

## VI. CASE REPORTS AND RETROSPECTIVE STUDIES

Case 1: Discolouration of Primary Teeth due to Prenatal Administration of Tetracycline.

A. Chief Complaint:- Two brothers, John and Stephen, aged 5 years and 2<sup>1</sup>/<sub>2</sub> years respectively, were brought to the Department of preventive Dentistry of the University of Sydney for routine dental checkup. The mother complained that the teeth of both her children were severely stained.

B. Clinical Examination:- The primary teeth of both patients were coloured yellow to grey-brown and fluoresced under ultraviolet light (3650 Angstrom). The fluorescence was more intense in both the upper and lower posterior teeth. The anterior teeth of John, the older of the two, had a more greyish brown hue, whereas Stephen's teeth exhibited the more vivid yellow colour characteristic of tetracycline deposition. John's teeth were photographed using Kodachrome II film and electronic flash of 5600°K colour temperature (See Plates 1A - 1D).

C. Medical History:- The boys were born full-term. They were not jaundiced at birth, nor during the lactation period. There was no history of hepatitis. John received tetracycline (Mysteclin) therapy for bronchitis in short courses during the first twelve months of life. Stephen had colitis when he was 18 months old, for which he was given pencillin.

The mother further reported that she had been taking tetracycline (Achromycin) for the treatment of bronchiectasis 8 years prior to John's

Case 1. Discolouration of the primary teeth associated with both prenatal and postnatal administration of tetracycline in a 5 year old boy.



Plate 1-A - The anterior teeth of the patient showing the greyish colour of the incisal  $\frac{2}{3}$  of the labial surface and the yellow colour in the gingival  $\frac{1}{3}$  of the same surface.



Plate 1-B - A more detailed illustration of the anterior teeth showing the distribution of the grey and yellow colouring.

Plates 1 C and D - Photographs of the upper left anteriors and upper right molars showing the difference in staining of the anterior and posterior teeth.



Plate 1-C - Upper left anterior and posterior teeth.



Plate 1-D - Upper right anterior and posterior teeth.

birth. She had been taking this drug continuously during both pregnancies and after the birth of both children up to the present time. She has had parts of her right and left lungs removed and the tetracycline is being used as a prophylactic measure. The mother now takes 250 mg. tablets of Achromycin, four times daily, and previously took larger doses.

D. Diagnosis:- From the medical history, it is apparent that the discolouration of the teeth arose from prenatal administration of tetracycline. This is a positive case of tetracycline crossing the placenta and affecting the developing teeth. The subsequent pigmentation manifested by the younger sibling further strengthens this explanation.

Tetracycline therapy of the mother during the prenatal period of both siblings affected the developing dentition. It is to be expected that if the mother continues to take the drug, as she probably will, the teeth of future children will also be affected.

Case 2:- Tooth discolouration and hypoplasia associated with prenatal tetracycline therapy.

A. Chief Complaint:- Gary B., an 18 month old boy, was brought to the Department of Preventive Dentistry of the University of Sydney by his parents who were very much concerned about the generalised staining and hypoplasia of the teeth.

B. Medical History:- The patient was born prematurely on 18 August 1966. The mother recalled that she took a drug which was probably tetracycline, during the 6th to 8th month of her pregnancy for acute toxemia. No tetracycline was administered after birth.

C. Clinical Examination:- The gingival two-thirds of the central incisors were both stained and hypoplastic. The cusps of the molars, the incisal half of the canine as well as the whole crown of the laterals were affected. (See Plates 2A - 2H.) The characteristic yellow colour of tetracycline pigmentation was observed under ordinary light. The teeth were exposed to ultraviolet light of 3650 Angstrom Unit and they fluoresced a golden yellow colour. The teeth were photographed in Kodachrome II film both in white light of 5600 degrees K and under ultraviolet light.

D. Diagnosis:- This is a case of tetracycline-induced discolouration as a result of administration of the drug during the latter months of pregnancy which stained the enamel and dentine of the teeth developing at the time. The hypoplastic changes

Case 2. Teeth discolouration and hypoplasia associated with prenatal tetracycline therapy in an 18 month old boy. Plates 2 A,B,C,D photographed on Kodachrome II illumination white light 5600°K.



Plate 2-A - Upper anterior teeth showing hypoplasia and staining.



Plate 2-B - Lower anterior teeth showing hypoplasia and staining.



Plate 2-C - Right canines and molars showing hypoplasia and staining.



Plate 2-D - Lower left canine and molar showing hypoplasia and staining.

Plates 2 E,F,G,H photographed on Kodachrome II film illumination ultraviolet light 3650 Angstrom Units.

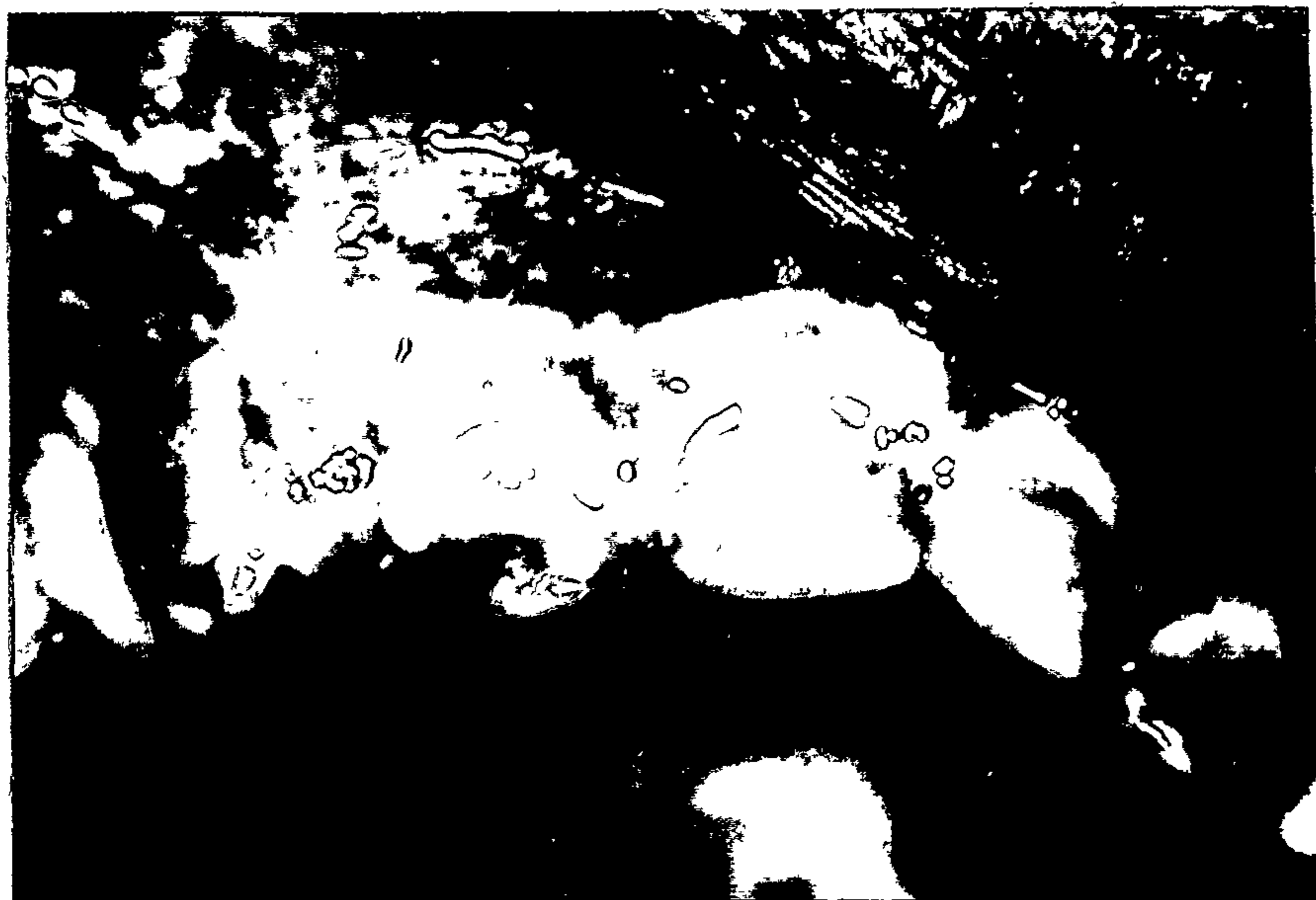


Plate 2-E - Upper central and lateral incisors and upper right canine showing the hypoplasia and staining.



Plate 2-F - Upper left central and lateral incisors, canine and molar showing hypoplasia and staining.



Plate 2-G - Lower left primary molars showing hypoplasia and staining.



Plate 2-H - Lower right primary molar showing hypoplasia and staining.

are typical of a neo-natal hypoplasia and do not conform to the stained areas of the teeth which are more extensive. These stained areas appear equally extensive under ultraviolet light indicating tetracycline deposition. The lack of conformity between the stained and hypoplastic areas could well indicate two separate factors in the etiology of the staining and hypoplasia. The hypoplasia could be the result of the local anoxia subsequent to the haemolytic anaemia as the occurrence of hypoplastic tooth defects and staining are observed in many premature children whose mothers have not been given tetracycline.

