STAINING OF CHILDREN'S TEETH BY TETRACYCLINE

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From recent literature[1,2] it has become apparent that the primary teeth of a number of premature and full-term infants may become discoloured because of tetracycline administered to these babies during the neonatal period. The discolouration varies from bright yellow to yellow-brown. When such teeth are examined under an ultraviolet lamp they show a bright yellow fluorescence.[2] Wallman and Hilton[1] demonstrated that the ultraviolet spectra of solutions of the extracted tooth pigment gave an absorption band at 270 mμ, and tetracycline hydrochloride suitably suspended showed absorption bands at 220, 270, and 350 mμ. The same authors discuss the frequent association of enamel hypoplasia with discolouration of the teeth in their series.

CASE HISTORIES

Four case histories are described to illustrate these features.

Case 1

M.V. was born at 30 weeks gestation and weighed 2 lb. 10 oz. She was asphyxiated at birth, but soon breathed spontaneously. She received prophylactic tetracycline phosphate complex ('tetrex') intramuscularly for the first 6 days of life to a total of 300 mg., and a further 125 mg. at intervals during the following 2 weeks by mouth and by intramuscular

injection. She received no further tetracycline during her first year of life. Other antibiotics used in the neonatal period to treat a lung infection were streptomycin, chloramphenicol, and ampicillin ('penbritin'). She developed mild physiological jaundice. She received 35 ml. of blood by scalp vein for mild anaemia at the age of 2 months. Her subsequent progress was satisfactory, and she was discharged from hospital 2½ months after birth weighing 5 lb. 1¼ oz. She cut her first tooth at the age of 10 months. At 13 months there were 7 teeth which were well formed and showed no apparent signs of enamel hypoplasia, but they were all uniformly canary yellow in colour. There was no evidence of pigment staining of her skin, sclerae or nails. At the age of 15 months she weighed 25 lb. Her milestones were normal, and 8 teeth were present. The cutting edges of the teeth were sharp and thin. They were dull yellow in colour with irregular brown mottling of the enamel. Under ultraviolet light the teeth gave a yellow fluorescence which was especially noticeable in the distal half of the teeth.

Case 2

E.E. was the first of twins who were born prematurely. Birth weight was 4 lb. 4½ oz. The infant was blue and limp at first. He slowly improved, but 3 hours after birth respiratory distress developed. Physical signs showed cyanosis and moderate sternal recession and poor air entry over the lower zone of the right lung. Treatment included a total of 225 mg. of tetracycline phosphate (tetrex) intramuscularly over a period of 3½ days. The baby improved and was discharged 22 days later weighing 5½ lb. Only slight icterus neonatorum was observed.

He was breast fed for 6 months. The first tooth erupted at 5 months. He was seen at 16 months for acute bronchiolitis. He weighed 26 lb. He had 12 teeth which were yellow in colour. The anterior molars were noticeably yellow, but there was no evidence of enamel hypoplasia. The teeth fluoresced under ultraviolet light. An iron-deficiency anaemia (Hb=65%) was treated at the same time as the chest.

Case 3

E.E. was the second twin and brother of Case 2. He weighed 4 lb. 14¾ oz. at birth and he also showed signs of respiratory distress. He received 275 mg. of tetracycline phosphate (tetrex), 75 mg. of which was given intramuscularly and 200 mg. orally. He made an uneventful recovery. At 16 months he had 12 teeth which were bright yellow in colour, slightly hypoplastic, and they also fluoresced under UVL.

Case 4

T.T. was a full-term infant born after a perfectly normal delivery. Several hours after birth he became cyanosed and distressed, and atelectasis was diagnosed. Treatment included 6 days of intramuscular and oral tetracycline phosphate compound (tetrex).

The parents noticed that the infant's teeth were yellow when they first erupted. At the age of 4 years the child had 20 teeth. All the teeth were discoloured brown, particularly at their distal ends. The enamel of the bicuspids was hypoplastic so that the cusps appeared sharp and saw-like. The canines were narrow, sharp and hypoplastic. Several dental caries were also present. The teeth gave a slight yellow fluorescence under UVL. In comparison, the teeth of his 2 older sisters were well-formed, unstained, and relatively free of caries.

DISCUSSION

Discolouration of teeth was reported several years ago in children who suffered from mucoviscidosis and who were on long-term tetracycline therapy.[3,4] It is now known that tetracycline can be deposited in bone and in the dentine and enamel of teeth, possibly by forming complexes with calcium ions. Yellow-staining of bones caused by tetracycline and chlortetracycline has been shown to develop in animals,[5] and stunting and malformation of bones in chick embryos have been demonstrated when tetracycline was administered.[6,7] However, there is no evidence of teratogenic effect in the human embryo.

Enamel hypoplasia, pitting of the enamel, and malformed cusps may go hand-in-hand with yellow or brown discolouration of childrens' teeth after tetracycline therapy (Case 4). This usually follows in teeth where the yellow staining is at first intense. Whether tetracycline deposition causes enamel hypoplasia in every instance is uncertain, since enamel hypoplasia without discolouration may be observed in premature infants who have never received tetracycline.[9] Proved tetracycline-stained teeth may show no evidence of enamel hypoplasia, as in Case 2.

According to Wallman and Hilton[1] the severity of pigment discolouration of the teeth is related to the high total dosage of tetracycline rather than to the duration of therapy. Another observation is that the more premature the baby, the greater is the extent of enamel involvement. The colour of the teeth varies according to the age of the child. The younger the child, the brighter the yellow pigment, while in older children the pigment is more brownish. The teeth change from yellow to brown with the passage of time, and eventually parts or the whole of the brown-discoloured teeth may lose their fluorescence. This change in colour is probably brought about by the oxidation process of the tetracycline compound in the teeth.

