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## The 'grey toddler' Chloramphenicol toxicity

Reports of neonatal death associated with the administration of chloramphenicol first appeared in 1959 (Sutherland, 1959; Lischner *et al.*, 1961). In most cases therapy had been instituted in the first 2 days of life and symptoms became apparent 36 to 48 hours later. The characteristic features were abdominal distension, vomiting, progressive pallid cyanosis, irregular respiration, hypothermia, and vasomotor collapse (the 'grey baby' syndrome). Death followed if treatment was continued, but rapid and complete recovery usually took place if chloramphenicol therapy was terminated. The babies had high serum chloramphenicol concentrations because of slow glucuronide conjugation within the immature liver (Weiss, Glazko, and Weston, 1960).

The toxic effects of chloramphenicol have not been described in children more than 2 months old. We therefore describe a child of 25 months with features characteristic of the 'grey baby' syndrome and a high blood chloramphenicol level, and 2 younger children with similar symptoms in whom estimates of blood chloramphenicol concentrations were not obtained.

### Case reports

**Case 1.** A 25-month-old boy was admitted to hospital in September 1972 with a 7-hour history of progressive pallor and withdrawal. Examination revealed a sick child who had a good peripheral circulation and normal blood pressure. Rectal temperature was 38.7 °C and there was moderate neck stiffness. Lumbar puncture produced a cloudy fluid with 5000 polymorphs/mm<sup>3</sup>, protein 472 mg/100 ml, and glucose less than 10 mg/100 ml. A Gram stain showed pleomorphic Gram-negative bacilli in the film; a diagnosis of *Haemophilus influenzae* meningitis was made and later confirmed by culture. Intravenous treatment was started with sulphadimidine 150 mg/kg per day and chloramphenicol sodium succinate 110 mg/kg per day, together with 250 mg streptomycin twice a day intramuscularly. The child was much improved, taking notice of his surroundings, and was apyrexial within 18 hours.

Then, 36 hours after treatment was started, he vomited a small amount of bile-stained fluid, the abdomen became slightly distended, and bowel sounds became sparse. Intravenous fluids were continued and he was treated with nasogastric suction, but after 68 hours he rapidly worsened with a grossly distended abdomen, absent bowel sounds, deep sighing respiration, and an ashen-grey appearance. A severe metabolic acidosis (pH 7.23, base excess -14) was partially corrected with sodium bicarbonate and plasma was later given for peripheral circulatory collapse. At 71 hours he had a cardiac and respiratory arrest but received immediate cardiac massage and responded after 14 minutes.

The possibility of this very unusual picture being due to chloramphenicol toxicity was suggested by Professor J. K. G. Webb and treatment with this drug was therefore discontinued. Within 12 hours of substituting ampicillin for chloramphenicol the abdomen was softer, and within 24 hours there were bowel sounds and other signs of general improvement. The blood chloramphenicol concentration was measured during the period of recovery using a microbiological assay (adapted from the method described by Grove and Randall, 1955) and a biochemical assay (Kakemi, Arita, and Ohashi, 1962), the results being summarized in the Fig. Serum

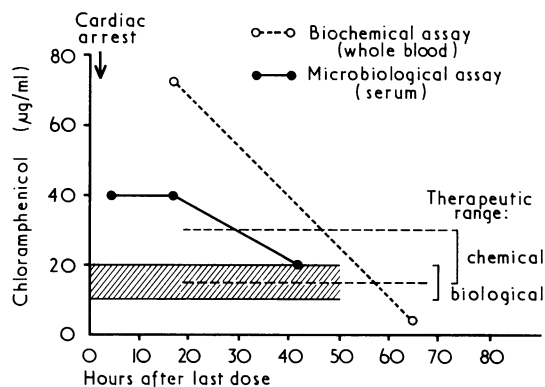


FIG.—Chloramphenicol concentrations as determined by microbiological assay of serum and a biochemical method of whole blood. (The difference in the results from the two assays is due to the high affinity of red cells for chloramphenicol.)

bilirubin was 0.7 mg/100 ml and serum glutamic oxaloacetic transaminase 70 IU/l. shortly after cardiac arrest; 48 hours later these had risen to 3.0 mg/100 ml and 163 IU/l, respectively, but they returned to normal over the next 7 days.

