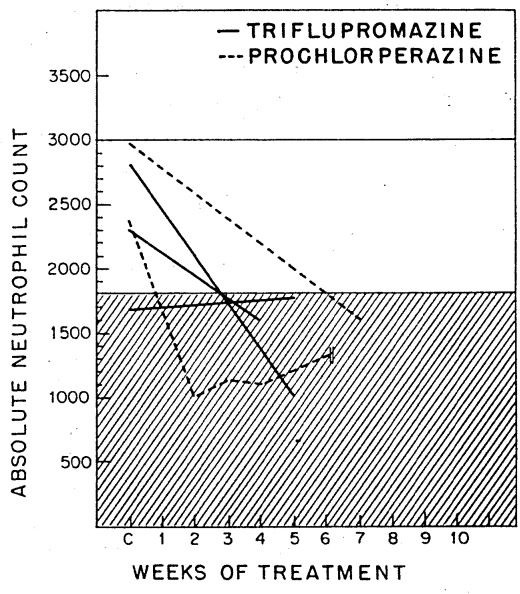

Fig. 5.