Case 3:- Tooth Staining Associated with Postnatal Tetracycline  
Therapy and Cystic Fibrosis of the Pancreas.

A. Chief Complaint:- Dianne, a 7 year old girl, was referred to the Department of Preventive Dentistry of the University of Sydney because of generalised and unaesthetic discolouration of her teeth. The mother stated that the teeth were pigmented from the time of eruption and the colour was of persistent intensity.

B. Family History:- The patient was the second child, the first having died of cystic fibrosis of the pancreas 8 months after birth.

C. Past Medical History:- The child was a full-term infant and was given tetracycline (Mysteclin) when she was 3 months old for cystic fibrosis of the pancreas. The therapy had continued since then as a prophylactic measure. Two and a half years ago, however, the drug was discontinued and she was given penicillin. She now occasionally receives short courses of Mysteclin. The child did not receive any local or topical medication of any kind which could possibly contribute to the staining observed.

D. Clinical Examination:- The patient appeared healthy and according to the mother is of high scholastic standing in her class. No facial assymetries were noted and the teeth were free from caries. The lips, mucous membrane, tongue and gingival tissues were normal. The occlusion is normal for her age.

Both the primary and secondary dentition were discoloured and an unsightly grey-brown to black. Under ultraviolet light of 3650

Angstrom, the first secondary molars and the gingival portions of the lower secondary central incisors showed fluorescence characteristic of tetracycline deposition. The gingival regions of the remaining teeth exhibited less extensive fluorescence (Plates 3A - 3E).

D. Diagnosis:- Discolouration of teeth associated with Cystic Fibrosis of the Pancreas and Postnatal Tetracycline Therapy.

It has been known for a considerable period of time that patients with cystic fibrosis of the pancreas may develop erythrodonia of both the primary and the secondary dentitions. The exact cause, however, has not been specifically determined. There is a possibility that the staining may be due to: (a) certain antibiotics (tetracycline), deposited in dentine and/or enamel of teeth; and (b) that the disease itself through some unknown mechanism is directly responsible for this discolouration.

Case 3. Tooth Staining Associated with Postnatal Tetracycline Therapy and Cystic Fibrosis of the Pancreas in a 7 year old girl. Plates A,B,C,D photographed on Kodachrome II illumination white light 5600°K.

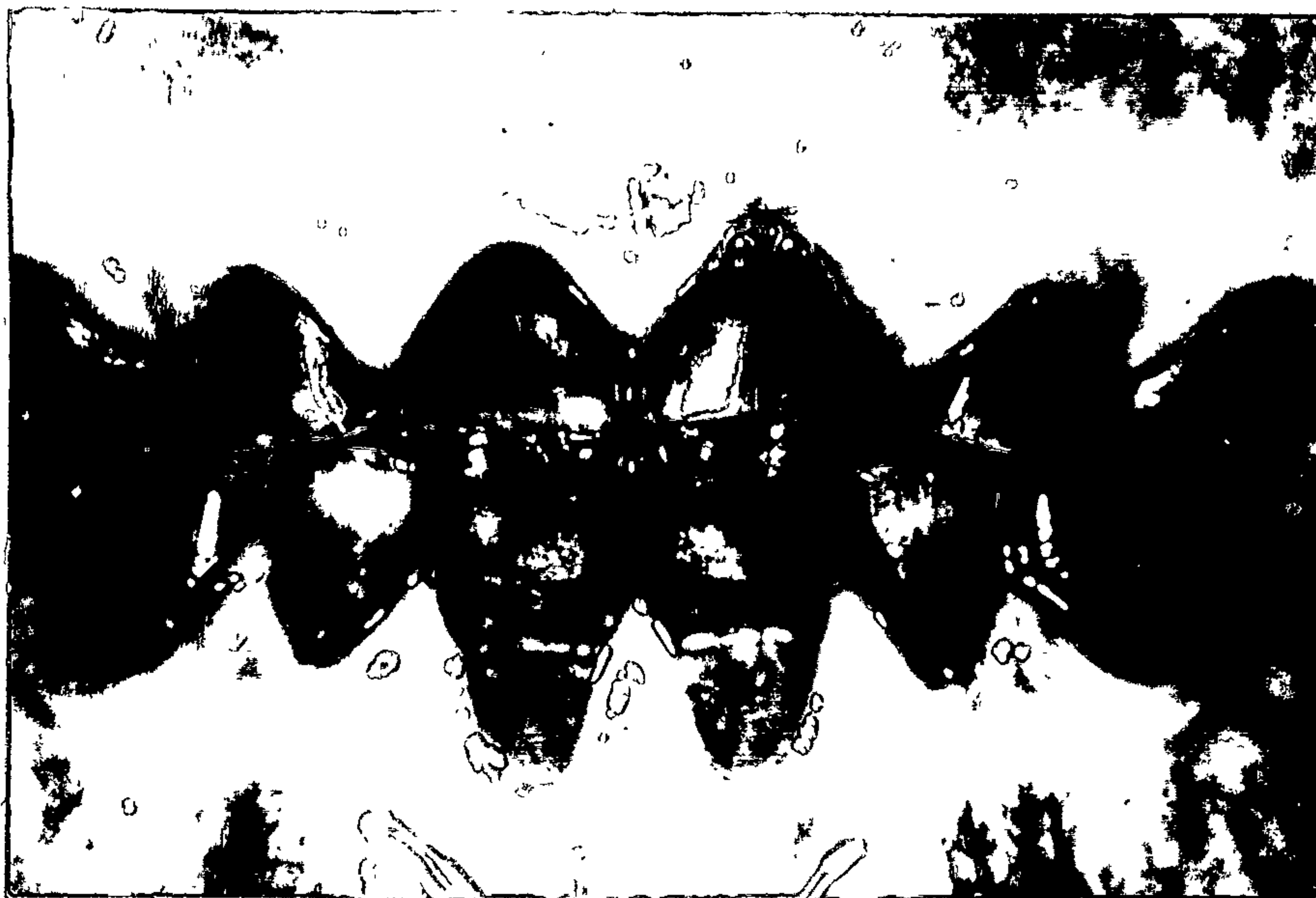


Plate 3-A - Anterior primary teeth and lower secondary central incisors showing grey-black staining and yellow staining in the gingival area of the labial surface of the secondary centrals.



Plate 3-B - Lingual of the upper primary anteriors showing the brown and black staining.



Plate 3-C - Lower right primary molars and secondary first molar showing the grey-black and brown staining as well as the yellowish staining at the gingival third of the labial surface.



Plate 3-D - Lower left primary molars and the secondary first molar showing the same distribution of the grey-black, brown and yellowish staining.

Plate 3-E - Anterior primary teeth and lower secondary centrals photographed on Kodachrome II illumination ultraviolet light 3650 Angstrom Unit.



Plate 3-E - This shows the typical yellow fluorescence of the gingival third of the labial surface of the secondary lower central incisors and to a lesser extent, the gingival labial areas of the primary lower anteriors and several upper anteriors.

Tamworth Survey: The dental survey team of the Department of Preventive Dentistry (Martin and Barnard)<sup>71</sup> examined 4,690 children of Tamworth, New South Wales. The examination of school children whose ages ranged from 4 to 17 years (kindergarten to high school) was part of a long-term study of fluoridation in Tamworth. The children were examined under ultraviolet light to determine the prevalence of tetracycline compounds present in the clinical crowns of teeth as shown by the characteristic golden-yellow fluorescence. A darkened room was used for this purpose, and the teeth were illuminated with 3650 Angstrom ultraviolet lamp (Black-Ray Lamp, Ultraviolet Inc., San Gabriel, California). To facilitate the recording of the presence of golden yellow fluorescence, the upper and lower jaws were divided into three segments, one anterior, and one each, right and left posteriors. The examiners who had no knowledge whatsoever of the child's exposure to antibiotic or medical history, conducted the ultraviolet examination independently after the routine clinical examination in connection with the fluoridation study had been completed.

The colour of the teeth, the area and the size of the region of the teeth involved, were used as criteria for recognition of tetracycline staining and/or fluorescence. The teeth in question were creamy-yellow, yellow brown colour, and pigmentation was always the full width of the tooth at affected level. The staining should be bilaterally symmetrical and may extend laterally in a curvilinear distribution across a number of teeth.

The presence of developmental hypoplasia and/or opacity in both deciduous and permanent dentitions was recorded, not only for correlation with tetracycline fluorescence, but as a part of the routine annual dental examination.

Clinical records of children suspected of having tetracycline-induced fluorescence were studied, and the teeth with characteristic staining and ultraviolet fluorescence, were photographed at 1 X magnification of Kodachrome II film. Five of these cases are shown in Plates 4A - 4C; 5A - 5C; 6A - 6C; 7A - 7C; 8A - 8F; 9A - 9B. The transparencies from which these prints were made were analyzed in detail together with the records of the fluorescence pattern of individual children, to determine the relation of visible staining of the clinical crowns of teeth and the distribution of the fluorescence. To enable machine processing, the examination data was transferred to IBM punch cards from the clinical records. Teeth of children showing fluorescence with or without staining and/or hypoplasia and opacity, were analysed into these various groups. For each of the children whose teeth showed evidence of fluorescence, a medical history was taken from either the parents, or cross-checked with the child's history at Tamworth Base Hospital, and others with the child's family doctors. These medical histories specifically relate to antibiotic experience.

