Epithelial Remnants and Pearls in the Secondary Palate in the Human Abortus: A Contribution to the Study of the Mechanism of Cleft Palate Formation

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A number of theories have been advanced to account for the development of cleft palate. The majority of these have been based upon observations of clefts induced in mice and rats by various teratogenic agents. A few are based on the study of several human abortuses. However, there has been no extensive investigation of normal palatal development in man, nor has there been available a large series of human abortuses with cleft lip and/or palate.

The following are some of the theories and speculations pertaining to the mechanism of cleft palate formation which have been reported in published form are: a) interference with the intrinsic 'shelf force' that supposedly elevates the palatal shelf (*7*); b) failure of the tongue to descend, thus preventing the shelves from elevating (*7*); c) rapid growth in width of the head so that the palatal shelves are unable to meet and fuse in the midline (*7*); d) the absence of cleft palate in offspring of pregnant mice given cortisone after fetal palate closure (*22*); e) defective circulation leading to arrested development of the primordia of lip and palate (*16*); f) retardation and disorganization of the vascular system, leading to failure of the palatal shelves to elevate (*9*); g) failure of nerve influence, leading to faulty or incomplete union of the palatal shelves (*24*); h) failure of bony union in the palate and the effect of pressure of the lower jaw and tongue, resulting in separation of the shelves *along the line of fusion* (*3, 4*); i) epithelial hypertrophy, whereby the basal cells of the palatal epithelia proliferate so rapidly that mesenchymal fusion between the palatal shelves would be effectively prevented, thus resulting in a separation *at the midline where fusion should have taken place* (*1*); and j) the rupture of the midpalatal cysts which might cause clefts of the palate (*14*).

Stark and Ehrmann (*17*) concluded that 'Once the shelves have fused above the tongue, and the lip has formed, they remain fused or formed throughout development despite any environmental alterations.'

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Fraser and associates (*6*) reported that a few cleft palates were found in the offspring of females that were said to have been treated after the time of palatal closure. Fraser, however, made no effort to interpret the occurrence of post-closure clefts. Two years later (*22*), a paper published from his laboratory indicated that 'Since the timing of the gestational stage in the previous work was not by vaginal plug, but by palpation, or counting back from day of birth, it is probable that some, *if not all, of the previously reported cases of post-closure clefts were actually treated before palatal closure.*' Recently Fraser (*5*) made the statement: 'In the A/Jax strain no treated embryos were seen with shelves touching, whereas in the C57BL/6 strain the majority of embryos did have the shelves meeting, but later than in untreated animals. The pathogenesis of cleft palate in this case is *delay in shelf movement rather than, say, a breakdown of shelf tissue after normal fusion.*' (Italics are present author's.)

In all previous work, except for the above statement, there seems to be general agreement that once mesenchymal fusion has taken place there is no longer any possibility of a cleft palate occurring.

This paper is designed to present, briefly, information about the normal development of the secondary palate in the embryonic stage; and to describe a) the fate of the fused epithelia of the palatal shelves, that is, breakdown of the laminated epithelia followed by mesenchymal penetration and the formation of the mid-palatal cysts (so-called epithelial pearls); b) the meaning of the presence of these cyst-like structures in the palatal shelves of the cleft palate specimens; and c) the possibility of a cleft palate occurring even after the palate has formed on the basis of the fact that these cyst-like structures are found in the cleft palates, and the peripheral part of the palatal shelf in such cases, which is supposed to be torn, is covered with regenerated epithelia.

Materials and Method

The present study was based upon the examination of some 500 non-cleft aborted human embryos and fetuses as well as 80 specimens with cleft lip and/or palate. The embryos ranged in age from 33 days to full term, according to Streeter's method of computation (*18, 19, 21*). All specimens were fixed in 10% neutral formalin solution or Bouin's fixative. Frontal paraffin and celloidin sections of the head were cut serially from the lip to the oropharynx, six to 10 microns thick (one-thousandth millimeter) for the specimens younger than 10 weeks, and 20 to 50 microns thick for the older specimens. Hematoxylin and eosin, Mallory's triple stain, and Masson's trichrome stain were used routinely.

Results

In order to appreciate the occurrence of a cleft in the palate, it is essential to describe briefly the normal development of the secondary palate.

TABLE 1. Chronology of normal development of the secondary palate, from 33 to 60 days of ovulation age.

Age in days (crown-rump length in mm)	*Manner of development of the palatal shelves*
33 ± 1 (8–10 mm)	The primordium of the palatal shelf begins to appear at the oral side as a partial swelling of the maxillary process, which extends from the back of the oral ending of the posterior nasal blind sack to Rathke's pouch.
35 (11–13 mm)	The primordial palatal shelf begins to form process-like projection in the later stage. Bucconasal membrane ruptures.
37–41 (14–23 mm)	Remarkable development of the palatal shelf occurs.
43 ± 1 (22–24 mm)	
earlier stage	Both shelves locate vertically, enclosing the tongue.
middle stage	Vertically located shelves elevate to assume a horizontal position. Elevation takes place simultaneously by ameboid movement of the shelves.
later stage	Both shelves locate horizontally above the tongue.
45 (25–27 mm)	Horizontally located shelves develop, approximating each other.
earlier stage	The anterior half portion of the shelves develop to a marked extent, so that they may come to contact each other.
47 ± 1 (28–30 mm)	
middle stage	Fusion of the shelves takes place at the middle of the anterior half of the secondary palate, extending anteriorly to the junction of the primary and secondary palate and posteriorly to the middle part of the entire palate. The posterior part of the palatal shelf comes to lie more closely to each other as compared with the remaining part of the soft palate.
later stage	The major portion of the hard palate is fused.
51 (32–34 mm)	The entire hard palate is fused. No opening remains at the junction of the primary and secondary palate. The soft palate is still open. Some of the disintegrated laminate epithelia form clumps of epithelial cells, while the other of them are being broken down to be absorbed.
53–55 (33–37 mm)	The soft palate (including the uvula) is fused in most cases, although not in all. Mesenchymal penetration is not complete, epithelial remnants being clearly visible in the soft palate.
60 (45–47 mm)	Mesenchymal penetration is entirely complete and no obvious epithelial remnants are found in the soft palate. The clumps of epithelial cells become cystic structures in the hard palate.