The boy later developed severe pneumonia and diarrhoea with monilial overgrowth of the bowel, but made a complete mental and physical recovery and was discharged home after a total of 3 weeks in hospital. The parents are unwilling to countenance further liver function studies at present but they feel he is none the worse for his experience.

**Case 2.** An 8-month-old girl was admitted because of sudden anorexia, increasing irritability, and vomiting without localizing signs of infection, followed by a left-sided convulsion. An immediate lumbar puncture produced blood-tinged fluid without an excess of polymorphs and was later reported to be sterile on culture, but treatment with penicillin G, sulphadimidine, and 90 mg/kg chloramphenicol intravenously each day in divided doses was started directly after lumbar puncture because early bacterial meningitis could not be ruled out. (CSF from a second lumbar puncture 4 days later contained 25 lymphocytes/mm<sup>3</sup>, but was otherwise normal.) The child remained irritable and withdrawn, and 48 hours after admission there was evidence of further deterioration with renewed vomiting followed by ileus and gross abdominal distension; there was increasing pallor, the peripheral circulation became poor, body temperature became subnormal, blood pressure fell to 70/45 mmHg, urine output decreased, and there was evidence of increasing metabolic acidosis. The child's condition improved slightly after the dose of chloramphenicol was halved 60 hours after admission, but ileus persisted for 48 hours after chloramphenicol was completely withdrawn 3 days later. Rapid improvement occurred after this but abdominal distension remained a feature for a further 2 days. Liver function tests at this time were normal. The girl subsequently made a full recovery from this unexplained encephalitis.

**Case 3.** A 6-month-old boy was admitted with pyrexia and signs of an upper respiratory tract infection which settled rapidly after admission. Then, after 2 days, the child suddenly developed a high pyrexia, neck stiffness, and a faint fleeting petechial rash suggestive of meningococcal infection. CSF appeared normal on lumbar puncture and later proved sterile on culture, but treatment was started with 150 mg/kg sulphadimidine and 100 mg/kg chloramphenicol intravenously each day in divided doses. The child seemed much better 36 hours later but then developed marked abdominal distension and ileus with hypotonia, weakness, vomiting, and pallor, all of which subsided as soon as chloramphenicol was withdrawn after 3 days' treatment. The boy subsequently made a complete recovery and was discharged home after 13 days, but has since received anticonvulsant therapy because of febrile convulsions.

### Comment

These 3 children developed similar symptoms while being treated with chloramphenicol. They had a higher dose than is sometimes recommended, but a dose well within the 150 mg/kg recommended by Hutchison (1972). In each case vomiting followed by abdominal distension, pallor, and ileus became noticeable 2 days after treatment was started, and in Cases 1 and 3 these features developed quite unexpectedly at a time when the children were showing signs of recovery. A defect in glucuronide conjugation might conceivably explain the intolerance to chloramphenicol, but none

of the children had shown any evidence of liver dysfunction before their illness. The blood chloramphenicol level was very high at the time the first child collapsed, and remained in the therapeutic range for 2 whole days after treatment was withdrawn; this seems to confirm our assumption that the near-fatal collapse of this 2-year-old child was the result of chloramphenicol toxicity. Blood chloramphenicol levels were not estimated in the other 2 children, but the early symptoms were similar and improvement was apparent within 24 to 48 hours of treatment being withdrawn.

Much has recently been written regarding the virtue of employing ampicillin on its own in the treatment of bacterial meningitis (Murray *et al.*, 1972; Girgis *et al.*, 1972). We do not feel that evidence of occasional chloramphenicol toxicity should necessarily influence the choice of treatment in this condition, but we do wish to draw attention to the risk of toxicity when a high dose is employed in young children. Failure to recognize the early signs and symptoms and to adjust therapy accordingly could be fatal.

### Summary

Three children aged 6, 8, and 25 months are described who exhibited a combination of symptoms and signs characteristic of the 'grey baby' syndrome after the administration of chloramphenicol. It is suggested that this should be a nonfatal condition if the clinical picture is recognized early enough.

We thank Professor J. K. G. Webb for his help with Case 1; Drs. T. C. Noble and C. E. Cooper for permission to report Cases 2 and 3; and Drs. G. Dale and G. M. Williamson for the chloramphenicol assays.