Tetracycline is slowly removed from teeth and bones of affected children, and any ill-effects of prolonged retention of the drug in these and in other organs are as yet unknown. Teratogenic effects, which are reported to occur in the chick embryo,[6] should nevertheless not be overlooked in humans.

The permanent teeth are unlikely to be affected by tetracycline administered during the newborn period or later in infancy, since the evidence is that the chief risk of tetracycline pigment deposition occurs during the period of rapid development of the tooth bud. Once the enamel is laid down and the teeth are mature, there is little likelihood of significant tetracycline deposition. Tetracycline is thus unlikely to damage the teeth of children over the age of 6 months. On the other hand, the more immature the infant, the greater the chances of tetracycline deposition in growing teeth and bones. It is unlikely that the poor glomerular filtration rate of the immature kidney of the premature baby causes higher blood levels of tetracycline and consequently greater tissue penetration.

Administration of tetracycline during pregnancy has not definitely been shown to affect the teeth of the foetus, but if given during the last trimester of pregnancy in big doses and for long periods, that possibility can arise.[8] Tetracycline passes freely through the placental barrier to the foetus.

Great care should be taken in the choice of antibiotics for prophylactic and curative therapy in premature as well as full-term infants. The number of side-effects of antibiotics is increasing, and alarming results are seen from time to time. Chloramphenicol, for instance, may cause the 'grey syndrome' owing to the inability of the immature liver to metabolize and detoxicate the drug as rapidly as the mature liver. Novobiocin may give rise to yellow pigmentation of the skin and eyes and occasionally to liver

damage.[10] The sulphonamides, e.g. sulphafurazole ('gantrisin') are not without dangers in premature infants since they elevate the unconjugated form of bilirubin in the blood, and this in turn may lead to kernicterus in susceptible babies.

Tetracycline is normally a bright yellow compound. It stains the skin when handled and it turns the urine yellow. We can now add to these minor drawbacks the more serious ones of staining the teeth, hypoplasia of the enamel, and the staining of bones and certain other organs, e.g. the eye, particularly in premature infants. Other effects, such as malformation of bones and stunting of growth, are not certain,[11] but Bevelander[7] reports that when newborn infants are given tetracycline in doses of 100 mg./kg. for 10 days, the result is a decrease of up to 40% in the linear growth of the fibula as compared to the normal growth rate. After cessation of drug therapy the rate of growth returns to normal. He also attributes a number of cases of dental caries in children to tetracycline administration during infancy which has led to enamel hypoplasia.

Tetracycline is otherwise safe and popular and it has a wide antibiotic spectrum. Its use should not be lightly discarded in the newborn period, but before prescribing any antibiotic in this age group, the dosage and side-effects of this antibiotic preparation should be carefully considered. Wallman and Hilton[1] pointed out that oxytetracycline did not produce staining of teeth in their cases. While chlortetracycline is known to stain the bones of animals,[5] there is no reliable evidence to date that this drug and related demethylchlortetracycline can affect the teeth and bones of infants.[11] Demethylchlortetracycline is normally broken down in the body with the release of chlortetracycline or free base.

The soluble salts of penicillin, streptomycin, erythromycin, and the newer penicillins,[12] e.g. ampicillin, methicillin and cloxacillin, are well tried and relatively safe antibiotics and few infections of the neonatal period fail to respond rapidly and completely when these antibiotics, singly or in combination, are given.

SUMMARY

The case histories of 4 children are presented whose primary teeth were discoloured yellow from past tetracycline therapy in the newborn period.

Their teeth frequently show enamel hypoplasia which may be an important factor in the development of dental caries later on in childhood.

Antibiotics are often needed for the treatment and prevention of infections in the neonatal period. Great care should be exercised in the choice of an antibiotic for infants of this age group. Side-effects may be harmful, while the correct dosage of the antibiotic should be ascertained before prescribing the drug.

Tetracycline-stained teeth are not only unsightly but they may also be costly because of the dental attention required later. It would appear that tetracycline should be given with great circumspection to infants under the age of 6 months, considering the complications of tetracycline.

REFERENCES

1. Wallman, I. S. and Hilton, H. B. (1962): Lancet, **1**, 827.
2. Davies, P. A., Little, K. and Aherne, W. (1962): *Ibid.*, **1**, 742.
3. Zegarelli, E. V., Denning, C. R., Kutscher, A. H., Juoti, F. and Di Sant'Agnese, P. A. (1960): Pediatrics, **26**, 1050.
4. Shwachman, H., Fekete, E., Kulozycki, L. L. and Foley, G. E. (1958 - 59): *Antibiotics Annual*, p. 502. New York: Medical Encyclopaedia Inc.
5. Buyske, D. A., Eisner, H. J. and Kelley, R. G. (1960): J. Pharmacol., **130**, 150.
6. Bevelander, G., Nakahara, H. and Rolle, G. K. (1959): Nature (Lond.), **184**, 728.
7. Bevelander, G. (1963): Brit. Med. J., **1**, 54.
8. Rendle-Short, J. (1962): Lancet, **1**, 1188.
9. Miller, J. (1962): *Ibid.*, **1**, 1072.
10. Hargreaves, T. and Holton, J. B. (1962): *Ibid.*, **1**, 839.
11. Leading article (1962): *Ibid.*, **1**, 847.
12. Stewart, G. T. and Holt, R. J. (1963): Brit. Med. J., **1**, 308.