The result of the present study on the chronological and morphological development of the normal palate are shown in Table 1 and Figure 1.

After the opposing palatal shelves make contact on the 47-day stage, their fused epithelia take on a laminated appearance (Figures 2 and 3). Soon afterward, the epithelial laminae begin to break down so that only clumps of epithelial cells or epithelial remnants can be observed. These are separated by mesenchymal cells that have penetrated the epithelial lamina from both palatal shelves (Figures 2–4).

Some of these disintegrated laminate epithelia begin to form a cystic structure surrounded by a layer of basal cells (Figures 7 D–F, and 8 A). The inner cells then become vacuolated and keratinized (Figures 7 G–J). Eventually some of them take on a cystic structure in which more or less keratinized dead cells are packed in onion-skin-like structures (Figures 7 J–K). They are termed 'so-called epithelial pearls'. Such pearls (Figures

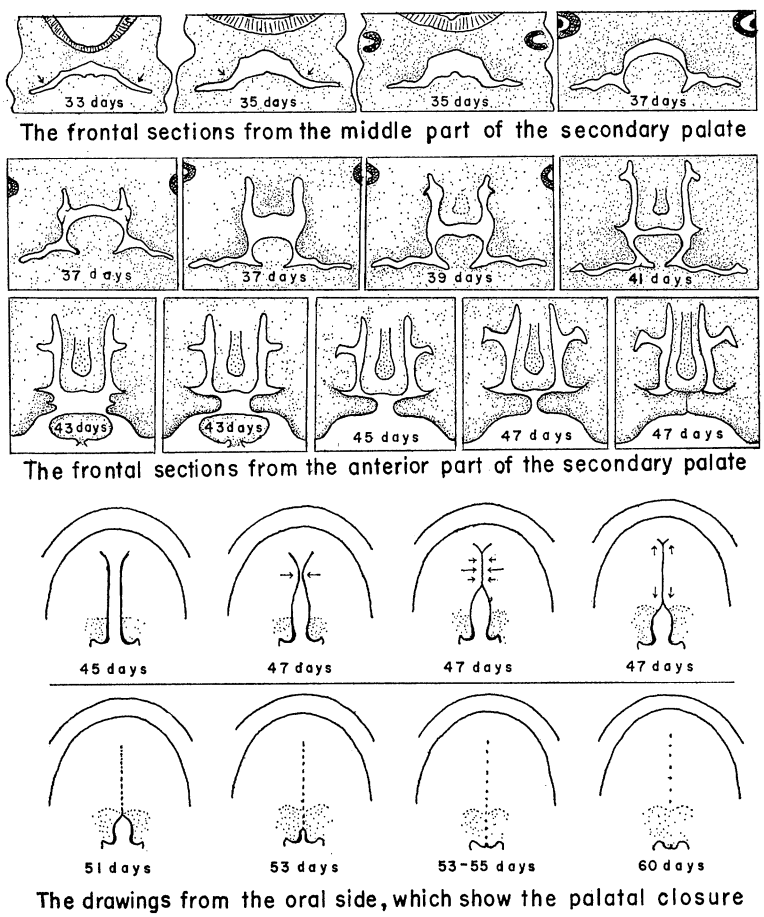

FIGURE 1. Morphology of normal development of the secondary palate, from 33 to 60 days of ovulation age.

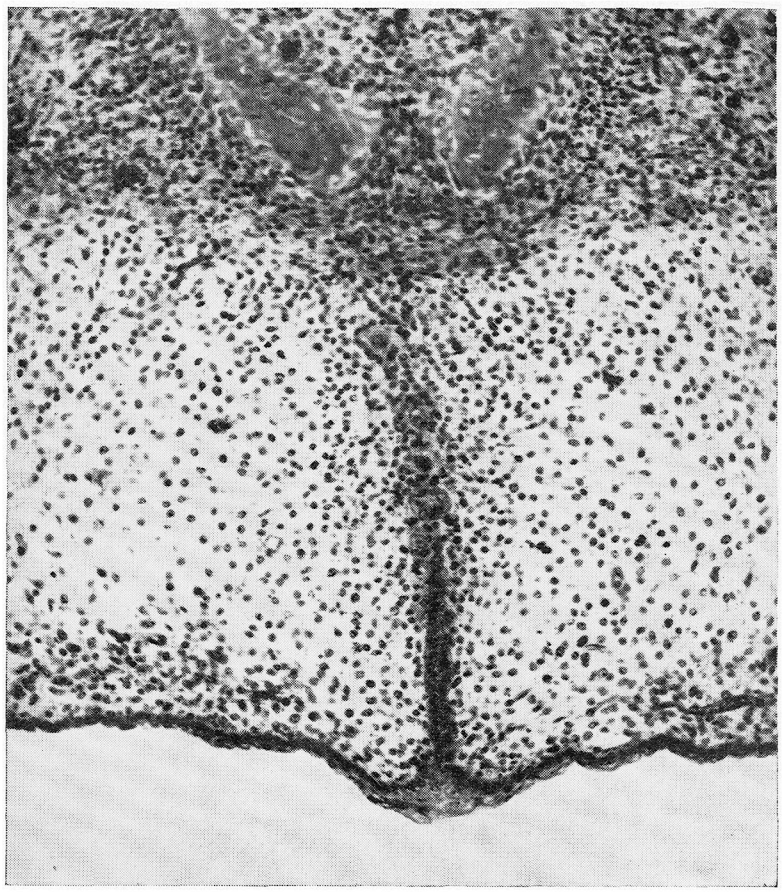

FIGURE 2. Specimen X-490, 51 days of age, Masson trichrome, center of the hard palate, 219×. The epithelial laminae still remain in the oral half of the palate, but in the nasal half of the palate, the epithelial lamina has broken down and ingrowth of surrounding mesenchyme has occurred.

