Section of Odontology

President Professor M A Rushton CBE MD FDS RCS

Meeting October 28 1963

President's Address

Hereditary Enamel Defects

by Professor M A Rushton CBE MD FDS RCS
(*Department of Dental Medicine, Guy's Hospital, London*)

While all anomalies of human enamel can be regarded as the product of genetic and environmental factors, there are certain types in which the effect of genetic factors appears to be of outstanding importance. This has been determined on the basis of inspection of pedigrees in which the distribution of the anomaly has been found to correspond with that of other conditions which are regarded as, or can be shown to be, due largely to genetic factors and in the absence of environmental causes which can be identified. In the case of defects of enamel structure the compilation of pedigrees has been notoriously difficult owing to the rapid disintegration of the teeth or their early extraction to correct an unsightly appearance. For that reason often only hearsay evidence is available as to which members of the family were affected and which not, though in the case of the more striking anomalies this evidence may often be correct.

In general, it is characteristic of hereditable enamel defects that all teeth are affected and that the defects are not distributed in a pattern related to short periods in the life of the individual. A distinction can be drawn between conditions in which defects of the enamel appear to be the principal disorder inherited and those in which defects of skin or other tissues can be found as important concomitants. The former only will be considered here.

On June 2, 1890, at a meeting of this Society, that is to say of the Odontological Society of London, as it then was, Mr Sydney Spokes 'read the notes of a case of faulty enamel' as a Casual Communication. He showed a model and a genealogical tree prepared from information supplied by the patient. The description is brief and, as regards the appearance of a microscopic section, far from clear. But this appears to have been the first account of a hereditary enamel defect, not accompanied by other obvious disorders, which can now be definitely recognized as such.

Finn (1938) pointed out that it is impossible to discover from most early reports whether what was being described was a primary defect of enamel or one of dentine, usually hereditary opalescent dentine. Of 41 reports earlier than 1938 which he examined, 28 were thought to refer to opalescent dentine and only 3 to primary enamel defects. The rest were doubtful.

A convincing feature of Spokes's description is his reference to vertical grooves in the enamel of the one member of the family, a woman, whom he had examined:

'In ordinary cases of defective enamel we are accustomed to see transverse grooves across the teeth marking the period at which something occurred to interfere with the due formation of this tissue, but in the present case there are grooves in the long axis of the tooth, showing that the process was modified throughout the whole of the time occupied by calcification. In some places there is a total absence of enamel, and the exposed surface of dentine seems to have been sufficiently hard to survive without the protection of the usual covering. In other places the enamel is laid on in irregular masses.'

This grooving in the long axis of the tooth is something which we can recognize as highly characteristic of, if not peculiar to, a certain variety of hereditary enamel hypoplasia as seen in affected females.

Among subsequent reports of inherited defects of enamel, that of two families by Bampton (1914)

is noteworthy because it led Haldane (1937) to suggest that they illustrated 'a probable new sex-linked dominant in man'.

An important step towards the classification of inherited enamel defects was the paper of Weinmann *et al.* (1945) who divided them into two types: (1) Hereditary enamel hypoplasia, in which teeth were chiefly characterized by an enamel deficient in quantity but hard in quality. (2) Hereditary enamel hypocalcification, characterized by a deficiency of calcification of enamel which was soft but normal in quantity and histological pattern. Both were thought to be inherited through autosomal dominant genes. This broad division is still of great value, though it is appreciated that in many cases elements of hypoplasia and hypocalcification are present concurrently and that there must be more than two genetic types.

Darling (1956) noted five morphological and clinical varieties and examined slices of teeth radiographically: Group 1 with general pitting of the enamel. Group 2 with vertical grooving and wrinkling. Group 3 with marked deficiency in enamel thickness and resorption of unerupted teeth (corresponding in many ways to the hereditary enamel hypoplasia described by Weinmann *et al.*). Groups 4 and 5 thought to be characterized by defective calcification and different in degree and distribution. This was a valuable paper but it is clear that classification by morphology alone is insufficient.

Schulze's (1956) important study defined one group in particular with great precision. This resembles the hereditary enamel hypoplasia of Weinmann *et al.* in some respects but differs in others. It is inherited as a sex-linked dominant but is more severe in males; in females it shows the special form in which there are vertical wrinkles and grooves in the enamel. He also considered that there were two forms of hereditary enamel hypocalcification, morphologically and histologically similar to each other, but one inherited as an autosomal dominant and one as either a recessive or an irregular dominant.

