The accompanying photographs illustrate several of these areas. The table is based only upon clinical estimation of the condition, but in conjunction with the photographs it may serve to give a comprehensive picture of the result up to the time of writing.

FIG. 1.—Right arm (a) before treatment; (b) eight days after treatment was begun, showing complete regression of ichthyosiform skin. (Left arm shows exactly the same picture.)

FIG. 2.—Legs seen from right (a) before treatment; (b) four weeks after treatment, showing complete regression of ichthyosiform skin in some areas and improvement in others. (The left sides of the legs show the same picture.)

FIG. 3.—Skin of right thigh (a) before treatment; (b) one month after treatment was begun.

The improvement in the patient's mental state has been as dramatic as his organic improvement. Previously his schooling and social contact had been reduced to a minimum, his sensitivity towards his smell and appearance causing him to become lonely and solitary, with a hopeless attitude towards future friendship and employment. Now he has become a happy, normal boy, though still educationally retarded, and is already being employed as an electrician's assistant.

Whereas during the first few weeks clearance of the affected areas was rapid and dramatic, during the last few months there has been no appreciable change. There has, however, been no relapse of the improved areas over a period of one year.

Conclusions

From this response to hypnosis one of two inferences may be drawn. Either there is a hitherto unsuspected psychic factor in the aetiology of the disease or this is a case of a congenital organic condition being affected by a psychological process. A combination of both these factors is of course a third possibility. Whichever is true, the improvement in this case seems to be totally unprecedented, and was effected after the failure of all recognized methods of treatment.

I wish to thank Mr. F. T. Moore for permission to publish his case, and Mr. Gordon Clemetson for the photographs.

FATAL APLASTIC ANAEMIA AFTER CHLORAMPHENICOL TREATMENT

BY

L. A. HAWKINS, M.B., B.Chir., M.R.C.P., D.C.H.

AND

H. LEDERER, M.B., D.P.H.

(From the Royal Infirmary, Doncaster)

Two children living in the same town, but having little else in common, had whooping-cough treated by chloramphenicol in January and February, 1952, jaundice in March, and minor purpuric manifestations in May, ending in mid-June in the death of both from uncontrollable haemorrhages with an aplastic bone marrow. The close parallelism between the two cases led to the only known common factor, chloramphenicol, being suspected as the cause soon after the second patient was admitted to hospital.

A number of deaths from aplastic anaemia after treatment with chloramphenicol have been reported in the United States, and the literature was reviewed in a leading article in the *Journal* of July 19, 1952 (p. 136). It seems highly probable that the aplastic anaemia in these two children was also due to chloramphenicol, and it is on this supposition that the cases are reported.

Case 1

A girl aged 4 years who was known to have been a contact of whooping-cough began to cough in the last week of January, 1952. On February 6 her doctor made a diagnosis of whooping-cough, and prescribed chloramphenicol palmitate, 250 mg. three times daily. This treatment was continued to a total of 20 g. in about 27 days. The cough persisted, but the child's general condition remained good. On March 16, 39 days after the start of treatment with chloramphenicol (C+39), she was listless and tired and generally unwell, she vomited, and the stools were noted to be pale

and the urine dark. The next day her doctor found her "well jaundiced." In spite of fairly severe jaundice she seemed to feel comparatively well, ate well, and lost little weight. The jaundice had almost completely faded by April 9 (C+63). The child, however, was not really well, and was apt to come indoors from playing to rest.

On May 2 (C+86) an unusual amount of bruising on her legs was noticed, and between one and two weeks later there was widespread painless bruising of the left thigh. On May 29 she complained of slight headache, and two days later (C+115) had a sore throat with fetor oris, shivered, and was tired. Her nose bled and a cut on the lip appeared to bleed longer than normally. On June 2 (C+117) she was thought to be paler than usual, and this pallor gradually increased afterwards. On June 4 and 5 she vomited "coffee grounds," and on the 5th she also vomited fresh blood.

On June 5 (C+120) she was extremely pale and evidently gravely ill, although she was afebrile and the pulse, at a rate of 110, was of comparatively good volume. Her tonsils were much enlarged and haemorrhagic but showed little sign of inflammation. There were slight oozing from the gums and many fading subcutaneous ecchymoses. No enlargement of liver, spleen, or lymph nodes was found, nor any other abnormality. She was admitted to hospital and a transfusion of 2 pints (1.1 litres) of blood was given. Blood counts are shown in Table I.