7 G–K) are very commonly found in the midline of the hard palate in noncleft specimens (Figures 4, 7, and 8).

Epithelial pearls were noted in one or both palatal shelves in all cleft fetuses of ages 13 weeks to full term (Figures 5, 9, and 10). They were not observed in any of the fetuses, cleft or normal, at the site of fusion of the nasal septum in either of the two palatal shelves. In fetuses of 12 weeks of age, whether normal or cleft, either the pearls were present or epithelial remnants of them were observed. Some of the remnants were clearly in a stage precursory to pearl formation, while others were in a process of being resolved (Figures 3, 4, 7, and 8). Only epithelial remnants were observed before 11 weeks of age (Figures 4, 7 B–D, and 8 A).

The presence of epithelial pearls or remnants in the shelves in all cleft

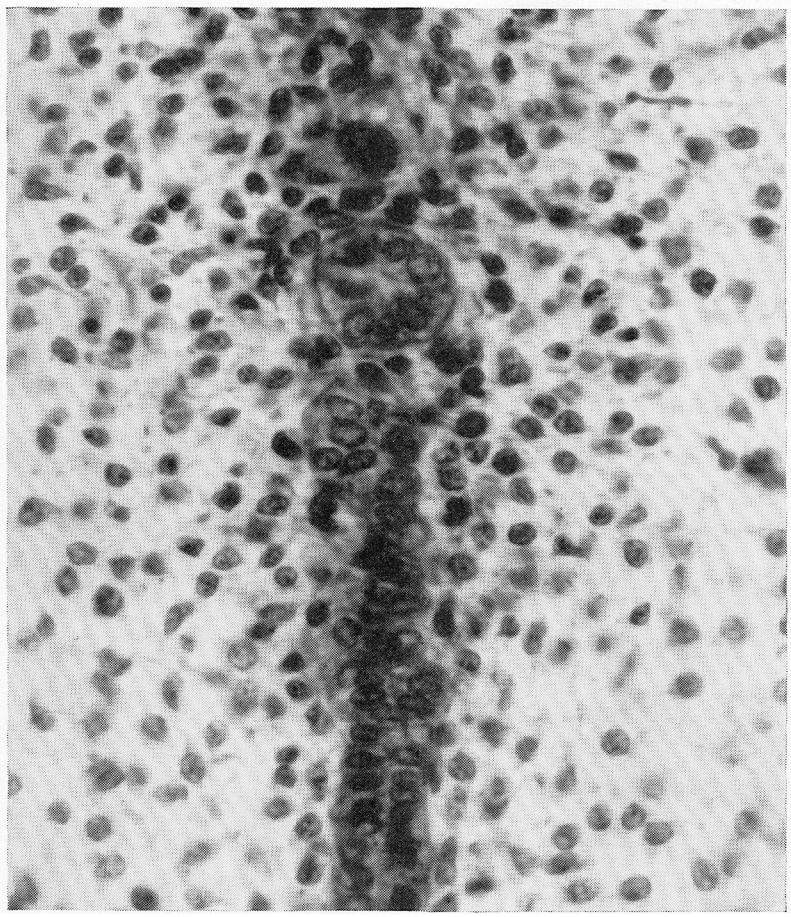

FIGURE 3. Higher magnification of the epithelial laminae after fusion of the palatal shelves, from the same slide as Figure 2, 767×. A partial or almost complete breakdown has occurred in some of the clumps of epithelial cells. In the upper-most epithelial remnant, the basement membrane has disappeared completely and the clump of epithelial cells is being resolved.

palate fetuses over nine weeks of age indicated to the author that the cleft was a post-fusion phenomenon. In other words, the palate had ruptured after normal midline fusion had occurred, probably due to pathologic tissue degeneration. The nature of this pathologic degeneration is being studied further in a parallel investigation.

In this study, all of the cleft specimens which are younger than 11 weeks of age were severely degenerated. The oral and nasal epithelia of the palatal shelves and the nasal septa were detached or completely missing. However, in most of the specimens which are 13 weeks and older, the tissue was fairly well preserved and the epithelial lining was intact.

