instance no other drug was administered, no intercurrent disease could be demonstrated, and the original infection, pertussis, tends to produce leucocytosis and not agranulocytosis. A primary aplastic blood condition unrelated to drug therapy can occur but is a comparative rarity. In the present case hepatitis and aplastic anaemia occurred together, suggesting a single aetiological toxic agent, and hence, on the basis of this criterion and the fact that well-authenticated cases of aplastic anaemia following chloramphenicol administration have already been recorded, this drug would seem to be incriminated as the cause of aplastic anaemia.

At the time of writing 19 cases, both adults and children, with granulocytopenia or aplastic anaemia following chloramphenicol therapy have been noted in the American literature, and of these 11 have been fatal. In the first nine cases recorded, bone-marrow changes appeared after prolonged administration of the drug. In the most recent reports all 10 patients received short but repeated courses of the drug and came to a fatal termination (see Table). The incidence

19 Cases of Bone-marrow Depression Following Chloramphenicol Therapy

No.	Author	Age of Patient	Total Amount Given (g.)	Duration of Administration	Result
1	Gill (1950)	13 months	6.3	12 days	Recovery
2	"	2 "	1.75	"	"
3	Volini <i>et al.</i> (1950)	11 years	53	18 "	"
4	"	41 "	53	19 "	"
5	"	14 "	26	9 "	"
6	Rich <i>et al.</i> (1950)	63 "	57	12 weeks	Death
7	Wilson <i>et al.</i> (1952)	39 "	56	28 "	"
8	"	37 "	52	26 "	Recovery
9	Lloyd (1952)	28 "	7.5	5 "	Death
10	Claudon and Holbrook (1952)	71 "	24	Over 9 mths.	"
11	"	92 "	9.5	2 mths.	"
12	Smiley <i>et al.</i> (1952)	29 "	12	Over 8 mths.	"
13	"	6 "	7.5	"	"
14	Sturgeon (1952)	22 mths.	8	" 4 "	"
15	"	5 1/2 years	"	" 2 "	"
16	"	6 1/2 "	"	" 6 "	"
17	"	6 "	6	4 days plus	"
18	"	Child	To be reported	"	"
19	"	"	"	"	"

of hepatitis, however, is not mentioned in any of these cases, and the present report would seem to record a new toxic feature in addition to the blood dyscrasia.

The therapeutic efficiency of chloramphenicol has been established in a wide variety of infections (Smadel, 1949), and observation of a large number of patients treated with the drug has failed to reveal any clinical toxicity. However, Kracke and Parker (1934) pointed out that drugs containing the benzene ring with an attached amine could cause bone-marrow depression in a susceptible person. It is possible, therefore, that the nitrobenzene radical occurring in chloramphenicol is the cause of the toxic effect, and, although numerous patients may receive the drug without danger, some idiosyncrasy may be responsible for its effect on the bone marrow in certain individuals. This toxic effect, however, has occurred after long or repeated periods of administration, but, as a leading article in the *Journal* of July 19, 1952 (p. 136), has pointed out, prolonged treatment is unjustified in any circumstance, as eradication of infection should be complete within a week, and failing this other therapy should be adopted. Furthermore, chloramphenicol, by its interference with the bacterial flora in the gut and the resulting synthesis of prothrombin or other substances, may initiate a process which leads to these severe changes in the bone marrow.

Summary

A fatal case of aplastic anaemia and hepatitis occurring in a boy of 6 years following chloramphenicol therapy is reported. The danger of prolonged administration of the drug is stressed.

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Medical Memoranda

Three Cases of Weil's Disease

The following cases illustrate the necessity for considering the diagnosis of Weil's disease even if at first sight there seems to be no obvious indication of the origin of the infection.

CASE 1

A man aged 27, of no special occupation, was admitted to hospital on October 30, 1946, with a four-days history of rigor, cough, dyspnoea, constipation, aching in the body and limbs, and general weakness.

On examination—T. 103° F. (39.4° C.), P. 126, R. 28—he appeared flushed, with a dry tongue. Air entry was weak at both lung bases, with occasional rhonchi and crepitations. A provisional diagnosis of influenzal pneumonia was made, and penicillin was given three-hourly. On October 31 jaundice developed, and on November 2 the spleen became palpable. The jaundice deepened and petechiae appeared in the flanks and on the palate.

Investigations.—*Leptospira icterohaemorrhagiae* agglutination was negative on November 1, but positive 1 in 1,000 on November 5. The blood count on November 12 showed: red cells, 4,820,000; Hb, 96%; white cells, 15,000 (71% polymorphs). The sedimentation rate was 31 mm. in one hour (Westergren). Liver-function tests (November 13) showed serum bilirubin 13 mg. per 100 ml.; icterus index 100; thymol turbidity 5 units; Takata-Ara weak positive. Urine (November 4) contained bile pigments, salts, urobilin (in excess), and hyaline casts. The urine was negative for leptospire on November 12.

The patient received a total of 1,500,000 units of penicillin in seven days, and was discharged quite well on November 20.

CASE 2

A salesman aged 27 was admitted to hospital on December 25, 1948, with a three-days history of anorexia, abdominal pain, constipation, and pains in the head and back.

On examination—T. 98.8° F. (37.1° C.)—his chest was normal, there was some epigastric tenderness, and the urine contained some albumin and blood. A provisional diagnosis of acute nephritis was made. On December 27 jaundice appeared.