TABLE I.—Blood Counts in Case 1

Date	Haemo- globin	R.B.C. (millions)	W.B.C.	Poly- morphs	Lympho- cytes	Plate- lets	Trans- fusion
June 5	23	1.0	4,800	144	4,656	6	2 pints
" 9	60	2.6	2,700	162	2,538	0	—
" 10	47	2.25	1,800	234	1,494	—	—
" 11	48	—	1,100	77	990	0	—
" 13	34	—	1,600	48	1,536	—	2 pints
" 17	36	2.28	4,100	0	4,100	—	—
" 18	25	1.10	950	0	931	0	1 pint
" 19	44	1.70	1,100	0	1,078	0	—

After the initial transfusion she improved considerably, but on June 7 (C+122) her temperature rose to 103° F. (39.4° C.) and haematuria and melaena occurred and continued until the next day. A haematoma of the lower lip appeared. On June 9 there was persistent bleeding from the wound after iliac puncture. After three days of little change a gross haematoma appeared deep in the left buttock, with much swelling of the left leg. Her general condition deteriorated rapidly on June 13 (C+128), when dyspnoea and adventitious sounds in the chest developed. Her condition again deteriorated on June 18, and death occurred on the 20th (C+135).

Treatment

Before Admission to Hospital.—Apart from chloramphenicol the whooping-cough was treated only by simple linctuses. No drug treatment was given for the jaundice. "Cremotresamide" 2 dr. (7 ml.) thrice daily, was given when the sore throat developed on May 31, and penicillin on June 4 and 5.

After Admission.—Chloramphenicol palmitate, 250 mg. six-hourly, was given for the first three days, then replaced by penicillin for two days, after which sulphadimidine was given. Chloral was used as a hypnotic. "Kapilon," 1 ml. twice daily, and ascorbic acid, 50 mg. thrice daily, were given initially. A.C.T.H. was begun on June 17 in a dosage of 10 mg. eight-hourly for three doses, and then 5 mg. six-hourly until death.

Case 2

A girl aged 7½ had a cough starting in December, 1951. About three weeks later it became paroxysmal and there was a whoop. On January 16 she saw her doctor, who prescribed chloramphenicol palmitate, 250 mg. three times daily. This treatment was continued to a total of 24 g. in 32 days, suspended for about a week, and then continued with another 4 g. in five days: in all she received 28 g.

within a period of about 44 days. She was not ill enough to be in bed with whooping-cough, but the cough persisted in some degree until her admission to hospital and she had never seemed in full health since it began. She was, however, thought to be well enough to return to school on March 3 and 4.

On March 5 (C+49) jaundice was noticed, the motions being pale and the urine dark. Otherwise she seemed no more ill than before. She did not vomit. Her doctor noted that the jaundice was slight on this day, but it increased in intensity for about 10 days. She was cheerful and lively, and ate well throughout the jaundice, remaining indoors, but not in bed. The jaundice lasted five to six weeks, and had almost gone on April 9 (C+84).

During the next two to three weeks she had two episodes of nasal discharge, with exacerbation of the cough, and in mid-May (approximately C+120) painless bruises appeared on the fronts of the legs, and soon after there were small blotches on the upper arms and above the clavicles. Fresh lesions continued to appear every few days. On May 31 (C+136) bleeding from the gums occurred, for which she was treated at the school dental clinic on June 4 and 6. On June 4 a red mark appeared over the left eye. She had a severe headache in the evening and a "black eye" the next day. On June 7 (C+143) she was still bleeding from the gums and was admitted to hospital.

On examination she was seen to be a girl of slender build, weight 49 lb. (22.2 kg.), who did not look particularly ill, but seemed fairly well and lively. Her skin looked pale, but the mucous membranes were fairly well coloured. There were multiple ecchymoses on the left upper arm and around the neck, petechiae on both forearms, and bruises on the legs. Lymph nodes, little enlarged, were palpable in both posterior triangles of the neck, but not notable elsewhere. There was no pyrexia; the pulse rate was 112. Blood counts are shown in Table II.

TABLE II.—Blood Counts in Case 2

Date	Haemo- globin	R.B.C. (millions)	W.B.C.	Poly- morphs	Lympho- cytes	Plate- lets	Trans- fusion
June 7	60	3.3	5,300	1,378	3,610	Grossly reduced	—
" 9	55	2.6	—	—	—	0	—
" 10	50	2.2	3,800	608	3,040	<5,000	—
" 11	44	2.2	4,500	270	4,230	0	1 pint
" 15	50	—	—	—	—	—	2 pints
" 16	70	3.3	1,300	220	1,040	—	—

For the first five days in hospital the child remained well and had a good appetite, though on June 11 (C+147) bleeding of the gums and lips recurred and continued with little interruption until death. There was also persistent bleeding from the skin puncture wounds for blood counts, the marrow puncture wound, and the site of blood transfusion. This bleeding was controlled in some measure by the local application of "hemoplastin." On June 13 her temperature was 101° F. (38.3° C.). Next day she was much worse, with gross haematuria, and a transfusion of 1 pint (570 ml.) of blood was given, but in spite of some improvement in colour her general condition deteriorated steadily from this time until her death.