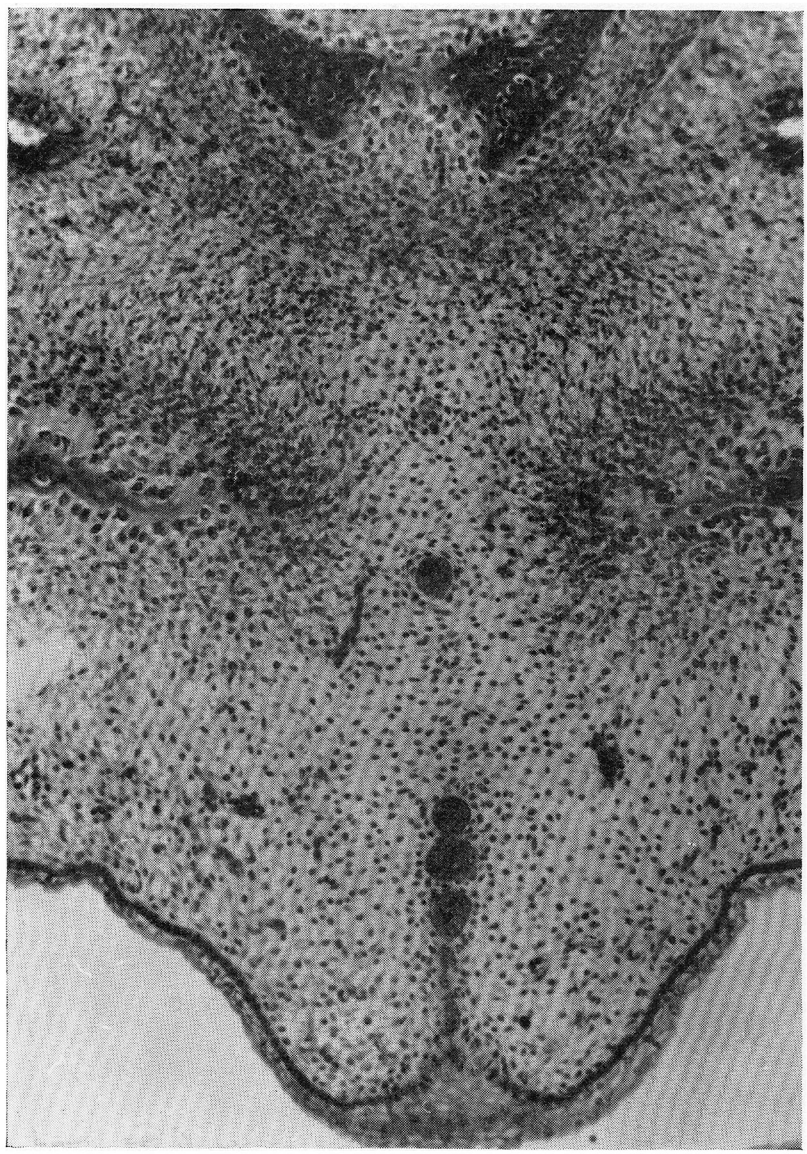

FIGURE 4. Specimen X-653, 63 days of age, Masson trichrome, 170×. Center of the hard palate. The breakdown of the epithelial lamina is advanced in the oral half of the palate and mesenchymal ingrowth has occurred. In the nasal half of the palate, most epithelial clumps have been resolved.

Discussion

In 1909, Bergengruen (*12*) studied human material ranging in age from five fetal months to two months after birth. He found epithelial pearls in the raphe of the hard palate and noted that they were remnants

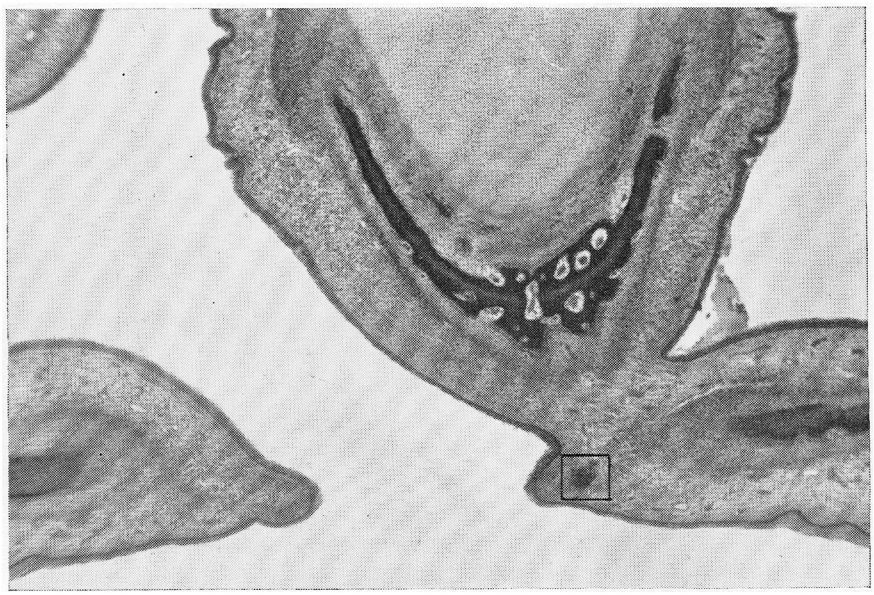

FIGURE 5. Cleft specimen I-29, 13 weeks of age, Masson trichrome, 36×. Center of the hard palate. An aggregation of epithelium-like cells is visible at the middle of the palate beneath the vomer bone, which resembles the epithelial remnant derived from the fused epithelial margins of the palatal processes.

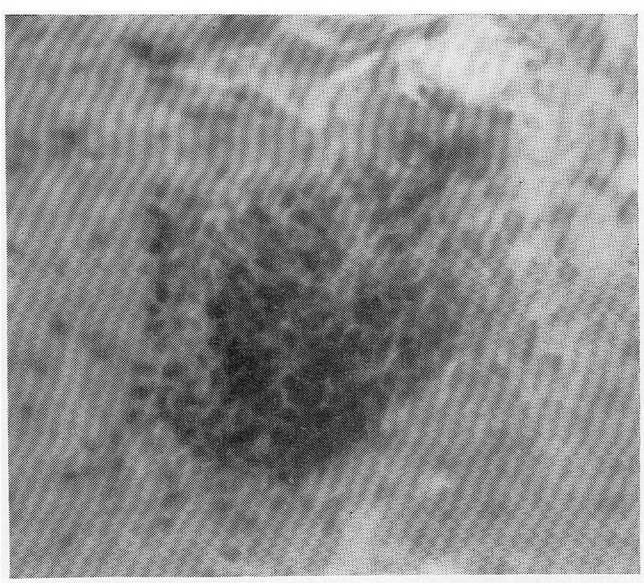

FIGURE 6. Higher magnification of the aggregation of the epithelium-like cells, from the same slide as Figure 5, 460×. No basement membrane is visible around the group of the epithelium-like cells. The nuclei vary in size and shape.