Fluorescence characteristic of tetracycline deposition was observed in 161 or 3.4 per cent of the 4,690 children at all age groups examined (Table VIII). Of these 161 children, 103 had visible

tetracycline staining of some teeth and the staining in all, except 2 children, was limited to primary or posterior secondary teeth. Only in 1 case was the "unacceptable" category found as a result of tooth staining. Except for two children, a history of systemic tetracyclines was definitely established among the 161 children whose teeth fluoresced. It may be pertinent to mention here that administration of tetracyclines in Tamworth in 1967 was 0.25 prescriptions per person per year. This figure is almost similar to that for New South Wales, 0.27, and Australia, 0.27. The 1960-61 prescription figures for tetracycline for New South Wales and Australia was 0.19 per person per year. These data were the earliest available for New South Wales and Australia (Martin).<sup>24</sup>

In spite of the fact that intrinsic tetracycline tooth staining was visibly evident when the photographic transparencies of 103 of the 161 children were examined, only in 26 of these was pigmentation obviously exhibited during the dental examination. The 26 patients were all aged 10 or under, and the clinically obvious discolouration was confined to the primary teeth in 24 of them. In four patients of the 4,690 sample, the teeth did not fluoresce, although they were observed to have tooth staining similar to that known to be tetracycline-induced.

Table IX will show that of the 103 with visible tetracycline staining, there was a greater number of children with secondary teeth involved than with the primary teeth. Anterior secondary teeth were affected in two of the group. Only one, however, of the

161 was classified as unacceptable.

A comparative prevalence of developmental defects of primary and secondary teeth for the group of 161 with tetracycline fluorescence and the total group examined in Tamworth is also shown in Table X. The unacceptable category of all developmental defects in the Tamworth school children was found to be 3 per 1,000. Enamel defects, not showing characteristic fluorescence were classified as hypoplasia and/or opacities. They were found to be more prevalent in the secondary dentition of the tetracycline group. Greater prevalence of opacities of enamel rather than hypoplastic defects was observed. Prevalence of hypoplasia in secondary dentition was low and similar in both groups and even lower was the prevalence of severe hypoplasia. No significant difference in prevalence of enamel defects for the primary dentition was observed in the tetracycline group compared with the total child population examined. Hypoplasia prevalence was low in the primary dentition and occurred with the same frequency in the tetracycline group as in a similar age sample of all children.

In this study, examination has been limited to clinical crowns of both primary and secondary dentitions. The presence therefore of tetracycline deposits are detectable only in the enamel or crown dentine of the teeth affected. It is of particular interest that such tetracycline compounds deposits were seen mostly at the gingival margin or neck of the tooth or teeth in question. This is where the enamel is thin and pigmented dentine shows through. It could be

surmised that the findings of this study (Table VIII), i.e. that only 161 out of 4,690 children exhibited tetracycline deposition, are not indicative that the total number of teeth would give evidence of tetracycline binding in the root dentine of teeth examined after extraction. Furthermore, in only 103 of 161 having fluorescence was this visible staining shown by both clinical and photographic records. In all the cases except one, the visible discolouration was not of grave concern ... not a functional or cosmetic handicap to the patient. Some of the children of the 36 whose primary teeth exhibited tetracycline discolouration could have been considered "unacceptable" but because these stained teeth were to be replaced by secondary teeth from the age of 5 to 6 years they were not classified as such. Clinically observable generalised staining, mostly of the primary teeth and from all causes, were very obvious in 30 children. Out of these 26 were confirmed as tetracycline-induced by ultraviolet examination and medical history. Only one child whose secondary dentition was affected would warrant treatment for aesthetic reasons. Most tetracycline staining was observed in the primary dentition, the clinical findings having been supported by the photographic records. Likewise, the greater prevalence of staining in the posterior secondary molars was observed, but in only 2 children was there involvement of anterior secondary teeth (Table IX).

There was no clinical evidence in this study of non-fluorescent pigmentation typical of the tetracycline staining pattern in the secondary teeth of these children up to 17 years of age. Based on the

photographic records, the ratio between fluorescence and visible staining appeared consistent throughout all age groups (Table VIII). Analysis of the prevalence of all developmental defects (hypoplasia and/or opacity) revealed that there was a higher prevalence of these defects than expected for the group exhibiting tetracycline fluorescence in both the primary and the secondary teeth (Table X). In the tetracycline group the prevalence of enamel hypoplasia was similar to that for all children. Enamel matrix formation did not appear to be influenced by the tetracyclines. Regarding disturbance in mineralisation, manifested by opacities, greater prevalence in all age ranges of the tetracycline group was evident.

From previous studies in New South Wales, enamel opacities in secondary teeth are normally present in 40 per cent or more children over the age of 9 years.<sup>71</sup> The same prevalence was found in Tamworth, although the tetracycline group in that city has a higher percentage of opacities than that which would be expected for a random group of similar size and age in the same city. The major cause of enamel opacities or localized hypomineralisation may be attributed to metabolic disturbances during tooth formation. Increased prevalence of opacities observed in the tetracycline group in the Tamworth study could be correlated with childhood metabolic disturbances necessitating the administration of tetracycline, rather than the tetracycline medication per se.

The extremely low prevalence of severe staining of the anterior secondary teeth (approximately 1 : 5,000), in the present school child

population in Tamworth suggests that tetracycline tooth staining cannot be considered to constitute a dental public health problem affecting either the aesthetic or functional properties of the teeth.

Table VIII. Distribution of Children Examined by Age, Ultraviolet Fluorescence and Visible Stain in the Tamworth (1967) Study. (Martin and Barnard)<sup>71</sup>

Age	Number Examined (Male & Female)	Children with Fluorescence		Children with Fluorescence plus visible Staining	
		Number	Per cent	Number	Per cent
4	93	10	10.7	8	8.6
5	470	31	6.6	19	4.0
6	511	22	4.3	15	2.9
7	478	13	2.7	8	1.7
8	455	11	2.4	2	0.4
9	450	19	4.2	11	2.4
10	389	8	2.1	4	1.0
11	396	13	3.3	9	2.3
12	429	7	1.6	5	1.2
13	349	8	2.3	5	1.4
14	314	6	1.9	6	1.9
15	206	7	3.4	7	3.4
16	124	5	4.0	3	2.4
17	26	1	3.8	1	3.8
<b>Total</b>	<b>4690</b>	<b>161</b>	<b>3.4%</b>	<b>103</b>	<b>2.2%</b>

Table IX. Distribution of Visible Staining in 103 of the Group of 161 Children with Ultraviolet Fluorescence in the Tamworth (1967) Study. (Martin and Barnard)<sup>71</sup>

Teeth Affected	Number of Children
Deciduous Teeth	36
Deciduous teeth and first permanent molars	8 - 44
Permanent Posterior teeth	57 - 65
Permanent Anterior teeth	2 - 2
Total	103

Table X. Comparative Prevalence of Enamel Hypoplasia and Opacities  
in all Children and Tetracycline Group in the Tamworth (1967)  
Study. (Martin and Barnard)<sup>71</sup>

AGE	NUMBER OF CHILDREN		HYPOPLASIA AND/OR OPACITY						
	Total Group	Tetracycline Group	DECIDUOUS TEETH			PERMANENT TEETH			
			Total Group %	Tetracycline Group Observed	Tetracycline Group Expected	Total Group %	Tetracycline Group %	Obs.	Exp.
4	93	10	19	2	2	-	-	-	-
5	470	31	13	7	4	7	19	6	2
6	511	22	14	1	3	23	27	6	5
7	478	13	9	1	1	29	38	5	4
8	455	11	8	2	1	39	55	6	4
9	450	19	6	4	1	40	42	8	8
10	389	8	4	2	3	42	75	6	3
11	396	13	-	-	-	42	61	8	5
12	429	7	-	-	-	43	57	4	3
13	349	8	-	-	-	46	63	5	4
14	314	6	-	-	-	43	83	5	3
15	206	7	-	-	-	43	71	5	3
16	124	5	-	-	-	44	80	4	2
17	26	1	-	-	-	44	-	1	-
TOTAL	4690	161		19	12			69	46
PREVALENCE %		161		12%	7%			43%	29%

\* Children showing tetracycline fluorescence of clinical crowns.

Tamworth Study Patient 1.

Discolouration of the Primary Teeth Associated with Prenatal Tetracycline Therapy in a 4½ Year Old Boy. Plates 4 A,B,C were photographed on Kodachrome II illumination white light 5600°K.



Plate 4-A - Anterior primary teeth showing the yellow staining of the gingival third of the labial surface.