Witkop (1958) listed 5 types with 'probably at least two more'. Three were characterized by hypocalcification or hypomaturation and were thought to be of dominant, recessive and sex-linked recessive types. He accepted the sex-linked dominant type of hereditary enamel hypoplasia as described by Schulze and added another type which he called local hypoplasia of enamel. This has a restricted distribution, chiefly on the labial sides of anterior teeth and may affect the first dentition only. It was thought the gene was dominant with incomplete penetrance. The appearance seems to correspond with Darling's group 5. Witkop also found that inherited enamel defects of one kind or another occurred once in 14,000 to 16,000 children.

It will be appropriate to say something further about the type which Schulze appears to have established as of sex-linked dominant inheritance on the basis of six large families studied in quite a small area between Göttingen and Hanover. To this variety Spokes's case may well have belonged, although unfortunately no affected men are shown as having had children in the large pedigree he gave.

Hereditary Enamel Hypoplasia: Sex-linked Dominant Type

In this type the abnormal gene is presumed to be carried on the X chromosome and to be dominant (or more properly intermediate). The effect of this is that an affected heterozygous mother will be expected to hand on the abnormality to half her sons and half her daughters but the affected father, with normal wife, will hand it on to all of his daughters and none of his sons or their offspring. A further interesting feature in this sort of hypoplasia is that males and females are differently affected. The males have only a very thin smooth layer of enamel which appears nearly homogeneous and lacks the usual rod structure; but the females have enamel which is in parts much thicker and in many parts prismatic. Macroscopically the girls' teeth show a remarkable pattern of vertical grooves separating vertical strips of better enamel, though this is more clearly seen on some teeth than others (Fig 1).

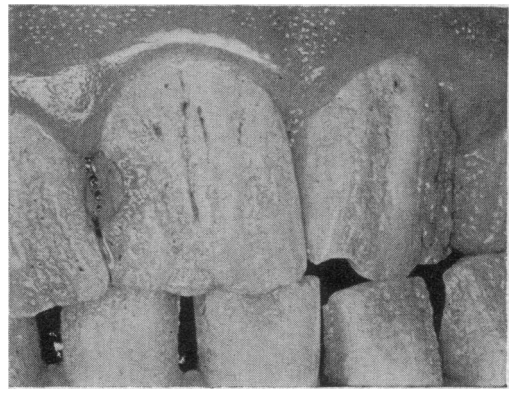

Fig 1 *Incisors of a young woman showing vertically arranged defects characteristic of affected females in a sex-linked dominant type of hereditary enamel hypoplasia*

Among the few female patients of ours who appear to fall in this group was a girl who, with her affected sister, had already been described by Fish (1948) as autosomal dominant but whose pedigree is very suggestive of dominant sex-linkage. Darling (1959, personal communication) has also given me details of two families which appear to be of the same type and one of which shows the sex difference well in the teeth of brother and sister. We do not know that all cases in which vertical grooves are a prominent feature belong to this group. I think all the published cases and nearly all those of which I have been able to obtain particulars have been in females. One exception is a model in the Odontological Collection, Royal College of Surgeons (D.33. 9123), mentioned below.

It is not certain that all females with this type of sex-linked hypoplasia show the vertical markings, since Schulze thought that a few might show a more severe manifestation like that in males, though he says that this might have been an acquired state due to fracture and abrasion. In the special population group he studied in S. Lower Saxony there might even have been women homozygous for the defect but considerable variation among the heterozygotes would not be surprising and at least one girl was affected only very slightly. In half Schulze's families affected males and a few females also had an open bite, but this feature has not, I think, been reported elsewhere.

The difference between males and females in this variety of hypoplasia has been held to be due to the fact that the somatic cells of females have two X chromosomes, of which one would carry the normal gene. It was thought that in some way the normal gene in one X chromosome exerted a mitigating effect upon the abnormal gene in the other, so that in its functions the ameloblast was less disturbed (Schulze 1956).