On June 15 another 2 pints (1.1 litres) of blood was given. Fresh purpuric haemorrhages appeared and there was intermittent haematuria. On June 16, with gradually increasing clouding of consciousness, a left spastic hemiparesis appeared, and the next day there were athetoid movements of the right arm. She died on June 18 (C+154).

Treatment

Before Admission to Hospital.—No treatment was given for the whooping-cough apart from chloramphenicol. The patient was treated for threadworms with pil. violae crys., ½ gr. (32 mg.) twice daily for seven days, two courses at a

week's interval, in January and February, and with aspirin tablets for a while during jaundice in March. She attended the school clinic during the month of May and was treated with a malt and iron mixture and ultra-violet light.

After Admission.—Folic acid, 10 mg. thrice daily, was given from June 10; aureomycin, 250 mg. six-hourly, was begun on June 13; and A.C.T.H., 10 mg. eight-hourly, was begun on June 17, only three doses being given before death.

Other Laboratory Findings

No reticulocytes or normoblasts were found at any time. The Coombs test was negative in both cases. The urine showed no abnormality when tested in haematuria-free intervals. In Case 2, on June 14, the serum bilirubin was less than 1 mg.; serum alkaline phosphatase, 13.5 (King) units; thymol turbidity, 2 units; colloidal gold, 0; blood urea, 31 mg. per 100 ml.; serum protein, 7 g.% (serum albumin 4.1 g., globulin 2.9 g.%).

Iliac and tibial punctures carried out on successive days in Case 1 and iliac puncture in Case 2 provided films void of bone marrow elements and differing from peripheral capillary blood only by a slight increase of lymphocytes. On two occasions the aspirate contained a considerable amount of fat globules.

Necropsy Findings

The outstanding feature common to both cases was severe anaemia, multiple large, small, and petechial haemorrhages into skin, mucous and serous membranes, and into the parenchyma of most organs, varying only in intensity and localization. Inflammatory or necrotic lesions were minimal. The lymphatic organs were not enlarged.

In Case 1 a number of small haemorrhages about 2 mm. in diameter were scattered throughout the brain, and a larger haemorrhage 7 mm. in diameter was present in the left frontal lobe. The tonsils were enlarged as a result of parenchymal haemorrhage but not ulcerated. The distal third of the oesophagus was covered by a thick, adherent, brownish red slough, consisting histologically of necrotic and haemorrhagic mucosal debris invaded by massive thrush mycelium and a variety of cocci and bacilli. The vertebral bone marrow and the marrow of the iliac crest at the site of the puncture were pale brown and the femoral epiphyses pale pink. The metaphysis was of pink jelly-like appearance. The liver was congested and weighed 750 g.; the spleen weighed 22 g.

In Case 2 a massive haemorrhage into the right frontal lobe had resulted in bulging of the lobe, which, with additional smaller haemorrhages of pea size into the right thalamus, the anterior commissure, and the left parietal, left occipital, and right cerebellar lobes, had caused increase of the intracranial pressure. The tonsils were large and superficially ulcerated. The spleen was small (45 g.), the liver of normal size (700 g.). The appearance of the bone marrow was identical with that of Case 1 except for a fatty yellowish appearance of the femoral metaphysis.

The histological appearances were almost identical in both cases. Sections of bone marrow taken from lumbar vertebrae, femoral metaphyses and epiphyses, and from the site of previous iliac punctures showed pronounced reduction of cellular elements. The marrow consisted almost entirely of fat and a network of capillaries with only scanty nucleated cells distributed uniformly or forming a few small islands of densely packed lymphocytes and plasma cells. It was difficult to identify with any degree of certainty erythroid or myeloid elements. In addition, scanty phagocytic reticulum cells containing a small amount of haemosiderin were scattered through the marrow. Oedema with small zones of focal necrosis were present in the subchondral zone. No erythrophagocytosis or haemorrhages were noted in the examined sections. The lymph nodes showed blood in their sinusoids and the same changes as the spleen—namely, reduction in size and number of follicles and absence of germinal centres, which in a few follicles were replaced by

a necrotic zone. The cells lining the sinusoids were conspicuous; some contained fine haemosiderotic pigment, and a few showed erythrophagocytosis. Haemosiderin-containing macrophages were also noticed in the pulp and in the lumen of sinusoids. There was no myeloid metaplasia. The liver showed light portal infiltrates of lymphocytes and plasma cells, and no condensation of reticulin or collagen. The liver cells, apart from changes attributable to anoxia, showed no gross changes. Kupfer cells were conspicuous and a few contained a minimal amount of iron pigment. The kidneys showed degenerative changes of the tubular epithelium and, apart from pelvic haemorrhages, no pathological changes. These findings strongly resemble the changes described by Mallory *et al.* (1939) in bone marrow, spleen, and lymph nodes in fatalities resulting from exposure to benzene.