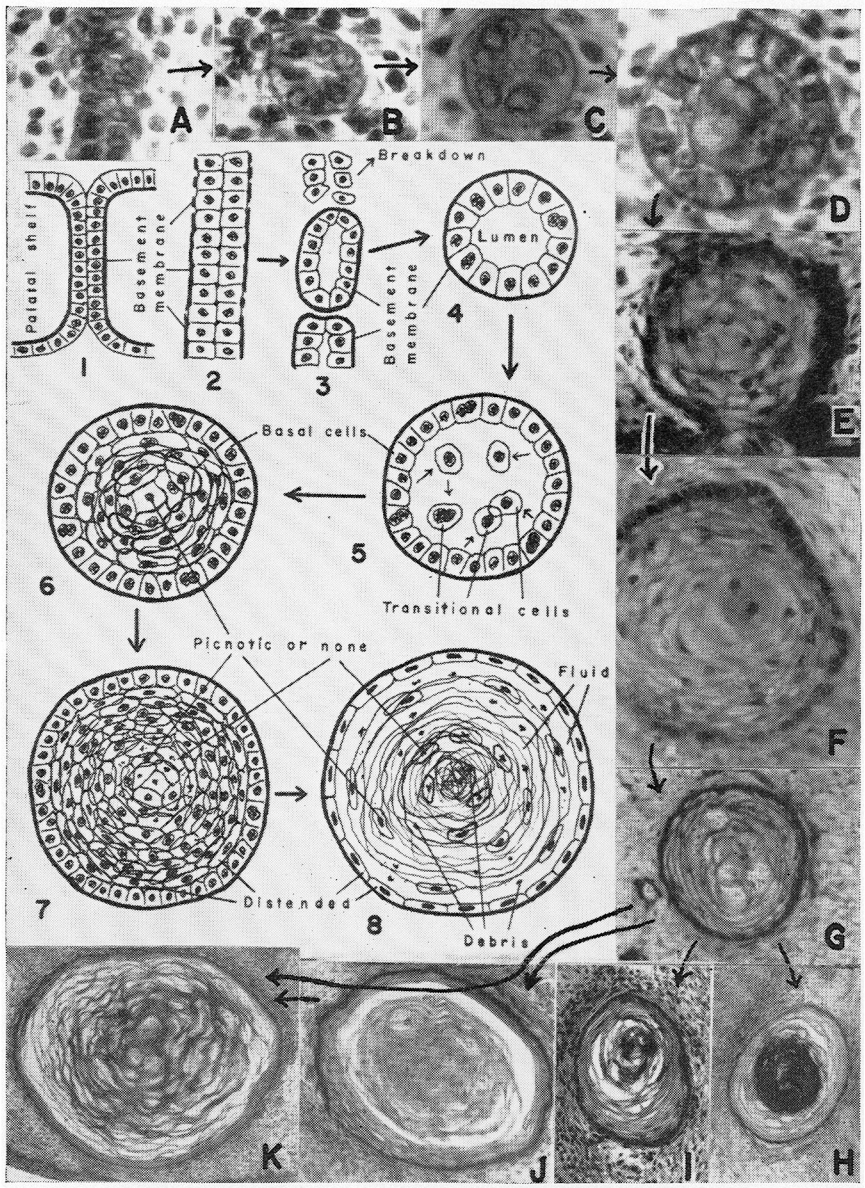

FIGURE 7. Micrographs which show the process of 'pearl' formation in the secondary palate after fusion.

1 to 3. Soon after fusion of the shelves takes place, the epithelial laminae begin to break down. Some of the disintegrated laminate epithelia begin to form cystic structures, while the other groups of cells are broken down to be absorbed (cf. photos A to C). For absorption after breakdown of the disintegrated laminate cells, see Figure 3.

4 and 5. Basal cells multiply. Some of them remain for growth of the wall of the cyst, while the remaining multiplied cells are shed in the lumen to become transitional cells (cf. photos D to F).

of the epithelial margins of the two palatal shelves after fusion had occurred. However, his interpretation was that the cleft palate was the result of primary nonfusion of the palatal shelves, because no epithelial pearls had ever been found in the shelves of the cleft palate.

According to Schumacher (*15*), in 1927, the epithelial pearls in the raphe of the hard palate persist as long as three years after birth. On the other hand, Scott (*14*) stated, 'Cysts of the palate are not common in postnatal life, although they appear to be constantly present in foetal material after the fourth month. They are usually related to the back of the hard palate, lying in the mucous membrane below the bone and sometimes extending into the soft palate.'

In 1931, Veau (*23*) illustrated the frontal sections of the palates of a six-month and an eight-month old human fetus, each with a cleft. Both of his illustrations show very large epithelial pearls. In the six-month fetus the pearl is located on the noncleft side between the vomer bone and the maxilla. Veau considered this to be the result of fusion between the shelf and the nasal septum, although he noted Peter's statement (*11*), 'Epithelial pearls are never found at the site of union between the nasal septum and palatal processes.' In the eight-month old fetus the pearl is located on the cleft side beneath the palatine bone. Veau made no attempt to interpret the presence of this pearl.

According to the present study, such structures were not normally found at the site of fusion of the nasal septum with either palatal shelf. They were not found in the soft palate normally, although in rare instances some were found in severely degenerated fetuses. However, they were frequently found in the soft palate of the cleft specimens, as will be discussed later. Such structures also occurred normally in the alveolar ridge as a consequence of the degeneration of the dental lamina in conjunction with the development of the tooth bud.

It is my opinion that the presence of epithelial pearls or remnants in the palatal shelf of a cleft palate fetus indicates the former site of original fusion of the two shelves. Consequently, the cleft itself must have occurred after mesenchymal penetration had taken place. This means that the tear of the palate does not always occur along the line of fusion (Figures 9 and 10).

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6. Transitional epithelial cells are packed in the lumen. They lie on top of each other in a swirled fashion. Cells in the core begin to degenerate (cf. photos E and F).

7. Peripheral transitional cells close to the basal cells wrap around the group of the cells in a concentric fashion. Further degeneration of the cells is followed by vacuolation and keratinization (cf. photos F to I).

8. Cytoplasm of the dead cells connects each other, forming an onion-skin-like structure. The cyst stops growing and persists for a certain period of time to be absorbed (cf. photos H to K). Photographs are at the following ages: A and B, 51 days; C, 60 days; D, 63 days; E, 12 weeks; and F, 11 weeks. B to D represent precursory stages to pearl formation, while E to G represent intermediate stages. It should be noted that the degree of development of 'pearl' is not always age-dependent, therefore it is more advanced in some instances while it is less advanced in the other of the same age.

