CHLORAMPHENICOL-INDUCED BLOOD DYSCRASIAS: ANALYSIS OF 40 CASES

BY

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Presented on behalf of the Haematology Committee
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Ten years have elapsed since the first reports were published to inform the medical profession that chloramphenicol could act as a bone-marrow poison and that the resulting aplasia could be irreversible and lead to the death of the patient (*British Medical Journal*, 1952).

Since then reports of the toxic effects of chloramphenicol have continued to appear, but the drug has remained in use as a popular and useful antibiotic. The *British Medical Journal* (1961) was again provoked to give warning of the dangers of this drug, but deaths attributable to chloramphenicol have continued to be reported. The latest report of the Study Group of Blood Dyscrasias of the American Medical Association (January, 1962) recorded 73 cases of pancytopenia, 4 with thrombocytopenia, 4 with leucopenia, and 17 with anaemia which were caused by this drug.

The Haematology Committee of the Association of Clinical Pathologists decided to ask members of its association how many cases of chloramphenicol-induced blood dyscrasias they had encountered and to report such cases to the secretary of this Committee. To date, reports of 35 hitherto unpublished and five published cases of suspected chloramphenicol blood dyscrasias have been received. This is admittedly a random sample of such cases, and while there are obviously still an unspecified number of unpublished cases it was thought worth while to report an analysis of the clinical and laboratory data supplied with these case reports.

Analysis of Clinical Data

Time.—These 40 cases occurred in the period 1953–62.

Severity.—Thirty-one of the 40 patients have died. In 27 death was attributed directly to chloramphenicol therapy.

Age and Sex.—There is no obvious specific age or sex incidence.

Interval between Therapy and Diagnosis of Marrow Damage.—The commonest interval was 1–3 months after the cessation of therapy; in two cases the blood dyscrasias developed immediately after the drug had been given, in two cases at approximately 9 months, and in one case 1 year after cessation of therapy.

Dose.—In 18 patients the total dose of chloramphenicol was 10 g. or more, and in four it exceeded 50 g., one receiving 250 g. In eight patients, however, the total dose was less than 10 g., and in one infant the amount given did not exceed 2 g. Six received intermittent or continuous courses of unspecified amounts over one year, and 12 had more than one course of the drug. In 14 cases details of therapy were insufficient to assess the total dosage of the drug the patient had received.

Blood Picture.—In 21 cases the peripheral blood showed a severe pancytopenia (anaemia, leucopenia,

and thrombocytopenia). Twelve cases showed selective aplasia with either leucopenia or thrombocytopenia. No case showed selective red-cell aplasia. In seven cases specific data relating to the peripheral blood picture were not given.

Clinical Presentation.—The commonest presenting symptom was spontaneous bleeding—for example, epistaxis, purpura, menorrhagia. In one case jaundice was the earliest sign of complication.

Prognosis.—The details of the marrow changes were available in only 25 reports. All 12 patients with aplastic marrows died. In eight the marrow was classified as hypoplastic, but they too died. The marrow derived from five of the nine patients who recovered was hypoplastic. Therefore recovery may take place if the marrow is not completely aplastic. Complete marrow aplasia would appear to carry a hopeless prognosis.

Discussion

Chloramphenicol is an efficient antibiotic, but its use is justified only in the treatment of life-endangering infections when no other effective antibiotic is available—for example, typhoid fever.

Yet this series has shown that fatalities apparently due to chloramphenicol therapy have occurred in numbers sufficient to cause concern. Further, it would seem that this drug has been used indiscriminately in the treatment of a wide variety of mild infections and that extravagant doses of the drug have been administered.

Hutchison and Pinkerton (1962) have suggested that the incidence of blood dyscrasias due to chloramphenicol might be 1 in 80,000 patients treated, in which case it might be argued that this risk justifies the use of this antibiotic in even trivial infections. However, these authors based their imputation on the number of deaths reported to the Registrar-General, and incidence based on the Registrar-General's report can be misleading; it is likely that more cases do exist than are officially recorded.

Dameshek (1960) has stated that in the majority of fatal cases the patient would not have died if he had not received this drug. There would appear to be no justification for using chloramphenicol to treat non-specific pyrexial illnesses or nasopharyngeal infections in childhood, or recurrent bronchitis, asthma, chronic or post-prostatectomy urinary infection, recurrent boils, or superficial skin infections unless it has been shown by careful bacteriological sensitivity tests that the offending organism is sensitive to no other antibiotic.

This present series shows that, while a high dose and repeated courses appear to be more likely to cause trouble, single courses of less than 10 g. can cause fatal aplasia.