The vertical pattern in females is a feature of great interest. It is not sufficient to comment as Spokes did that it shows 'that the process was modified throughout the whole of the time occupied by calcification', because this would also be true where the enamel was uniformly abnormal or randomly pitted. The vertical pattern must indicate not only abnormal function of many ameloblasts throughout the process of enamel formation but also that these defective ameloblasts were arranged in vertical columns. This strongly suggests that there was a mosaic arrangement of the stem cells around the base of the enamel organ from which the ameloblasts are derived in vertically disposed series, some groups of stem cells producing a race of normal and others a race of defective ameloblasts. While the two kinds of stem cells would be disposed in groups in random manner round the base of the enamel organ, their descendants would occupy an approximately vertical relationship to each respective group and be responsible for a vertical strip of good or bad enamel. If the groups of stem cells were small and closely alternating, a vertical pattern would probably not be evident. In this respect it is of interest that, according to the hypothesis of Lyon (1961), in the somatic female cell one of the two X chromosomes becomes inactive from an early stage, so that in heterozygotes for X-borne genes a mosaic is created, some cell groups being controlled by the X chromosome carrying the abnormal gene, the others by that with the normal allele. This kind of explanation may be applicable to these female teeth.

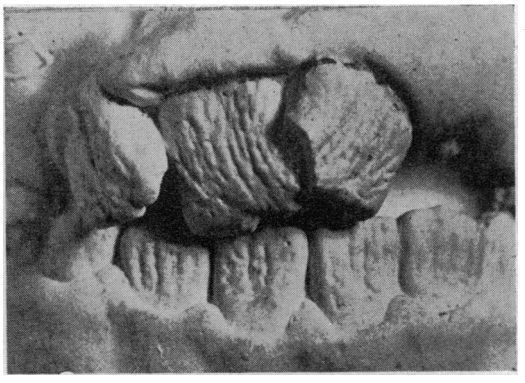

Fig 2 *Plaster model of the incisors of a boy of 8 years showing vertically ridged pattern. (Odontological Museum, Royal College of Surgeons of England, D.33.9123)*

It could not be applied to a similar pattern in the teeth of a boy (such as appears to be shown in the model (Fig 2) mentioned above, which the donor, Mr B R Townend, confirms to have been taken from a boy of 8 years whose brother also had hypoplasia) unless he had, for example, Klinefelter's syndrome with a karyotype of XXY. Since this condition occurs about once in 400 males, such a coincidence would not be too improbable. It would certainly be useful to know more about any males with the vertical pattern who can be found.

However that may be, it is possible that in this sex-linked dominant hypoplasia the defect in male and female teeth is the same in quality and different only in quantity. The nature of the defect is evidently an inability to form enamel prisms, and the stage at which it could operate is just before prism formation starts and after junctional

enamel and the first interprismatic enamel have been deposited (Nalbandian & Frank 1962).

Miles (1961) has summarized histochemical changes which have been observed in the ameloblasts at this stage, including the abrupt decline in glycogen content recorded by Ten Cate (1959); the interruption of one of these processes, perhaps by the formation of an inactive enzyme substitute, seems indicated.

The discovery of some convenient animal exhibiting hereditary enamel hypoplasia would be most useful. Colyer (1936) described several cases in animals 'simulating hereditary hypoplasia' and indeed illustrated one of two cases in a Musschenbroek's palm civet which shows a vertical pattern; it would be nice to hear of some less rare animal having a similar defect.

Autosomal Dominant Types with Thin Hard Enamel or Random Pitting

Though this sex-linked type (which is not perhaps due to the same gene as Bampton's but may be allelomorphic with it) has achieved some fame, it cannot be the only type of hereditary hypoplasia with thin hard enamel. The D family of Weinmann *et al.* showed no differences in manifestation between males and females, and the pedigree is not consistent with a sex-linked dominant gene but with an autosomal dominant. Moreover the very thin smooth enamel showed normal structural elements, though to what extent is not stated, and many teeth failed to erupt. Vertical markings were not evident.

One of our cases (Rushton 1950) rather resembled Weinmann's. The enamel was very thin but not smooth on a woman's remaining teeth, of which two unerupted molars were examined histologically. The earlier formed layers showed the rod structure in most parts but in many places were soon covered by a thin enamel of structureless glassy appearance. If she was right in claiming to have one unaffected sister and an affected father, this cannot have been of the sex-linked dominant type. In other families there is not such an extreme deficiency of enamel but a conspicuous pattern of deep pits, arranged in a random manner, not vertically. A good example from a woman is in the Odontological Collection, R.C.S. (D.33.912) (Fig 3). Both dentitions were affected in the same way and it is recorded that father and grandfather, brother and daughter had similar teeth, so the inheritance was autosomal dominant.