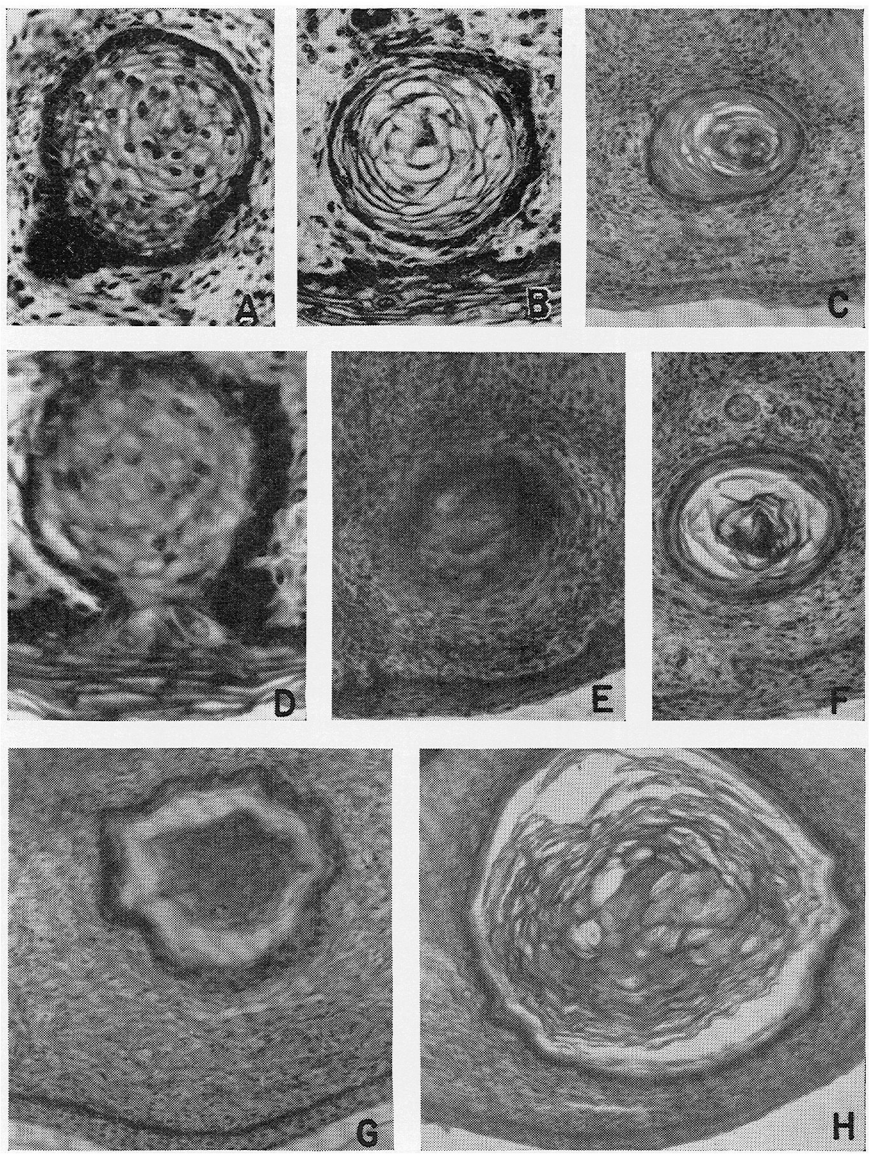

FIGURE 8. Variations of the epithelial remnants, in the center of the hard palate, derived from the fused epithelial margins of the palatal processes. A. 11 week-old specimen, H-E stain, 280×. An epithelial remnant surrounded by a layer of basal cells shows a precursory stage of the epithelial pearl. No keratinization has occurred. B. 12 week-old specimen, Masson trichrome, 280×. The epithelial pearl is located adjacent to the oral epithelium. Most of the inner epithelial cells are degenerated. Vacuolation and keratinization have occurred. C. 14 week-old specimen, Masson trichrome, 112×. Degeneration of the inner epithelial cells, vaculolation and keratinization have advanced. Onion-skin-like structure is being developed. D. 12 week-old specimen, Masson trichrome, 360×. The epithelial remnant is connected to the epithelium of the oral surface. No keratinization has occurred. E. 15 week-old specimen, Masson tri-

Two representative drawings, Figures 9 B and 10 B, show the manner of development of the tears in cleft formations in the hard palate, based on this study of many serial sections. In fact, the presence of epithelial pearls or epithelial remnants in one or both palatal shelves was recognized in all cleft palate fetuses that I have thus far observed. Moreover, in five cleft specimens of ages 17 weeks to full term, the epithelial pearls were also found in the soft palate area. This indicated that the tear of the palate occurred after the fusion of the soft palate (55 days of age).

The question arises: Could these epithelial pearls be formed in the palatal shelves without fusion?

McLoughlin (*10*) found, in the cultures of the epidermis combined with heart mesenchyme as well as the limb mesenchyme from the chick embryo, epidermal cysts in which compact keratin was formed. Some of these cysts were very similar to some of the so-called 'epithelial pearls' in the specimens shown here, that is, epidermal cysts in which keratinization had occurred.

According to Streeter (*20*) the period of post-mortem retention in utero of human abortuses is five to eight weeks. This intrauterine retention after the fetal heart has ceased to beat seems to have kept the fetus in a particular condition which resembles tissue or organ culture in vitro. Therefore, under such a condition this type of epidermal cysts or epithelial pearls might form anywhere in the palatal process without fusion. However, in the present specimens, neither epidermal cysts nor epithelial pearls which were indicative of post-mortem retention were evident, because epithelial remnants or pearls in the serial sections were found consistently in the palatal processes, always at the presumably former site of the original union of the palatal processes.

As far as the hard palate was concerned, no sign of epithelial structures which might later become epithelial pearls was found in any of the 45 to 49-day-old specimens in which the palatal shelves were 'hanging' down. On the other hand, it was found that some older cleft specimens had many epithelial pearls persisting in the cleft palate, which showed that the mesodermal penetration was more or less blocked. However, there was no sign which suggested that the presence of these epithelial pearls somehow prevented fusion by obstructing mesodermal penetration, nor

chrome, 112×. The section of a peripheral part of the epithelial pearl which is strongly keratinized. The lack of a distinct border between the pearl and the surrounding mesenchyme indicates that the peripheral part is being resolved. F. 14 week-old specimen, Masson trichrome, 112×. An epithelial pearl different from that which appears in above in C. Keratinization and vacuolation are more advanced than that in C. G. 15 week-old specimen, Masson trichrome, 112×. The border between the lower part of the outer epithelial wall and the mesenchyme is not distinct, which indicates that this cyst is being resolved. "Epidermal inclusion cyst" might be a more definitive term for this structure. (H) 18 week-old specimen, Masson trichrome, 80×. Note the marked growth of the epithelial pearl. This cyst-like structure contains the keratinized onion-skin-like substance. Macroscopically this structure resembles a pearl.