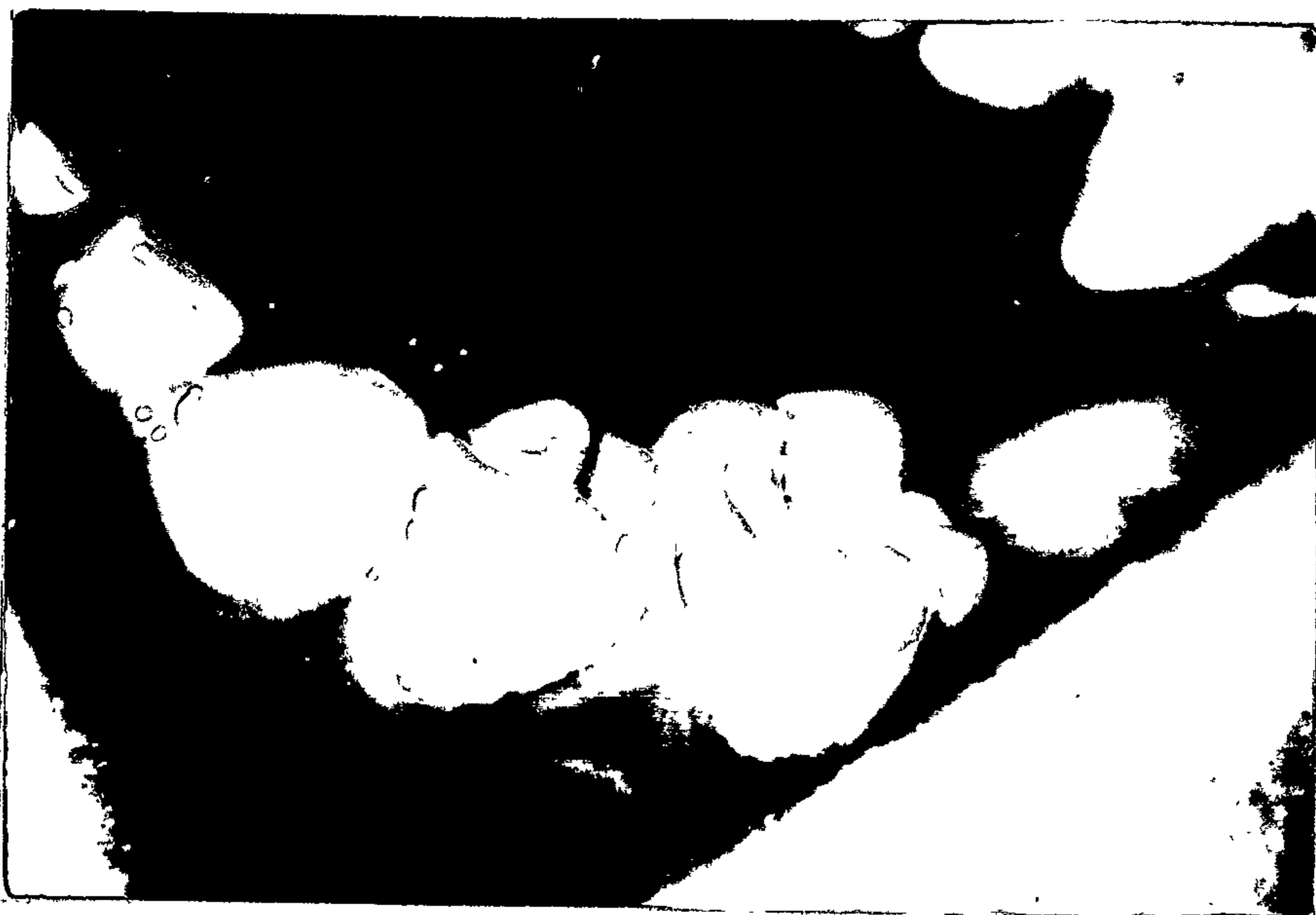


Plate 4-B - Lower right primary molars and canine showing the yellow staining at the gingival thirds of the labial surface and also the greyish colour of the lateral and central incisors.



Plate 4-C - Lower left primary canine and molars showing the yellow staining at the gingival thirds and grey incisal area of the lower lateral incisor.

Tamworth Study Patient 2.

Tooth Discolouration Associated with Tetracycline Administration  
in a 5 Year Old Boy. Plates 5 A,B,C were photographed on  
Kodachrome II illumination white light 5600°K.



Plate 5-A - Anterior primary teeth showing the typical yellow, brown and greyish staining.



Plate 5-B - Lower right primary canine and molars showing the yellow staining at the gingival thirds of the second primary molars and the greyish staining of the incisal and cuspal areas.



Plate 5-C - Lower left primary lateral incisor and canine showing the greyish staining of the incisal thirds of the labial surface. The primary molar shows greyish staining of the cusps.

Tamworth Study Patient 3.

Discolouration of the Secondary Anterior Teeth of a 9 Year Old Girl Associated with Tetracycline Therapy. Plates 6 A,B,C were photographed on Kodachrome II illumination white light 5600°K.



Plate 6-A - Anterior secondary teeth showing yellow staining.



Plate 6-B - Lower right canine and the posterior teeth showing the yellow staining. A greyish staining could be observed in the cuspal areas.



Plate 6-C - Lower left canine and posterior teeth showing the same distribution of yellow and greyish staining as in Plate 6B.

Tamworth Study Patient 4.

Discolouration of Secondary Teeth of a 13 Years 9 Months Old Boy  
Associated with Postnatal Administration of Tetracycline.

Plates 7 A.B.C were photographed on Kodachrome II illumination  
white light 5600°K.

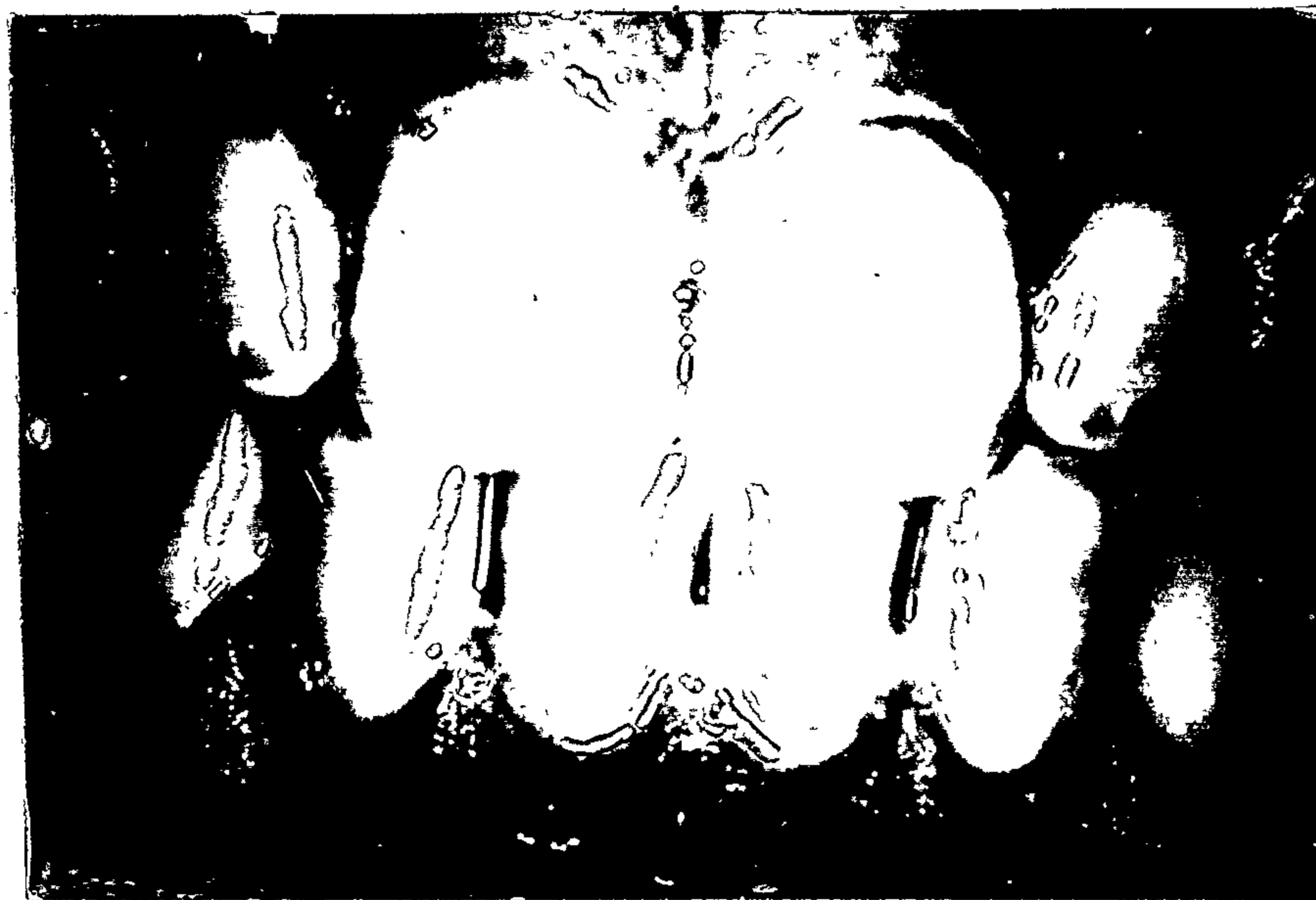


Plate 7-A - Anterior secondary teeth showing the yellow-brown staining.



Plate 7-B - Lower right posterior teeth showing a generalized yellow staining.



