First of all I will express my deep gratitude to the Scandinavian Society of Periodontology for awarding me The 1998 Jens Waerhaug Lecture in Periodontology. I feel very honoured and I admire the courage of the prize committee to select a person like me who is not a specialist in the field of periodontology. In my research I have been studying the development of the dental tissues including the periodontal ligament and alveolar bone. Research on the biology of mineralized tissues is now progressing very rapidly, and it will provide a better understanding of periodontal diseases and of the mechanisms involved in periodontal regeneration.

In recent years a number of special treatment procedures have been introduced to promote regeneration of lost periodontal tissues. These include different modalities of flap procedures often combined with implantation of bone grafts of various types of bone substitutes [1–3], demineralization of the root surface [4–7], guided tissue regeneration [8, 9] and combinations of these modalities. More recently growth factors and attachment proteins have been tried experimentally [10–13]. These studies have shown that although it is possible to modify the healing response in various ways, true periodontal regeneration, i.e. restoration of original structure and function of the periodontal tissues, has been an elusive goal. The most common divergence from the original morphology concerns the type of cementum and its cohesion to the dentine surface. The hard tissue formed at the root surface is often cellular, and it easily separates from the dentinitye [10, 14–17].

Studies on cementum formation and periodontal regeneration are hampered by the scarcity of suitable experimental models. Small laboratory animals such as mice and rats have molar teeth with limited growth and roots like human teeth, but the small size of these animals’ molars make experimental studies very difficult. In addition,
the formation of the roots of, at least, rat molars seems to differ from that of human teeth. Other animals commonly used in the laboratory such as rabbits and guinea pigs have molars as well as incisors that grow continuously, which excludes them from studies on periodontal regeneration. Dogs have frequently been used for studies on periodontal regeneration, but it seems as if results in dogs are not directly transferable to the human situation. In dogs, the regeneration of the bone around the teeth seems to be less dependent on a normal periodontium than in monkeys and humans. So far the teeth of monkeys seem to be the best model for experimental studies on periodontal regeneration [18, 19]. However, a number of ethical, economical and other reasons limit the possibilities for experimental testing in monkeys. In order to progress in our understanding of different factors that influence the progression of periodontitis as well as periodontal regeneration, new experimental models have to be developed.

A new, alternative approach to obtain periodontal regeneration is to try to mimic the events that took place during the development of the periodontal tissues. It should then be remembered that the development of the periodontal ligament and the alveolar bone is associated with the development of the teeth [20–27]. Experimental studies indicate that the maintenance of the periodontal ligament and the alveolar bone is also regulated by cells close to the root surface [28]. Thus, if the ambition is to regenerate the periodontal ligament and the alveolar bone that have been lost due to periodontitis, it should aim at re-establishing a new cementum and neighbouring cells. If this is accomplished, the periodontal ligament and alveolar bone are regenerated as a result of the cells at a healthy root surface.

Root formation is initiated by the downgrowth of Hertwig’s epithelial root sheath. The epithelial root sheath constitutes an apical extension of the enamel organ, and ever since Slavkin and Boyde [29] suggested that cementum is an epithelial secretory product, numerous studies have been carried out to investigate this secretory activity [30–35]. Most of these studies have shown that the root sheath cells form and secrete enamel matrix proteins during root formation, but there seem to be some differences between species.

At early stages the developing enamel consists of about equal amounts of proteins, minerals, and water with minor fractions of carbohydrates and lipids. Amelogenins are a family of proteins that is by far the most abundant of these proteins representing more than 90% of the protein content.

Figure 1. A frozen section of the apical end of a developing human premolar extracted for orthodontic reasons and incubated for immunohistochemical demonstration of the amelogenin fraction of enamel matrix. The staining (arrows) at the peripheral surface of the apical end of the root shows that amelogenin is present in the area where cementum formation is initiated. Bar = 100 µm.