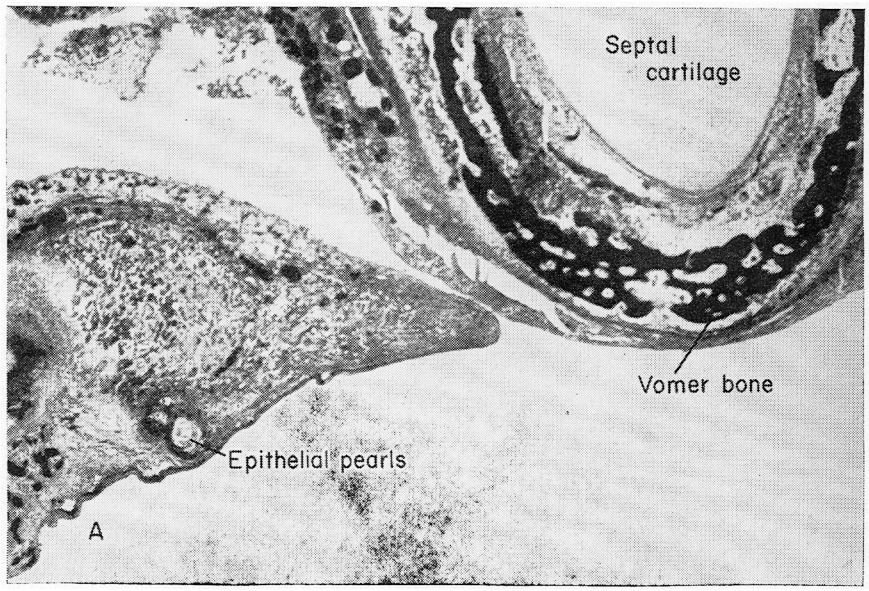

FIGURE 9 A. Cleft specimen X-193, 18 weeks of age, Masson trichrome, 27×.

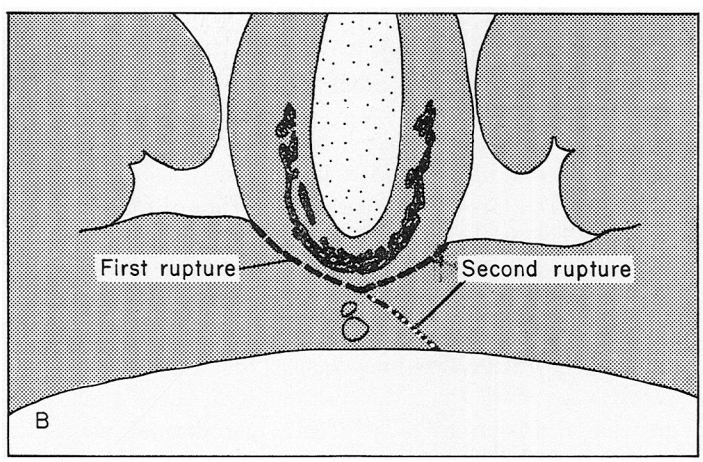

FIGURE 9 B. The drawing from the specimen X-193 shows the manner of development of the tears in cleft formation in the hard palate.

that the epidermal cysts (midpalatal cysts) grew very large and broke through into the nasal and oral cavities.

Another question arises: Are there any human cleft palates resulting from failure of the shelves to assume a horizontal position?

Hayward and Avery (*8*) described a cleft palate infant as evidence of a cleft resulting from failure of the shelves to elevate. That case showed a

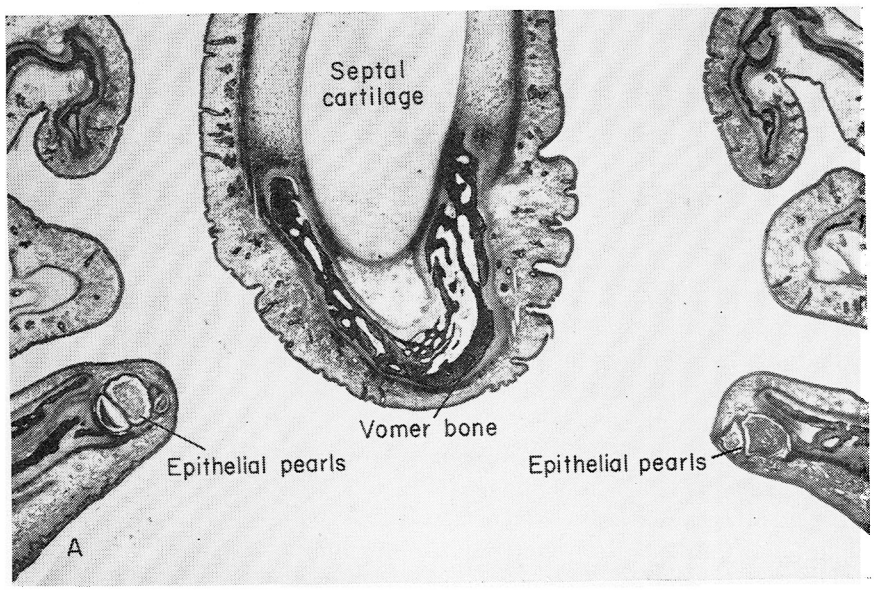

FIGURE 10 A. Cleft specimen W-85, 19 weeks of age, Masson trichrome, 11×.