Plate 7-C - Lower left posterior teeth showing a generalized yellow staining.

Tamworth Study Patient 5.

Tooth Discolouration Associated with Postnatal Tetracycline Therapy in a 16 Year Old Girl. Plates A,B photographed on Kodachrome II illumination white light 5600°K.



Plate 8-A - Lower right posterior teeth showing yellow staining particularly the gingival area of the buccal surface of the second molar.



Plate 8-B - Lower left posterior teeth showing yellow staining identical with that observed on the right side.

Plates 8 C, D, E, F on Kodachrome II illumination ultraviolet light  
3650 Angstrom Units.



Plate 8-C - Anterior secondary teeth showing the yellow fluorescence at the gingival thirds of the labial surfaces.

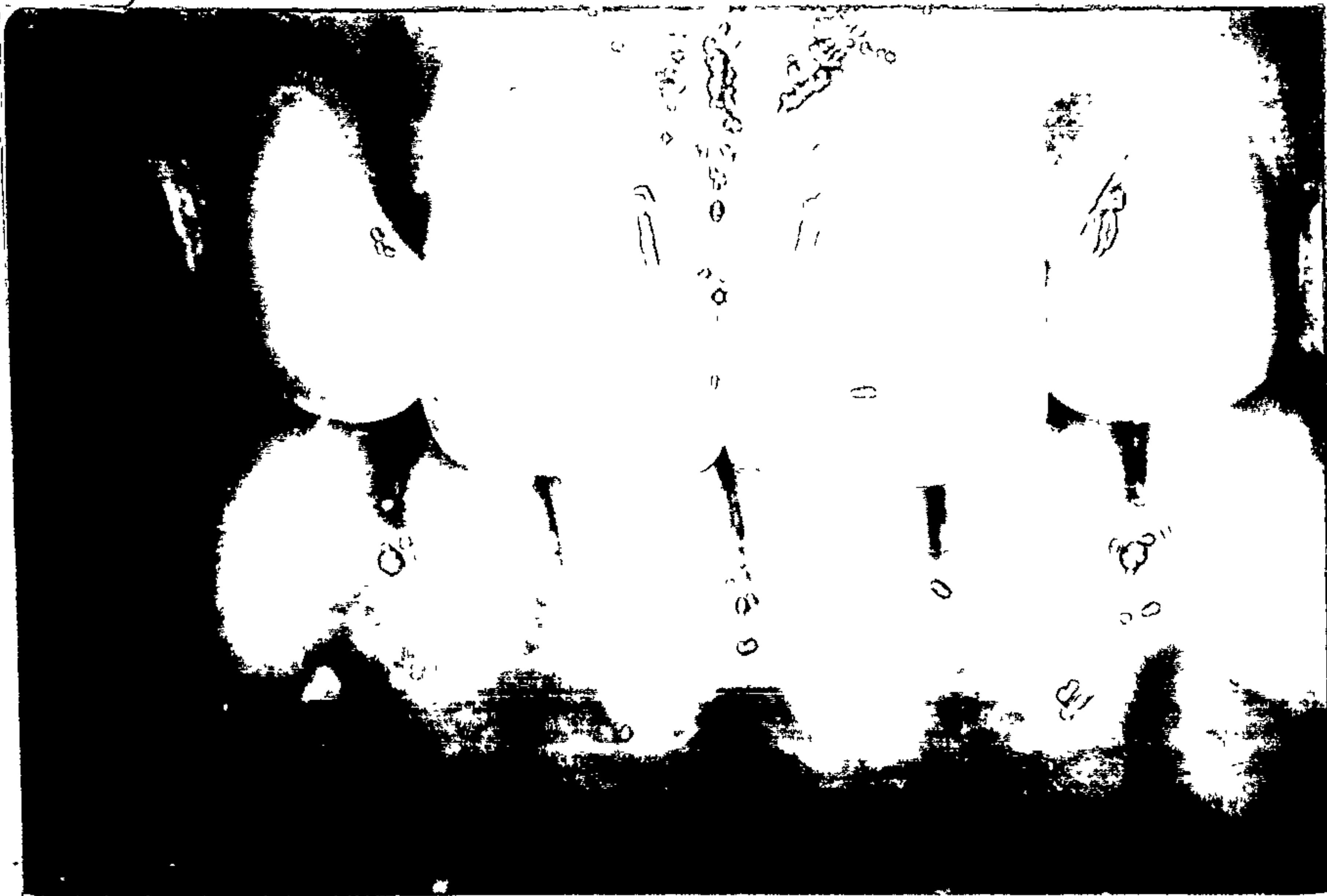


Plate 8-D - Anterior teeth showing the yellow fluorescence at gingival third of labial surfaces.



Plate 8-E - Upper and lower right anterior and posterior teeth showing the yellow fluorescence.



Plate 8-F - Lower left posterior teeth showing tetracycline fluorescence at the gingival margins of the buccal surfaces.

Tamworth Study Patient 6.

Discolouration of Secondary Teeth of a 16 Year Old Girl Associated with Tetracycline Therapy. Plates 9 A,B were photographed on Kodachrome II illumination white light 5600°K.



Plate 9-A - Anterior teeth showing generalized yellow staining of the labial surfaces.



Plate 9-B - Upper left molars showing the generalized yellow staining.

## VII. DISCUSSION AND EVALUATION

Despite the conflicting reports and findings of various investigators on the effect of tetracycline on teeth, agreement exists that tetracycline does stain the primary and secondary teeth when given in therapeutic doses during the period of tooth development. On the other hand controversy still exists on the intensity and duration relative to the particular tetracycline used. Hypoplasia and hypocalcification as associated effects of tetracycline therapy and the mechanism of staining, as well as uptake of fluorophore in dentine and enamel are still the subject of active research.

It is pertinent at this juncture to analyse more closely some of these aspects. Wallman and Hilton<sup>118</sup> suggested that age is related to the difference in colour observed in the various teeth. According to them, teeth with yellow pigmentation would change to brown when exposed to light. They were of the opinion that the younger children had yellow teeth whereas the older children would have brownish teeth. This suggests that degeneration of tetracycline occurs. Weyman and Porteus<sup>124</sup> proposed a contrary opinion and attributed the variation in the colour of the stain to the type of tetracycline used. Tetracycline produced yellow staining, and chlortetracycline a grey-brown colouration. They reported that yellow teeth erupt yellow, but the grey-brown teeth gradually become darker after eruption. These teeth never appeared yellow. A common factor in all the cases described with discolouration, whether yellow or brown, is tetracycline drugs were administered during the period

of tooth formation. There appears to be no correlation between the colour of the teeth and the medical histories of the patients. Since tetracyclines fluoresce under ultraviolet light, and since it has been shown that golden yellow fluorescence has occurred in two cases with yellow pigmentation, it can be concluded that tetracycline is present in these teeth. The non-fluorescence of the teeth with grey-brown colouration might be expected in the light of Wallman and Hilton's 1962 observations.<sup>117</sup> Weyman and Porteus, therefore, concluded as a result of this study that there is a direct correlation between the discolouration and the intake of tetracycline during the formative stage of teeth in children with different medical histories. Weyman<sup>126</sup> in 1965 categorized types of colour into grey-brown, yellow and brownish. The grey-brown pigmented teeth could be mistaken for dentinogenesis imperfecta. The teeth in the latter developmental defect, however, are hypertranslucent and prone to excessive attrition. Moreover, the teeth so affected have an abnormal appearance radiographically, in contrast to tetracycline-affected teeth. Also, tetracycline produced a slightly greyish shade. Under ultraviolet light the grey-brown stained teeth of children with a tetracycline history exhibit the normal bluish light autofluorescence. The second category, that of yellow pigmentation from tetracycline is not difficult to diagnose. It is golden yellow in colour and occasionally very vivid. Weyman observed the most highly stained teeth in children whose mothers received tetracycline continuously during the latter months of pregnancy. These yellow teeth present a golden

yellow fluorescence under ultraviolet light. The labial enamel gradually darkens to brown, but not the palatal or buccal aspects which remain yellow. The third category, the brownish pigmentation, produced by tetracycline, is akin to that produced by the "ageing" of yellow stain on the labial surface of incisors. De Veber<sup>30</sup> in his case report in 1962, suggested that staining was reversible by sunlight, and in time the normal colour returned.

Storey<sup>109</sup> demonstrated in rats that pigmentation by tetracycline was dependent upon dosage. The pigmentation varies from yellow to brown. Ibsen<sup>50</sup>, as a result of his experiments with rabbits in 1965, considered that the various types of tetracycline forms different degradation products as a result of exposure to sunlight. He found that sunlight bleached the colour of teeth exposed to chlortetracycline, N-pyrrolidinomethylchlortetracycline, and to a variable degree, oxytetracycline. This is not true, however, in the case of demethylchlortetracycline and tetracycline. The analogues which primarily follow acidic degradation pattern turn brown while those which are basic become colourless. Hence, Ibsen's opinion hinges on the fact that pigmentation was dependent upon type of degradation.

In 1964, Stewart<sup>107</sup> stated that the teeth with chlortetracycline stains change colour from yellow to brown even before eruption and he further reported<sup>108</sup> that most of the tetracycline deposits were not discernable when the whole teeth or the dentine were examined in visible light after sectioning. Clinical observations, however, showed that effect upon the primary teeth is invariably greater.