In one of our cases with random pitting in the permanent dentition there remained smooth, hard but thin enamel on the milk teeth; again the girl's father was affected but not her sister. Toller's (1959) No. 1 family and perhaps Hals (1958) No. 1 could be of autosomal dominant inheritance too.

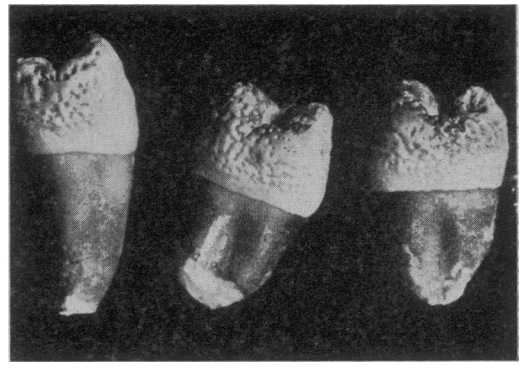

Fig 3 *Random distribution of enamel defects in an autosomal dominant type of hereditary enamel hypoplasia. (Odontological Museum, Royal College of Surgeons of England, D.33.912)*

In these types one must suppose that the pathological gene either operates in all the ameloblasts or in a randomly scattered proportion of them, unrelated to groups of stem cells from which the ameloblasts are derived. Its effect is to limit the thickness of prismatic enamel at all or some parts of the surface with production of a thin layer of a glassy substitute.

Besides a number of sporadic cases which, if genetically determined at all, might be dominant mutations, we must note the family reported by Cameron & Bradford (1957) in which 3 out of 6 brothers were affected and no other relatives. I also have noted a family in which 2 sisters, not twins, were affected but no other relatives. These must suggest the possibility of another and recessive variety.

The association which Weinmann *et al.* observed between hereditary enamel hypoplasia and failure of tooth eruption in 9 members of their D family they explained as resulting from early degeneration of the reduced enamel epithelium which was thus unable to play its usual role. This association has been observed by others, and recently Frank & Bolender (1962) described an isolated case in which extreme hypoplasia of enamel of both dentitions with early degeneration of the dental epithelium was accompanied by failure of eruption of 24 teeth.

Such an association is not unexpected, but on the other hand it is indeed surprising that failure

of eruption does not seem to be a feature of the sex-linked dominant variety, where in males at least the defects of ameloblasts are equally severe. Possibly the open bites recorded by Schulze may be related to some kind of delay in eruption, short of failure, or it may be that in this type there is dysfunction of the ameloblasts without premature degeneration of the rest of the enamel organ.

Hereditary Enamel Hypocalcification

In the broad group of hereditary enamel hypocalcification there are many families where the defect appears to be inherited as an autosomal dominant but others in which this is not obvious and where a dominant of low penetrance or a recessive factor has been suspected. I have not yet met the two special types which Witkop (1958) has distinguished as hypomaturation; they were thought to be inherited as sex-linked recessive and autosomal recessive traits respectively. In the others the histological pattern is approximately normal apart from the mineralization. There is great variation: in some cases the enamel resists destruction for a long time, in others it is so deficient that the enamel chips and crumbles away.

I do not propose to discuss this group of cases in detail but would agree with Schulze that no histological differences are evident between teeth from families in which the inheritance appears clearly to be dominant and those in which it is not clearly so. One feature which engaged my special interest appears to be common to both (Rushton 1962). This was the presence on unerupted or recently erupted teeth of an abnormal surface layer on the enamel, apparently a superficial addition to the quantitatively normal but insufficiently mineralized matrix (Fig 4). Under the microscope it is rather homogeneous in appearance, except for a very fine lamination parallel with the surface. It is not collagenous, though cementum may be deposited on parts of its external surface. Where covered with soft tissue, this is either the reduced enamel organ or simply connective tissue, the epithelium having disappeared. It may be as thick as 0·04 mm. When the layer is accidentally broken up in the preparation of sections of decalcified material, it seems to be formed of layer upon layer of cuticles but, unlike the epithelial attachment cuticle, it does not stain selectively with orcein. In ground sections it shows rather low birefringence, much less than the glassy enamel seen in hereditary hypoplasias.

Weinmann *et al.* thought that in hereditary hypocalcification the ameloblasts ceased to function in the early stages of maturation but the enamel organ maintained its integrity until the tooth erupted; a contrast in this respect was drawn with hereditary hypoplasia. This is certainly not always true, since the epithelium may disappear from large areas before eruption and there may in fact be no epithelial attachment evident in sections at the neck of recently erupted teeth.