Comment

Attention is drawn to the following points: (1) The dosage of chloramphenicol was large and the treatment prolonged. (2) Jaundice appeared 39 days and 49 days after chloramphenicol treatment was started, and 12 and 5 days after administration had ceased. (3) Though jaundice was well marked, and present for upwards of 24 and 35 days, other symptoms at this time were mild—milder than in most cases of infective hepatitis of similar duration. (4) The first purpuric manifestations were noted 86 and about 120 days after the start, and 59 and about 76 days after the end of chloramphenicol administration. (5) Depression of bone-marrow function seems to have occurred in the order thrombocytopenia, granulocytopenia, anaemia. There was little clinical evidence of the effect of agranulocytosis, and there seems to have been little anaemia until massive haemorrhage had occurred. (6) After a period of minor purpura lasting 34 and 29 days, massive haemorrhages began to occur, death following in 15 and 5 days. (7) Treatment with A.C.T.H. was started late in the period of massive haemorrhage. It had no apparent effect, but no conclusions can reasonably be drawn from this trial.

Discussion

Among the five cases reported by Volini *et al.* (1950) and Gill (1950), granulopenia occurred with a small dose of chloramphenicol and before the sixth day of treatment. The lowest neutrophil counts recorded were 918 in an infant of 13 months, 1,500 in an infant of 4 months (Gill), and 2,480 in a boy of 14 years (Volini *et al.*). In the other two cases the dose was over 50 g., and severe granulopenia (256 and 660 neutrophils) occurred 23 and 19 days after the first administration of chloramphenicol. In all five cases recovery occurred immediately after suspension of the drug and no gross bone-marrow changes were shown. In the three cases reported by Rich *et al.* (1950) and Wilson *et al.* (1952), administration of the drug was prolonged (12, 26, and 28 weeks), the total dosage exceeded 50 g., and purpuric manifestations developed while the drug was being given. Two of the patients died from aplastic anaemia and the third showed prolonged depression of bone marrow function. In our two cases the total dosage was equivalent to over 50 g. in an adult and was given for four and six weeks. In spite of suspension of the drug, purpuric manifestations occurred during the 13th and 17th weeks after treatment had started. In the interval both patients had an episode of jaundice.

While it is possible that the coincidence of an attack of infective hepatitis may have determined the aplastic anaemia, it is more reasonable to assume that both jaundice and aplastic anaemia were due to the same toxic agent. Rich, quoting Kracke and Parker (1934), Rebstock *et al.* (1949), and Smadel (1949), drew attention to the possibility that the nitrated benzene radical in chloramphenicol may be responsible for depression of the haemopoietic system. Thrombocytopenia, granulocytopenia, aplastic anaemia, lymphatic atrophy, liver damage, the great variation in susceptibility, and the occurrence of symptoms early or late in exposure or even at a considerable time after exposure has ceased are all features of the toxic effect of aminobenzene or nitrobenzene

derivatives. The occurrence of all these manifestations during or after chloramphenicol treatment supports the supposition that its toxic action is comparable with that of other aminobenzene or nitrobenzene derivatives.

Summary

Two fatal cases of aplastic anaemia in children, occurring at a considerable interval after chloramphenicol therapy, are reported. Jaundice preceded symptoms of blood disorder. Haematological and necropsy findings are described.

We are indebted to Dr. J. D. Bowie for detailed case histories.

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FATAL APLASTIC ANAEMIA AFTER CHLORAMPHENICOL

BY

B. WOLMAN, M.D., M.R.C.P., D.C.H.

*Consultant Paediatrician to Bury and Rochdale Hospitals;
 Clinical Lecturer in Paediatrics, University
 of Manchester*

A growing number of reports from the United States incriminate chloramphenicol as the cause of severe and sometimes fatal aplastic anaemia. The following case history is recorded in order to stress the danger of this new drug.