The wide distribution of the time of onset of symptoms attributable to the toxic effect of the drug suggests that two possible mechanisms exist: (1) a hypersensitivity reaction—immediately dangerous but probably reversible; this is often accompanied by immediate systemic symptoms; (2) a slow direct poisoning of marrow "stem" cells due to the accumulation and retention of the drug or its breakdown products in the blood or tissues and so to the delayed effect. The variation of the toxic dose suggests that an individual idiosyncrasy to this drug may exist.

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A retrospective survey such as that presented here can never be satisfactory, as significant data are not collected and not all cases are reported. Thus no statistical analysis of dose, time relationships, or incidence rates can be calculated. Only by insisting that chloramphenicol and other drug-induced dyscrasias are notified to some responsible authority as they occur can the case be made whether the popularity or efficiency of this drug as an antibiotic outweighs its established toxic effect.

The purpose of this paper has been to stress once more the dangers of using this antibiotic and to appeal for the compulsory notification of this and other drug-induced blood dyscrasias to a responsible central body in order that a true assessment of the relative risks can be made. This appeal is especially pertinent to the present concern of the medical profession and lay public regarding the dangers of modern drug therapy.

In the meantime this Committee would be grateful if any doctor encountering a case where it is suspected that chloramphenicol might have produced damage to the bone-marrow would send the relevant data to the secretary of this Committee.

The Committee expresses its thanks to the Council of the Association of Clinical Pathologists for their encouragement and permission to publish these data; to the Chairman of Council, Professor D. F. Cappell, for his criticism and advice; and to all those members of the Association who took the trouble to supply the Committee with case reports. It also wishes to thank Dr. M. M. Wintrobe, Chairman of the Study Group of Blood Dyscrasias of the American Medical Association, for his advice and encouragement.

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"A more detailed knowledge of the facts of life and death as they are; the creation through 'health planning'—in association with the other 'planners' of the essential public health services and an administrative structure to maintain and support them; the control and where possible the eradication of communicable diseases; the building up of a cadre of trained men and women to work in the health services, and research—both into the causes and cure of disease, and into the operations of the health services themselves. This is the prescription. Perhaps it may be described as 'administrative polypharmacy.' But for the completion of any such programme as I have outlined—and it should be remembered that it is also the programme of the conference—money is the essential prerequisite. We are only now beginning to study the relationship between health budgets and the overall expenditures of governments, and the available information is scanty. But one cannot escape the conclusion that in the cutting of the financial cake in many countries—the health portion not only should but might be greater. Money will be required for the great capital investment programmes in environmental sanitation; health centres, hospitals, laboratories, medical and other training schools. Funds will be required for the maintenance of all these installations and institutions and for the increased numbers of health personnel who will be required to staff them. All this is investment in health in the broadest sense and it will pay dividends in proportion." (Address by Dr. M. G. Candau, U.N. Conference on Application of Science and Technology for Benefit of Less Developed Areas.)

Special Article

WHY ARE THEY WAITING? A SURVEY OF OUT-PATIENT REFERRALS

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After 14 years of the National Health Service it is surprising to find that only four reports have been made concerning the varying habits of family doctors in referring their patients to hospital. Hopkins (1956), Logan and Forsyth (1958), Fry (1959), and Scott *et al.* (1960) each reported on the rates of referral of their patients to hospital in-patient and out-patient departments.

We, in one industrial practice, were interested in our out-patient referral rate, but were more concerned with the delays involved (a) in obtaining out-patient appointments, and (b) in receiving the report of these consultations—delays often prolonging the patients' absence from work.

To investigate this problem we designed a card which was printed for us by the medical department, Ardeer Factory (Nobel Division, I.C.I.). The data which interested us were: (1) the age and sex of the patient, (2) the clinic to which he was referred, (3) the date on which the request for an appointment was made, (4) the date on which the patient was seen, and (5) the date on which we received the specialist's report. We thought of incorporating the total time the patient was absent from work, the time spent in travelling to and from hospital, the time spent waiting in the out-patient department, and the number of return visits paid, but since we intended this as a pilot survey only, these important items of information were sacrificed for simplicity of recording.

Our secretary made out a card for each out-patient referred. These were filed in the patient's record envelope and extracted and completed when the specialist's report was received. Records were kept for one complete year. The number referred and their age and sex distribution are seen in Table I.

TABLE I.—Age and Sex Distribution of Patients Referred to Out-patient Departments

Males				Females			
Under 15	15-65	Over 65	Total	Under 15	15-65	Over 65	Total
60	161	23	244	37	228	19	284

There were 528 patients referred in the year. Our practice population for the survey year averaged 5,585 patients, giving a percentage referral rate to out-patient departments of 9.5%. In the year, 37,479 patient-doctor contacts were made in the home or surgery. Therefore an out-patient opinion was considered necessary in one out of 71 consultations given by us.

In our analysis of the overall waiting-time—from the request for an appointment to receipt of the report—