paign to encourage physicians to report to the Registry; and (2) not all instances of blood dyscrasia associated with the taking of some drug or other chemical agent necessarily represent true cause and effect relationships. In some instances the association may have been purely coincidental.

It is noteworthy, nevertheless, that of the above-mentioned 2,034 reports, 407 were associated with consumption of chloramphenicol. In 171 instances this was said to be the only drug to which the patient had been exposed. In an additional 33 cases, another drug had been taken which was not considered to be potentially harmful and in 133 cases the potential toxicity of the drugs taken in addition to chloramphenicol was uncertain. Only in 70 instances was the associated drug thought to be potentially toxic.

It can hardly be denied that data such as these make chloramphenicol suspect as a possible cause of blood dyscrasia. It is especially significant that of the 171 instances in which only chloramphenicol had been taken, the blood dyscrasia observed was aplastic anaemia, with pancytopenia, in 128; in an additional 18 cases there was erythroid hypoplasia without pancytopenia. Only in 7 cases was thrombocytopenia, without change in red or white cells noted, and only in 16 instances was leucopenia or agranulocytosis observed. This disproportionate incidence of aplastic anaemia is probably very significant.

Were these occurrences only a matter of coincidence, one would have expected that the number of cases in the various categories of reported dyscrasias associated with exposure to a single agent would have been similar to the incidence of various dyscrasias in the whole series. The data for the whole series of more than 2,000 reports are—

	Percent
Aplastic anaemia with pancytopenia	31.4
Thrombocytopenia	15.5
Leucopenia or agranulocytosis	38.1
Erythroid hypoplasia without pancytopenia	4.1
Haemolytic anaemia	5.8
Megaloblastic anaemia	2.5
Miscellaneous	2.6
Total	100.0

In contrast to these figures, it is to be noted that of the blood dyscrasias associated with chloramphenicol 74.9 per cent were reported as cases of aplastic anaemia with pancytopenia.

Aplastic anaemia is the most serious of the blood dyscrasias associated with drug therapy: the mortality rate is in excess of 50 per cent and, even when recovery does take place, it is only after months or years of serious illness.

Unfortunately, there are no adequate data by which one could estimate the likelihood of development of aplastic anaemia in association with exposure to chloramphenicol. However, even if the reports received represent only a very small fraction of the cases of aplastic anaemia which occur, in view of the wide use of this antibiotic the incidence must be assumed to be low. The mode of action of the drug in producing irreversible bone marrow injury also is unknown. A number of studies indicate that the administration of chloramphenicol in such doses that serum concentrations reach high levels is associated with (1) evidence of reduced utilization of iron for haemoglobin synthesis, as indicated by increase in serum iron and increased saturation of the iron-binding globulin; and (2) interference with the production or maturation of thhe erythroid cells, as indicated by vacuolation of erythroblasts, a progressive increase in the myeloid: erythroid ratio in the bone marrow, and reticulocytopenia. There is also some evidence that (3) modest reduction in the number of platelets; and (4) vacuolization of marrow granulocyte precursors and leucopenia may take place.

These changes, observed in human subjects, have been reversible. It remains to be determined whether the same or a different mechanism, perhaps one depending on a subtle congenital abnormality in the metabolic handling of chloramphenicol, is involved in the development of severe and irreversible aplastic anaemia. It is interesting that in a number of reported cases, bone narrow damage was observed after the second or third exposure to chloramphenicol, rather than following the first. No clear association with the amount of drug consumed has been observed. Paradoxically, in many instances of aplastic anaemia, the use of the drug could not have been justified on the basis of the recognized primary indications for the administration of chloramphenicol.