Case Report

A 6-year-old boy had been well until March 1, 1952, when he developed a pyrexial illness characterized by cough and bouts of vomiting. Although whooping was not reported, contact with a school friend with pertussis was established, and the family doctor, making a diagnosis of whooping-cough, prescribed chloramphenicol, 250-mg. capsules, one to be taken twice daily. Forty-eight such capsules were taken over a period of 24 days. His symptoms slowly abated, the illness lasting about six weeks. He returned to school during the last week of April.

On May 1 he seemed listless and apathetic, and the mother, noticing his yellow colour, kept him off school again. The jaundice, according to the mother, lasted for two days. On May 14 bruises were noted on his buttocks and back, and one week later, after severe epistaxis and the appearance of further bruising, he was admitted to hospital.

On admission (May 22) the boy was pale and ill. Blood was oozing from both nostrils. There was an icteric tinge to the conjunctivae, scattered petechiae were seen over the tongue and buccal mucous membrane, and numerous ecchymoses all over the body. The spleen and lymph nodes were not palpable. The liver was enlarged, its edge being palpable about 1½ in. (3.8 cm.) below the costal margin. A soft systolic murmur was audible at the cardiac apex. One petechial haemorrhage was noted on the left optic fundus, but no abnormalities were detected in the central nervous system.

Examination of the blood showed a haemoglobin of 48% (7.1 g.), and 2,000,000 red cells, 3,000 leucocytes, and 60,000 platelets per c.mm. No immature white cells and no reticulocytes were seen in a blood smear. Bleeding time was 15 minutes (Duke's method), and clotting time 4 minutes. The fragility of the red cells was within normal limits. Examination of a specimen of aspirated iliac marrow showed mainly fat and reticulum cells with hypocellularity of all blood elements. A diagnosis of aplastic anaemia was made on the marrow findings.

Despite the transfusion of 2 pints (1.1 litres) of blood on the next day there was little change in his condition. The haemoglobin rose to 65% (9.6 g.). The epistaxis continued despite nasal packing. A raised ulcerated plaque was noted on the mucous membrane of the inside of the right cheek, extending to the right faucial pillar, and the icteric tinge was still present.

Penicillin, pentnucleotide, and vitamin K were given in adequate doses, but fresh petechiae appeared. Despite a further transfusion of 3 pints (1.7 litres) of blood on May 31, next day the haemoglobin was recorded as 50% (7.4 g.) and blood was oozing from the nose, gums, and bowel. The patient gradually became hyperpyrexial and comatose, and, despite a further blood transfusion, died on June 2.

At necropsy, purpuric and ecchymotic haemorrhages covered the trunk and limbs, and were particularly marked at the transfusion sites. Petechial haemorrhages were scattered over the pleura, the visceral pericardium, and throughout the myocardium. There were scattered ecchymotic areas in the terminal ileum, and blood was present in the gastro-intestinal tract. There was no lymphadenopathy. The liver was enlarged and showed generalized fatty change. Fatty degeneration of liver cells and some periportal round-cell infiltration were noted on microscopical examination. The spleen was congested; no special features were noted histologically. There was a large haemorrhage in the pelvis of the right kidney, and scattered petechial haemorrhages were found throughout the parenchyma of both. The femoral bone marrow, pale yellowish red in colour, was mainly fatty and all blood elements were deficient.

Comment

This boy was given 0.5 g. of chloramphenicol daily for a 24-day period, thereby receiving 12 g. over a prolonged interval for an illness thought to be pertussis. This dosage, on a 25 mg. per kg. of body weight basis, falls within the suggested daily dose limits for children. In fact for the treatment of pertussis the suggested dose has been much higher—namely, 100 mg. per kg. per day—but a five-day period of therapy only has been recommended. This child therefore received the drug for a period almost five times as long as the suggested treatment time.

His illness began, about a month after cessation of chloramphenicol administration, with jaundice, which was still present, associated with hepatomegaly, on admission to hospital three weeks later. The clinical suggestion of hepatitis was confirmed at necropsy. He died from an acute fulminating aplastic anaemia, the symptoms of which became obvious about a week after the onset of the illness. The diagnosis of the blood condition was based on the bone-marrow findings, the depression of all elements being quite striking. There were no immature white cells in the marrow or peripheral blood, and the spleen and lymph nodes were not enlarged. The absence of leukaemic tissue was confirmed at necropsy.

It is admitted that the occurrence of severe bone-marrow depression during the course of treatment of a disease with a new drug does not of itself prove the drug to be the cause of the trouble. A blood condition of this type can occur spontaneously of unknown aetiology, or be a manifestation of the original or some intercurrent infection, or be due to some other medication. However, in the present