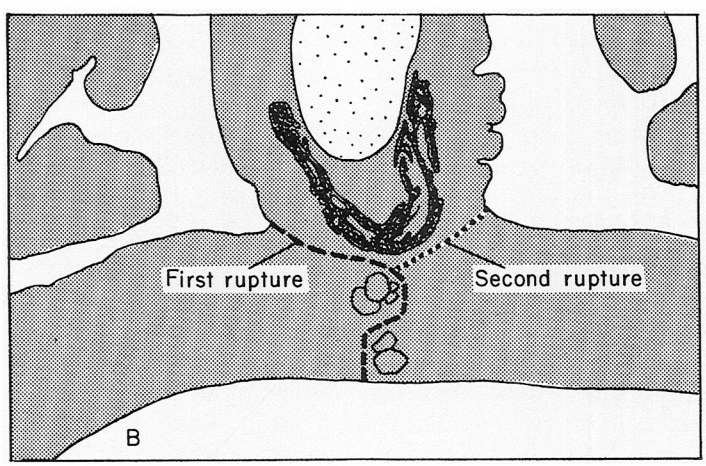

FIGURE 10 B. The drawing from the specimen W-85 shows the manner of development of the tears in cleft formation in the hard palate.

band of tissue, which originated superiorly from the margin of the cleft palate and extended downward as a curtain of mucous membrane which was adherent to the floor of the mouth on the left side. However, even in that case, it is questionable whether the fusion of the band between the palatal shelf and the floor of the mouth was established before or after elevation of the palatal shelves, or after fusion took place.

It is not difficult to assume that the horizontal palatal shelves could easily drop down before fusion. Even after fusion, the palatal shelves could 'hang' down if a secondary tear should occur. In either case, the palatal shelves would come in contact with the tongue and the floor of the mouth again. Under these conditions, they might fuse with the tongue or the floor of the mouth, if the breach in the epithelial covering of the palate and the tongue or the floor of the mouth was due to pathologic degeneration.

One of the 17-week-old cleft fetuses showed the palatal shelves 'hanging' down vertically, enclosing the tongue. This case might be misinterpreted as failure of elevation of the palatal shelves due to obstruction of the tongue. I am not convinced, in this case, that the cleft palate was the result of failure of elevation of the palatal shelves, since epithelial pearls were found in the cleft palate. The theory of 'failure of elevation of the palatal shelves due to obstruction of the tongue' would not be tenable as an explanation of the occurrence of the cleft palate associated with glossal agenesis (*16*).

Thus it is unlikely that cleft palates, in infants, are due to failure of the shelves, for one reason or another, to assume a horizontal position or to fuse once they had achieved this position.

Several specimens of 45 to 49 days in which the palatal shelves were 'hanging' vertically, were carefully examined. Normally in this stage the shelves were elevated to the horizontal position or fused. Therefore these specimens were suspect of failure of elevation due to a pathologic insult which terminated the pregnancy.

The cleft specimens mentioned above, which showed the palatal shelves still 'hanging' down vertically, are of the type which form the basis of the concept that cleft palate formation is due to failure of the elevation of the palatal shelves. It is hoped that research now in process will determine whether this is due to primary failure of elevation of the palatal shelves or due to 'secondary drop down' and the causes thereof.

It is also unlikely that the epithelial pearls found in the above mentioned 17-week-old cleft specimen were formed without fusion of the two adjacent processes for the following reasons: first, the epithelial pearls were found mostly in the right palatal shelf. They were found there consistently in the serial sections; secondly, one would expect to find epithelial pearls in both shelves if the epithelial pearls or cysts had formed without fusion of the shelves as in the previously mentioned cases of the in vitro cultivation.

Another question comes to mind: Could the epithelial pearls or clumps of epithelial cells be the result of proliferation of the epithelium of the oral surface?

If the cleft formation were due to post-fusion rupture of the palate as has been discussed earlier, the torn part of the palatal process should be healed. I found a complete covering of the epithelium on the entire sur-

face of the palatal shelf in the cleft specimens I-29, X-3881, and W-85, respectively 13, 17, and 19 weeks of age (Figures 5 and 10 A). In the 13-week cleft specimen (I-29), I found an aggregation of epithelium-like cells beneath the vomer bone, which resembled the epithelial remnants derived from the fused epithelial margins of the palatal processes (Figures 5 and 6). This clump of epithelium-like cells gave every evidence of the proliferation of the oral epithelium, in as much as: a) the group of epithelium-like cells was very similar to the epithelial remnants in this particular section, and was also connected to the oral epithelium in other sections adjacent to this one; b) most of the cells in this structure were still undifferentiated; c) no basement membrane was visible around the group of cells; and d) no keratinization had occurred.

The healing of the palatal shelves after rupture has been investigated and detailed information will be presented soon in another paper.

It is true that some of the epithelial remnants or pearls were connected to the epithelium of the oral surface (Figure 8 D). However, the epithelial remnants or pearls which were derived from the fusion of the palatal shelves were generally surrounded by basement membrane or encapsulated by an epithelial sheet, and keratinization of the inner cells was frequently observed. The group of newly proliferating or regenerative epithelial cells were completely devoid of basement membrane and were not keratinized (*12, 13*).

In the present paper, I have used the terms 'epithelial pearls' and 'epithelial remnants' as a matter of convenience. It should be noted, however, that these terms are not appropriate in a strict sense. The destiny of the remnants of the laminated epithelia of the united palatal shelves was so variable, not only due to the age of the fetus but also due to the environmental conditions in the mesenchyme of the palate, that the term 'epidermal cyst' or 'epidermal inclusion cyst' might have been more definitive for the cystic epithelial remnants, since they always contained some mucus and fluid. The content of the cysts varied. In some instances, the cysts contained small masses of keratin or keratinized onion-skin-like substances. In other instances, they contained the debris of necrotic epithelial cells or only mucus and fluid. Nevertheless all of these structures resembled the pearl macroscopically. These variations of the epithelial remnants are shown in Figure 8.

Summary

The occurrence of epithelial pearls or epithelial remnants in the palatal shelves in cleft palate human abortuses indicates the site of original fusion of the two shelves. In all cleft specimens so far examined, epithelial pearls or remnants have been found in one or both shelves. The author interprets this as evidence that most cleft palates in man are the result of post-fusion rupture of the palate and suggests that the rupture is the consequence of some embryopathic condition. Whether the embryopathy

leading to degeneration and necrosis is of viral, hormonal, or metabolic origin has not yet been established.

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