Relative to these teeth, both primary and secondary, it was observed that where the drug is incorporated during tooth formation, one out of three showed crown staining under ordinary light. The implication based on these results pointed to the equal probability of clinical discolouration in both dentitions. Stewart claimed this was contrary to experience. The natural colour of the primary teeth is whiter and their enamel considerably thinner and therefore, the colour of the underlying dentine is more readily visible.

Mello<sup>69</sup> suggested that the difference in tooth colour from yellow-grey to brown appears to be a result of at least four factors: (a) the natural colour and concentration of the drug; (b) the rate and degree of photosensitive colour change; (c) the thickness of overlying enamel and dentine; (d) and the location of the tetracycline in the enamel as well as the dentine.

Brearley and associates<sup>16</sup> classified the teeth involved in their studies as light yellow-grey (including grey), bright yellow or grey-brown and darker. In their experiments Brearley and Storey<sup>17</sup> were able to show, by using only one antibiotic and by altering the exposure to light, that the range of colours found in tetracycline affected teeth in vivo could be duplicated in vitro. Colour changes from yellow-grey to brown could be produced by varying the thickness of enamel and dentine through which visible light must pass before reflection by the antibiotic. There was usually a dark brown band of tetracycline at or near the dentino-enamel junction in severely

discoloured teeth. The overlying enamel appeared grey. However, where the enamel became thinner at the cervical part of the crown, the underlying brown colour was more obvious on macroscopic examination.

Martin and Barnard<sup>71</sup> used a colour range of creamy-yellow to yellow brown as criteria for the recognition of tetracycline staining and/or fluorescence and that this disturbance was always the full width of the tooth at the affected level. The stain may extend laterally in a curvilinear distribution across a number of teeth and the condition should be bilaterally symmetrical.

Researchers cannot agree as to the effect of tetracycline on the process of mineralization, either in human or animal subjects. In the literature reviewed<sup>3, 8, 9, 12, 16, 17, 46, 47, 57, 58, 71, 73, 86, 109, 116, 128</sup> tetracycline has been regarded as responsible for hypoplasia. Others, however,<sup>45, 55, 76, 105, 117, 125</sup> do not support the theory that there is correlation between hypoplasia and tetracycline administration. The latter group believed that prematurity, birth trauma or the disease for which the drug was given, were the contributory factors. However, further investigations are needed to clarify this hypothesis.

The exact mechanism of tetracycline staining or incorporation into bone and teeth is still debatable. Furthermore, recognition of such staining as being positively tetracycline-induced, can pose certain problems. Clinical diagnosis of severe tetracycline pigmentation is obvious, but staining of lesser degree may be hard to

recognize as positively of tetracycline origin. This is especially true if degradation of the antibiotic has taken place, and exposure to ultraviolet light has failed to evoke the characteristic golden yellow fluorescence. The value of ultraviolet light as a diagnostic aid is questioned by Brearley and co-workers<sup>14</sup> who stated that not all tetracycline-discoloured teeth fluoresced, and not all teeth which fluoresced were clinically discoloured. These findings were corroborated in the 1967 Tamworth survey.<sup>71</sup>

In a later study Brearley and Storey<sup>17</sup> said that the detection of tetracycline fluorescence depends upon four factors: first, the wave-length of the ultraviolet light used for diagnosis; second, the location of the tetracycline; third, the amount of antibiotic in the tooth crown; and fourth, the state of the tetracycline molecule in the tooth. The nature of the ultraviolet light emitted by the diagnostic lamp is important since fluorescence is only induced when light of appropriate wave-length is absorbed by the tetracycline molecule. Their findings showed that clinical examination in visible light was the best criterion of tetracycline tooth discolouration and had a high correlation with the evidence obtained by ultraviolet light microscopy. From the results of their study they concluded that there is a greater chance of staining of the teeth with/increasing number of courses of antibiotics. They noted, however, that even one band of tetracycline deposited in the dentine produces severe staining particularly if the antibiotic is located near the dentino-enamel junction. Their findings showed that in stained teeth the majority

of the bands were located in coronal dentine. This suggests that the time at which the antibiotic is given during tooth development is one of the most important factors determining the degree of clinical discolouration. Tetracycline given during the period of early dentine formation is likely to cause discolouration of teeth.

It must be taken into account that there are other factors affecting crown discolouration .... both hereditary and acquired, and that there are no precise standards for the normal tooth colour. This colour can vary within the same individual, within the same tooth, among the different teeth and may change with age. It is felt that a review of the etiology of dental discolouration and the colour of the teeth affected will be of great help in understanding the problem relative to the differential diagnosis of the various forms of staining. Keitel and associates<sup>56</sup> proposed the following classification:

ETIOLOGY	COLOUR OF TEETH
<u>I. Disease Process</u>	
1. Systematic:	
A. Hereditary:-	
(1) amelogenesis imperfecta	brown
(2) congenital mesodermal dysplasia	dark brown
(3) congenital porphyria	pink to reddish brown
(4) congenital syphilis	brown to black
(5) ectodermal dysplasia	brown
(6) hereditary dentinogenesis imperfecta	brown to blue grey

- |                                  |                   |
|----------------------------------|-------------------|
| (7) hereditary opalescent dentin | brown opalescence |
| (8) osteogenesis imperfecta      | brown             |

B Metabolic:-

- |                                    |        |
|------------------------------------|--------|
| (1) abnormal calcium metabolism    |        |
| (a) Hypoparathyroidism             | chalky |
| (b) hyperparathyroidism            | dark   |
| (2) enamel hypoplasia              |        |
| (a) acute exanthemata of childhood | brown  |
| (b) cerebral disorder              | brown  |
| (c) hypoparathyroidism             | brown  |
| (d) idiopathic                     | brown  |
| (e) prematurity                    | brown  |
| (3) neonatal jaundice              | green  |

C. Nutritional:-

- |                           |       |
|---------------------------|-------|
| (1) vitamin deficiencies: |       |
| (a) vitamin A             | brown |
| (b) vitamin C             | dark  |
| (c) vitamin D             | brown |

2. Localised to Tooth:

A. Metabolic:-

- |                                 |            |
|---------------------------------|------------|
| (1) internal resorption of root | pink spots |
|---------------------------------|------------|

B. Trauma:-

- |  |               |
|--|---------------|
| (1) necrosis of the pulp               | green         |
| (2) non-vital pulp                     | grey          |
| (3) pulpal haemorrhage                 | black         |
| (4) ruptured vessels in apical foramen | grey to black |

## II. Pharmacologic Agents

### 1. Topical:

#### A. Non-Chemical:-

- |  |                                |
|--|--------------------------------|
| (1) dental caries                                | chalky, then brown<br>to black |
| (2) poor oral hygiene                            |                                |
| (a) chromogenic bacteria of<br>acidogenic nature | green                          |

#### B. Chemical:-

##### (1) Metal

- |                            |                               |
|----------------------------|-------------------------------|
| (a) copper amalgam filling | green to black                |
| (b) fluorosis              | white flecks<br>turning brown |
| (c) iron compounds         | black                         |
| (d) silver nitrate         | black                         |

##### (2) Non-Metals:-

- |                       |                |
|-----------------------|----------------|
| (a) atabrine          | yellow brown   |
| (b) betel nuts        | black          |
| (c) coffee            | brown          |
| (d) chloroquine       | grey           |
| (e) cola beverages    | brown          |
| (f) some mouth washes | brown-green    |
| (g) oil of cloves     | brown to black |
| (h) snuff             | brown          |
| (i) tar               | black flecks   |
| (j) tea               | brown          |
| (k) tobacco           | yellow brown   |