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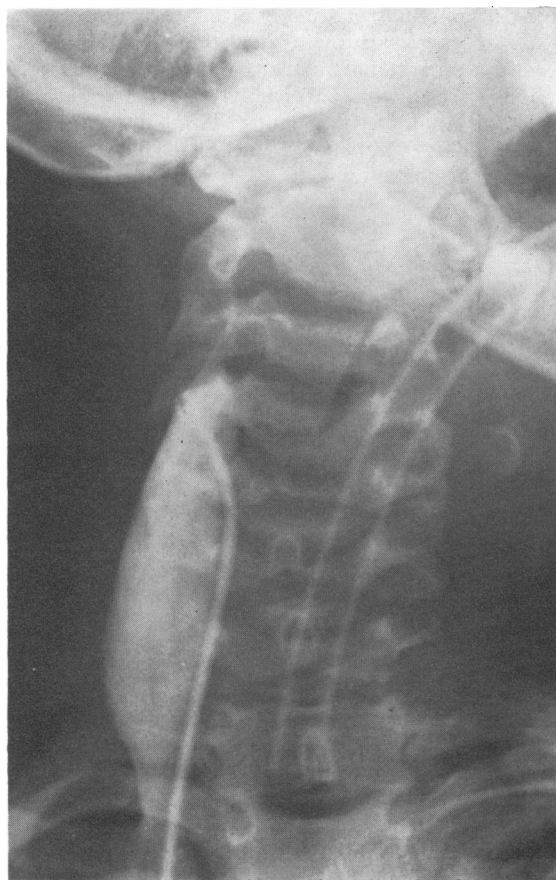
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## Effect of head rotation on jugular vein blood flow

During a cardiac investigation blood oxygen saturations in the innominate veins were noticed to vary when the child moved his head. It seemed



(a)

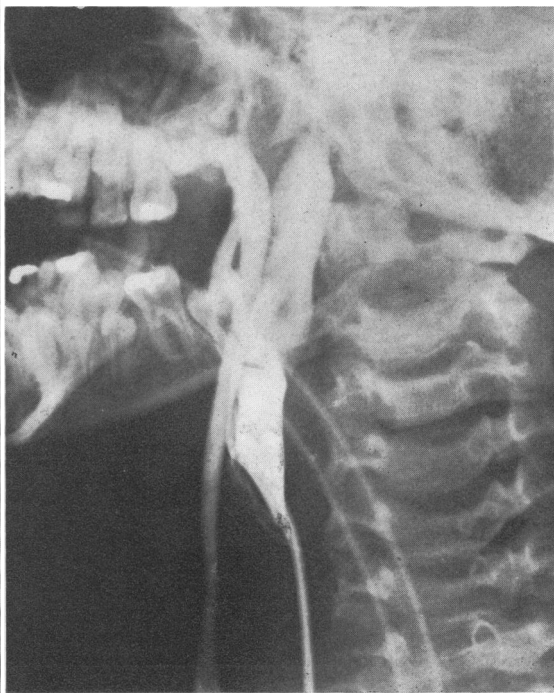
possible that alterations in jugular vein flow were responsible, particularly in view of the well-known changes in cervical venous hums caused by rotation of the head. To study this effect, internal jugular venography was performed by manual injections of radio-opaque medium under fluoroscopy at the beginning of cardiac catheterization in 60 infants and children who had various congenital cardiac anomalies but no other major malformations.

### Method

A catheter introduced from the leg was passed into one or both of the internal jugular veins where this could be done with a minimum of manipulation and without inconvenience to the child. The head was then rotated to varying degrees, as far as the child could maintain by himself if unanaesthetized. 16 children were anaesthetized for the cardiac investigation, and the others were sedated with trimeprazine, except for small infants who received no sedation. Though the 60 patients represented only a minority of the total number undergoing investigation, it is unlikely that the results were affected.

### Results

Flow in an internal jugular vein was not affected by contralateral rotation of the head (Fig. 1a), but



(b)

FIG. 1.—Right internal jugular venogram. (a) Head turned to left showing free downward flow, (b) head turned to right showing vein occluded; escape of medium to smaller veins.