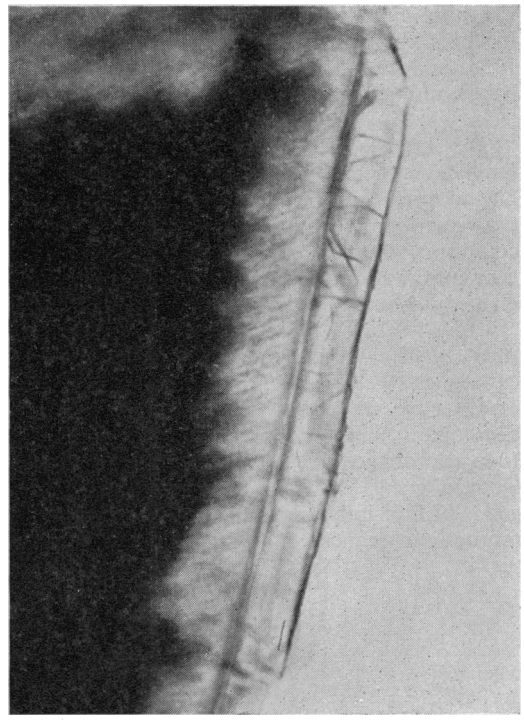

Fig 4 *Hereditary enamel hypocalcification. Ground section showing calcified homogeneous layer on surface of prismatic enamel.* × *540*

According to Miles (1961), 'There is evidence to suggest that the influx of mineral salts required for maturation is derived from the dental pulp and it is by no means certain that the ameloblasts play any part at all'. It is therefore of interest to note that in hereditary enamel hypocalcification failure of maturation and early disappearance of the enamel epithelium may occur together.

It has been believed that normally when the ameloblasts have produced the prisms they then produce the primary cuticle which covers the whole surface of the enamel. In hereditary enamel hypocalcification it would appear that the enamel epithelium not only fails to play fully any part it should play in the maturation of enamel but also becomes repetitively concerned with the apposition of multiple layers of cuticle-like material.

I have noted a few cases of the hereditary localized enamel defect named by Witkop (1957, 1958) and also described by Darling (1956) but have nothing to add to their descriptions.

Our knowledge of these disorders is very limited. At the present time it seems a possibility but no more that they could represent the effects of two series of allelomorphic genes, one of which comprises alternative substitutes for a normal gene on the X chromosome and the other for one on an autosome.

Acknowledgments: I wish to thank the many colleagues who have referred to me patients and material for study and Mr J E Hutchinson for histological preparations and photomicrographs. I am also obliged to the Honorary Curator of the Odontological Museum, Royal College of Surgeons of England, for permission to examine and reproduce specimens.

REFERENCES

Bampton E H (1914) *VI Int. dent. Congr.* p 167
Cameron I W & Bradford E W (1957) *Brit. dent. J.* **102**, 129
Colyer J F (1936) Variations and Diseases of the Teeth of Animals. London; p 591
Darling A I (1956) *Proc. R. Soc. Med.* **49**, 759
Finn B F (1938) *J. Amer. dent. Ass.* **25**, 1240
Fish E W (1948) Surgical Pathology of the Mouth. London
Frank R M & Bolender C (1962) *Rev. Stomat., Paris* **63**, 23
Haldane J B S (1937) *J. Hered.* **28**, 58
Hals E (1958) *Odont. Tidskr.* **66**, 562
Lyon M F (1961) *Nature, Lond.* **190**, 372
Miles A E W (1961) In: Structural Aspects of Ageing. Ed. G H Bourne. London; p 355
Nalbandian J & Frank R M (1962) *Bull. Group. int. Rech. sci. Stomat.* **5**, 523
Rushton M A
(1950) *Brit. dent. J.* **88**, 300
(1962) *Brit. dent. J.* **112**, 24
Schulze C (1956) Erbbedingte Strukturanomalien menschlicher Zähne. Munich
Spokes S (1890) *Trans. odont. Soc., Lond.* **22**, 229
Ten Cate A R (1959) *Proc. Nutr. Soc.* **18**, 65
Toller P A (1959) *Oral. Surg.* **12**, 325
Weinmann J P, Svoboda J F & Woods R W (1945) *J. Amer. dent. Ass.* **32**, 307
Witkop C J
(1957) *Acta genet.* **7**, 236
(1958) *Eugen. Quart.* **5**, 15