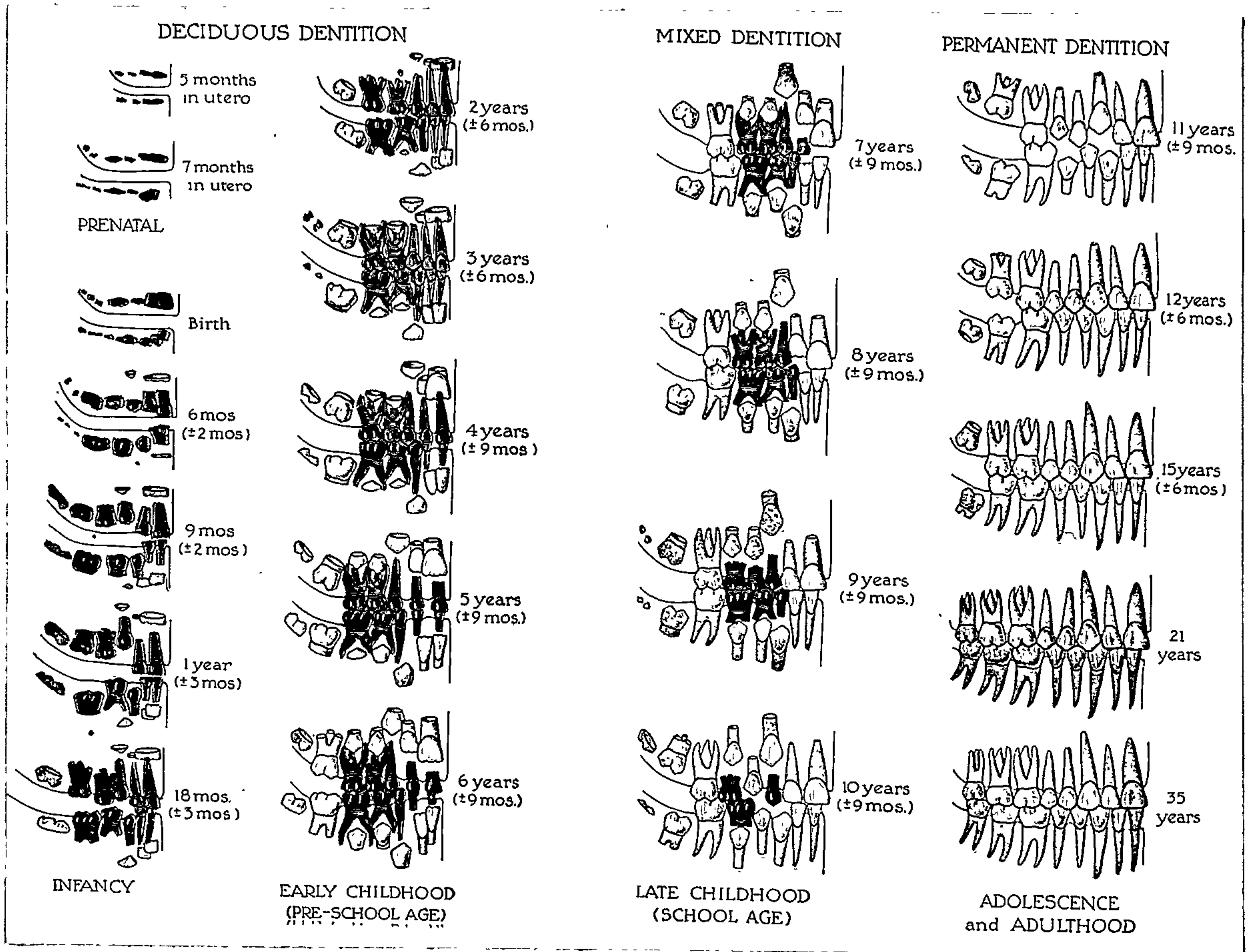


Fig. 7. Chronology of the development of the dentitions.

(Brauer et al)<sup>18</sup>

teeth is subject to extrinsic staining in developmental faults<sup>6</sup> or in areas of hypomineralisation.

In the dentine which is a calcified tissue of mesodermal origin, development commences as an uncalcified matrix, the predentine. Calcium salts are then deposited into the older layers to form dentine. Pigments like tetracycline and bilirubin which may be circulating in the blood stream during the period of dentine formation can be incorporated permanently. Enamel being translucent, transmits any colour which may be incorporated in forming dentine. Apparently the fading of pigmented teeth with age may be due to the loss of translucency of the ageing enamel, rather than the loss of pigment from dentine.

The uptake of tetracycline by both enamel and dentine is still the subject of controversy. Milch, Rall and Tobie<sup>74</sup> suggested that each of the tetracycline antibiotics localises in the skeleton in a specific pattern which is strikingly uniform. This pattern is apparently entirely independent of sex, the route of administration, and the dosage. They however observed that a distinct and direct relationship between the intensity and the localisation of skeletal fluorescence and the age of animal, existed. In almost all of their continuing series of studies they observed that the general distribution of the fluorescence is concentrated only in regions characterised by good blood supply. This tends to imply that localisation occurs as a consequence of the anatomical relationship to the vascular endothelium. Naturally, surface bone being in closest anatomical

proximity to tissue fluids containing high concentration of administered compounds would be expected to exhibit relatively greater amount of tetracycline compared to more internally located bone, and therefore, the physiologically more inaccessible bone crystals. Apparently, such regions would be expected to present more fluorescence on the basis of the total amount of material deposited. However, tissues other than bone, like the heart, kidney, spleen and lung, do not show persistence of fluorescence in spite of a greater vascular supply. It has also been observed in experimental bone defects where callus and established bone are in intimate anatomical relationship, that the new formed bone is the only one that fluoresces following the intake of tetracycline. Again, where new bones are formed in cartilage areas, a constant sharp macroscopic and microscopic junction between the two types is discernable. Bone fluorescence following tetracycline administration may be attributed to binding of either the unaltered compound, or a derivative, to calcium and/or the matrix of the newly formed bone. On the bone surface complex formation occurs between the fluorophore and calcium at physiological levels. For complexing to occur, it has been stated that a specific type of matrix is necessary. Milch and associates<sup>75</sup> further mentioned the possibility that tetracycline, or a metabolic derivative with similar fluorescent properties in ultraviolet light, was capable of binding into regions of reaction .... a phenomenon characteristic of the four-ringed naphacenecarbonamide nucleus of tetracycline itself.

Bevelander and co-workers<sup>11</sup> demonstrated the presence of fluorophore in the skeletal elements of the Larval Sand Dollar. They were able to show that tetracycline was responsible for an inhibition of skeletal formation. The addition of calcium ions to the sea water environment failed to protect against inhibition of crystal formation. With the assumption that this effect was a sequestration phenomenon, whereby the mineral available for crystal formation is withdrawn from the available pool, it will be necessary to determine whether binding of tetracycline on the fibrous membrane surrounding the crystal may be responsible in part for the reduction of crystal growth.

Buy and associates<sup>21</sup> made use of the fluorescent property of tetracycline to determine its localisation in living cells. Using animals, they found that this antibiotic, as well as the related antibiotics, chlortetracycline and oxytetracycline, specifically combine with mitochondria of living cells, either in tissue culture or in fresh preparations from various organs. Wallman and Hilton<sup>117</sup> proposed the idea that the deposition of tetracycline in bones and teeth is probably due to its chelating property. It is possible that this is a result of the formation of a tetracycline-calcium-orthophosphate complex. They suggested that short courses of tetracycline given in the neonatal period are extremely likely to produce abnormality of the teeth. The larger the total dosage relative to body weight the greater the abnormality.

In 1962 Mustakallio<sup>79</sup> observed that fluorescence of bones is

due to deposition of a calcium chelate of tetracycline in the collagen matrix and ground substance. This observation was corroborated by Wallman and Hilton.<sup>117</sup> In the same year Harcourt, Johnson and Storey<sup>45</sup> reported that administration of tetracycline to patients during tooth development was associated with both macroscopic and microscopic changes in the dentine of the crowns of primary teeth, but not the secondary teeth. Bands of yellow staining and golden yellow fluorescence in the dentine corresponding both qualitatively and quantitatively to administration pattern has been demonstrated histologically. The staining material, these authors claimed, was probably tetracycline pigment, as the colour was identical with the original solution. Harcourt and his co-workers<sup>45</sup> referred to Harris as having reported that the pattern of tetracycline lines in dentine marks the growth increments in teeth and provides an excellent indicator of growth. Distribution of the antibiotic in the teeth is determined by the age of the patient and stage of development of the dentition. Tetracycline when administered a few weeks after birth labelled the forming primary teeth at the dentino-enamel junction. With continued therapy lines appear towards the pulpal and apical regions of dentine. In older patients the yellow pigmentation of dentine is less conspicuous and confined to the area from the middle third of the root to the apex. Enamel, in contrast to dentine, does not appear to be stained by tetracycline. Owen<sup>89</sup> however demonstrated that the Hunter-Schreger bands fluoresced in the enamel of dogs following tetracycline administration. However, Harcourt<sup>47</sup> suggested that this effect is

due primarily to light scattering from the faces of the enamel rods and not to the fluorescence of interprismatic substance.

Zegarilli and co-workers<sup>131</sup> also suggested that one or more factors must be present, besides tetracycline, for the occurrence of such phenomenon, and that tetracyclines as a group collectively localise and deposit in tissues undergoing calcification at the time of administration. Urist and Ibsen<sup>115</sup> observed in an in vitro experiment that the binding of oxytetracycline molecules with calcium salts occurs on the surface of apatite crystallites. They believe that this is due to the large molecules of oxytetracycline taken up by the crystal surface. Steendijk<sup>106</sup> proposed that the molecular fixation may be a process for which cellular activity is necessary. He did not discount the probability of chemical exchange. Experimental evidence indicated that tetracycline was fixed to bone salt by absorption, as tetracycline is almost exclusively found in regions where mineralisation is taking place. Incorporation on growing surface of bone appears to occur very rapidly, and cannot be washed off once it is "cemented" in. It could also be possible that the tetracycline drug will interfere with normal osseous development besides the adverse action it has on rapidly growing bone. This will be through interference with crystal growth when given in high dosage. It is possible that this action of tetracycline involves the organic component of the tissue in addition to absorption on the crystal surface. Hodgson and Lewin<sup>49</sup> were of the opinion that the fixation of tetracycline by apatite is a surface absorption phenomenon. One

experiment in vitro used two synthetic apatites differing in crystallite size and the other, an in vivo experiment, used samples of developing rat enamel and dentine. They concluded that while both enamel and dentine take up tetracycline, the difference in uptake in the enamel is less than in dentine, and may be directly related to size of the crystallites.