Investigations.—December 27, *L. icterohaemorrhagiae* agglutination was positive 1 in 300. The blood count (December 29) showed 5,900 white cells, with 58% polymorphs. Liver-function tests (December 30) showed a biphasic van den Bergh reaction, serum bilirubin 6 mg. per 100 ml., icterus index 88, thymol turbidity 8 units, alkaline phosphatase 53 units, colloidal gold +, Takata-Ara + + +, serum cholesterol 225 mg. per 100 ml. Blood urea (December 29) was 18 mg. per 100 ml. The urine contained some bile and an occasional granular cast.

The patient received 100,000 units of penicillin four-hourly for 14 days, and was discharged on January 12, 1949, symptom-free.

CASE 3

A female bar attendant aged 48 was admitted to hospital on January 21, 1949, with an eleven-days history of rigor,

vomiting, pyrexia, pain across the back, oliguria, headaches, anorexia, hiccup, and insomnia. Jaundice appeared four days before admission.

On examination she appeared very ill; she was deeply jaundiced, with a normal temperature. The blood pressure was 170/100; chest normal. Petechiae were present over the arms and under the left breast. The spleen was not palpable. A hard lump was present in the left breast, and a provisional diagnosis of carcinoma of the breast, with secondaries in the liver, was made.

Investigations.—*L. icterohaemorrhagiae* agglutination was positive 1 in 300 on January 24. On January 30 the titre rose to 1 in 3,000, and *L. canicola* was positive 1 in 100. The latter fell to 1 in 10 on March 8, while *L. icterohaemorrhagiae* agglutination still remained 1 in 3,000. The blood count (January 24) showed: red cells, 3,900,000; Hb, 80%; white cells, 19,800 (85% polymorphs). The sedimentation rate was 46 mm. in one hour (Wintrobe). Liver-function tests on January 21 showed a direct positive van den Bergh, serum bilirubin 11 mg. per 100 ml.; thymol turbidity 7 units; alkaline phosphatase, 4 units. On February 12 the bleeding time was 1 minute, coagulation time 5 minutes, prothrombin index 86% normal. The blood urea dropped from 264 mg. per 100 ml. on January 21 to 40 mg. on January 27. Urine (January 21) showed: albumin ++, bile pigments ++, bile salts +, chlorides practically absent, hyaline casts ++, granular casts +, culture *Bact. coli*, urea 1.43 mg. per 100 ml. On February 11 (after penicillin was stopped) a centrifuged deposit of urine showed no leptospirae. Guinea-pig inoculation showed no lesions or leptospirae in the liver and kidney. The serum of the husband and that of their dog were examined on February 6, and were negative for *L. icterohaemorrhagiae* and *L. canicola*.

The patient was put on intravenous normal saline, a low protein diet, vitamin K, and alkalis. Four-hourly penicillin was begun on January 26 and stopped on February 10, 19,000,000 units having been given. The patient was discharged on March 26, symptom-free. (It is of interest to note that the lump in the breast, operated on later by Mr. Basil Hume, turned out to be a chronic non-malignant cyst.)

COMMENT

The usual occupation of a sufferer from Weil's disease is one which brings the person in contact with water polluted by rats—for example, miners, farmers, sewer workers, butchers, and those employed in the fish industry.

In Case 1 the patient had recently been chopping wood in a damp cellar, and, as Eagle (1948) points out, the organisms of *L. icterohaemorrhagiae* may remain viable in water for 22 days and in moist soil for three months. In Case 3 the surroundings of the public-house where the patient was working were damp and infested with rats, and she had been in the habit of daily preparing the chicken-run with straw. It is not known how the infection was contracted in Case 2.

My thanks are due to Dr. James Maxwell for the diagnosis and guidance in Case 3, to Dr. C. J. C. Britton for the pathological investigations, and to Dr. J. C. Broom for the agglutination and guinea-pig inoculation in this case. Cases 1 and 2 are published by kind permission of Dr. A. I. Suchett-Kaye.

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Alopecia Congenita: Report of Two Families

The number of families suffering from alopecia congenita reported in the literature is very small, and it is worth while to put on record two families which we came across at the Miller General Hospital as the result of certification for wigs under the National Health Service Act.

Various forms of the disease have been reported. Alopecia may be complete or partial; it may be associated with other

defects, such as abnormalities of teeth and nails, cataracts and strabismus, and syndactylism. Cockayne (1933) believes that there are more than one recessive and more than one dominant type of inheritance of this condition. Consanguinity has been observed in a number of families. In our families there was alopecia only, without associated defects.

FAMILY A

A brother and sister, of normal parents and both completely bald, married a brother and sister who were their first cousins, also of normal parents, only the brother being bald. The issue of the marriage of the two bald people was five children, all of whom were bald. One of these is married to a normal person and has two normal children.

FIG. 1.—Family A.

The other marriage resulted in eleven children, of whom four were bald. One of the normal children is married and has five normal offspring. Two of the children suffering from alopecia are married to normal people and have normal children. One member of the first generation and five of the second generation were examined. All were completely bald. Eyebrows were absent, there were only a few eyelashes, and pubic and axillary hair was scanty.

FAMILY B

A girl was seen suffering from total alopecia, which had been present since birth. She had six brothers and sisters,

FIG. 2.—Family B.

two of whom were twins. Her parents were first cousins. Her paternal grandmother, who was also seen, had lost her hair at the age of 13, for an unknown reason, but on examination sparse growth of normal hair was present.

I am indebted to Dr. C. V. Henriques for drawing my attention to these cases and to Dr. I. Magnus for his interest and help.

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