Bennet and Law<sup>9</sup> have also observed that enamel takes up less tetracycline than dentine. They attempted to resolve the problem by using dogs during the period of calcification of their secondary teeth. Firstly, they separated the enamel and dentine and determined the presence of tetracycline in each tissue; secondly, they attempted to measure the amount of tetracycline incorporated in the enamel and dentine and express this as a ratio. From these studies they concluded that tetracycline was incorporated into calcifying enamel and that there was approximately nine times as much tetracycline in dentine as in enamel. This finding also tended to support the theory that tetracycline combines with the surface calcium ions of the apatite crystallites.

Milch and associates<sup>74</sup> explained that a complex of ground substance collagen and mineral would be necessary, and since enamel has a lesser amount of organic substance, it would be expected that enamel would have a much lower uptake than dentine. Milch, Tobie and Robinson<sup>75</sup> postulated that the tetracyclines bind to the calcium of "seeded" crystal nucleation sites and their immediate derivatives on collagen fibrils. This is presumably via the oxygen atoms of

the D-ring (carbon atoms 1 through 7), and of naphacenecarbonamide nuclei. Urist and Ibsen<sup>115</sup> considered tetracycline uptake in relation to the size of crystals. Since enamel crystals are larger crystal, this would reduce the surface area in relation to that of dentine. A third suggestion pointed to the origin of the two dental tissues as being responsible for the difference in staining reactions; enamel being of ectodermal origin, while dentine being of mesodermal origin. Harcourt disputed this suggestion as his findings showed dentine and not enamel to be stained with tetracycline. Plaza-Roca<sup>92</sup> is of the opinion that the mucopolysaccharides must play a role in the reaction of bone substance and tetracyclines.

Johnson<sup>55</sup> pointed out that there are three possible sites for the binding of tetracycline fluorophore in mineralised tissues: (a) in the crystal surface as complexes with the calcium, (b) as complexes with collagen, or (c) in complexes that share calcium ions with polysaccharides. Plaza-Roca<sup>92</sup> again suggested that the chelation mechanism of tetracyclines with the calcifying structures is done directly to the apatite crystallites or with the polysaccharides, or both, in together in a complex.

Ibsen and Urist<sup>51</sup> explained tetracycline binding on the basis of chelation. Both citrate and tetracycline form a calcium chelate in solution and in addition are desposited in bone mineral of bone. It is suggested that the affinity of these compounds for bone is due to the establishment of a chelate with the calcium associated with

the apatite crystals. Naturally, the two ligands could compete for the same site if such chelation occurs. Ibsen and Urist exposed hydroxyapatite crystals to oxytetracycline under identical conditions. The simultaneous presence of one ligand could reduce the amount of the other which was found associated with the solid. Hence, the suggestion is that these organic compounds are taken up by skeletal tissue in the living animal mainly because they chelate with calcium ions on the hydroxyapatite crystallites.

It was demonstrated that more oxytetracycline remained associated with the solid phase when the hydroxyapatite was exposed to this drug alone than when it was simultaneously exposed to oxytetracycline and an equivalent quantity of citrate. Moreover, more citrate remained associated with the solid in the absence of oxytetracycline. This illustrated the competition of the two ligands for the same site. It was observed that nearly twice as many molecules of citrate as oxytetracycline were bound. This may be related to diffusion impedence, or it may be that one molecule of oxytetracycline chelates with two calcium ions simultaneously. Since the possibility of a calcium-oxytetracycline complex on the surface depends very much on the intercalcium distances at the crystal surface, the former possibility would appear to be the more likely. The theory that tetracyclines bind to calcium on the crystal surfaces as a complex has the greatest support.

However, there are a number of areas where there is lack of unanimity concerning the effects of tetracycline on developing teeth and uptake of tetracycline compounds by mineralised tissues.

### VIII. SUMMARY AND CONCLUSIONS

Since 1948 a group of antibacterial compounds, the tetracyclines, has been used in the treatment of a wide range of infections. Chlortetracycline, produced by streptomyces aureofaciens, was the first to be introduced. This was followed by oxytetracycline in 1950, tetracycline in 1953, demethylchlortetracycline in 1959 and N-pyrrolidinomethylchlortetracycline. Because of the wide range of organisms whose growth these compounds inhibit, they are frequently referred to as "broad spectrum" antibiotics.

While each of the drugs comprising the tetracycline group is bacteriostatic, superior qualities for individual compounds are often claimed. However, the chemical, pharmacological, antibacterial and therapeutic properties of all the group are similar. One of the side effects of the tetracycline compounds is that they are deposited in the calcified tissues and the yellow pigment which irreversibly formed is fixed in the tissues and is responsible for the resultant discolouration. While the mechanism of this process is not completely established, it is possible that the chelation mechanism of tetracycline with calcifying structures is directly with the apatite crystallites, with polysaccharides or even both.

Chlortetracycline, oxytetracycline and tetracycline have basically the same potency and therefore, dosage. The usual adult dose is 250 mg. by mouth every six hours. For children the dose is 20-40 mg/kg of body weight per day which is divided into four equal doses and given every six hours. These drugs are available in tablets,

capsules, syrups or pediatric drops. Demethylchlortetracycline because of its potency and lower renal clearance, is given in smaller doses and at less frequent intervals. The usual adult dose is 150 mg. by mouth every six hours. The dose for children is 6-12 mg/kg of body weight per day given in three to four equal doses. In no instance should the child dosage exceed that of the adult. All the tetracyclines are absorbed poorly in the presence of foods having a high calcium content, such as milk and other dairy products. It is therefore recommended that they should be administered at least one or two hours after meals.

In achieving morphologic and functional maturity, every tooth undergoes a series of well defined and characteristic stage during development. In relation to the effects of tetracyclines, the calcification and eruption stages are most important. If the sequence of eruption is known, other stages of formation can be established. While controversy concerning the appositional stage and the pattern of mineralisation still exist, the tables of tooth chronology are useful guides in interpreting the clinical situation, even though the current tables present averages which have wide ranges of variation.

The primary teeth begin to calcify between the fourth and sixth months in utero and erupt between six and twenty four months of age. Root formation is completed approximately a year after eruption. The period within which the teeth exfoliate ranges from six to eleven years of age. The average eruption age of secondary teeth is about six months later than the exfoliation age of primary teeth.

Calcification of the secondary dentition begins between birth and three years except for the third molars. Much later calcification has been observed in mandibular bicuspids. Eruption takes place between the age of six to twelve years and the enamel is completely formed about three years prior to eruption.

There is a need for further research to clarify the different hypotheses already proposed to explain the effect of tetracycline on developing teeth. Some conclusions, however, may be deduced from existing evidence.

1. Clinical studies on children who have been treated with tetracycline compounds during the period of tooth formation show:

(a) that both primary and secondary dentitions can be discoloured by the incorporation of tetracycline in the tooth structure;

(b) that tetracycline given from the fourth month in utero to the end of pregnancy will be transmitted to the foetus and deposited in the primary teeth.

2. The determining factor in relation to the type and intensity of the pigmentation appears to be related not to the duration of administration but rather to the total dosage.

3. Discolouration of the secondary dentition can occur when tetracyclines are given below the age of seven years. Deposition of tetracycline can also occur when the drug is given until ten years of age, but this will not be a cosmetic problem.

4. Deposition of tetracycline in teeth represents a permanent or irreversible change, but some deposited tetracycline is degraded

on exposure to sunlight. The degradation products may be of a darker or lighter colour than the compound originally formed in the tooth.

5. (a) The clinical diagnosis of tetracycline staining can be made on both the appearance of the teeth and the medical history of the patient. Examination of the teeth under ultraviolet light will cause the deposited tetracycline to fluoresce. This phenomenon can be used both clinically and in ultraviolet light microscopy to support the diagnosis;

(b) The available epidemiological evidence from a study of 4,690 children aged 4-17 years supports the clinical evidence that tetracycline will produce tooth discolouration. This occurs mainly in the primary dentition and at the gingival areas of the posterior secondary teeth.

The frequency of an aesthetic and/or functionally undesirable disturbance of the teeth however is extremely low and staining in anterior secondary teeth occurred in 1 in 5,000 children;

(c) Although large doses of tetracycline have been reported to cause hypoplasia of the enamel in experimental animals, the epidemiological evidence available indicates that the prevalence of hypoplasia in both the primary and secondary dentitions was not significantly different for children who were exposed to tetracycline and those who were not exposed.

6. Tooth discolouration in the primary dentition is of little total health significance when a serious childhood infection requires the use of a tetracycline compound with known tooth staining properties

as the primary teeth are exfoliated and replaced. In the case of older children where tooth formation is more advanced the possibility of unaesthetic tooth discolouration is extremely low in the secondary dentition (1/5000). This is a lower prevalence than the observed value for unaesthetic hypoplasia from other causes in the same group of children.

There is no evidence that at the present time the tooth staining potential of tetracyclines should prevent their utilisation in the treatment of serious infections in childhood. However, if an alternative effective antibiotic can be selected particularly for the treatment of chronic childhood diseases, it would be preferable to use such a compound to avoid possible unaesthetic tooth staining.

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