Figure 2. The enamel matrix of a maxillary developing molar of a 5-day-old rat exposed to the mesenchymal cells of the dental follicle for 10 days. A thin layer of a new hard tissue (arrows) has formed on top of the exposed enamel matrix. Bar = 50 µm.
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of the enamel. Studies of amelogenin from various species have shown that is remarkably well conserved, which means that there are very small differences in the composition between species [36, 37].

Amelogenin has been demonstrated in epithelial cells at the apical end of infected roots of rat molars [38]. It has also been found at the surface of the developing apical end of the roots of human premolars and within the peripheral root dentine [39, 40] (Fig. 1). In the peripheral root dentine of human teeth, the space occupied by amelogenin deposits remain as Tomes’ granular layer in the fully formed tooth. At the root surface, acellular cementum is formed in the area where the amelogenin has been found. The deposition of amelogenin in the peripheral dentine makes this part of the tooth a very special tissue. In the clinical treatment of periodontitis, no attention has been paid to this fact. Root planing aims at obtaining a smooth root surface with no concern for the biological function of the tissues that are removed. In my opinion, more attention should be paid to the possible role of the peripheral (mantle) dentine for a successful periodontal regeneration.

Experimental studies on developing rat molars have shown that cementum is formed when mesenchymal cells of the dental follicle are exposed to denuded enamel matrix [40, 41]. A few days after the removal of the enamel epithelium and exposure of the enamel matrix, a thin layer of a collagenous hard tissue can be observed (Fig. 2). It is interesting to note that coronal cementogenesis in a number of herbivorous species seems to be initiated by exposure of the mesenchymal cells of the dental follicle to the developing enamel. The coronal cementum formation starts as islets in fenestrations in the enamel epithelium. In some species it then continues to develop into a complete coverage of the enamel, while it remains as islets or pearls in others [42–46]. At the developing ends of the roots of human teeth, the epithelial root sheath also fenestrates in the area where cementum formation starts [47]. With increasing age the windows in the epithelium increase in size and the epithelial network becomes less dense [48].

The effect of enamel matrix proteins on periodontal regeneration has been tested in a buccal dehiscence model in monkeys. Those experiments showed that it was possible to regenerate acellular cementum as well as the periodontal ligament and alveolar bone. The model was also used for quantitative studies on the effect of different fractions of the enamel matrix on the periodontal regeneration. It was found that the amelogenin fraction was efficient...
while matrix components with a higher molecular weight did not promote periodontal regeneration [49] (Fig. 3). A product based on the amelogenin fraction, called EMDOGAIN® (BIORA AB, Malmö, Sweden) is now being marketed for the promotion of periodontal regeneration.

The observation that cementum formation seems to be associated with the enamel proteins should not come as a surprise, since a number of herbivorous animals have cementum on top of the enamel of the crown. In this position the coronal cementum constitutes a part of the occlusal surface and takes part in the grinding of the food. Human teeth also have regions with coronal cementum. Based on structural studies, most of the coronal cementum of human teeth has been defined as acellular, afibrillar cementum [50]. However, coronal cementum of some herbivorous animals has a structural appearance that is similar to that of the radicular acellular extrinsic fibre cementum [44, 45, 51] (Fig. 4).

Comparative studies of the developing teeth in various species are very informative for the understanding of the relation between the formation of all the dental tissues including enamel and cementum. It might be said that nature has made all the good experiments. The scientific challenge is to identify them and to compare and interprete them. After almost four billion years of evolution, nature has learned what works. Recently, biomimicry was introduced as a name for a new science that studies nature’s models and then imitates them [52]. The word biomimicry comes from the greek words bios (life) and mimesis (imitation). It introduces a new way of viewing and valuing nature and tries to find what we can learn from it. The use of enamel matrix proteins to promote regeneration of the periodontal tissues is, in my opinion, a good example of biomimicry.

**Summary**

During the last decades a number of methods have been introduced to promote the regeneration of periodontal tissues. These include different flap procedures, demineralization of the root surface, bone grafts, guided tissue regeneration, and administration of growth factors. This short presentation describes the background of the method that imitates the normal development of the periodontium and which involves the application of a fraction of the enamel proteins to the root surface to promote periodontal regeneration. The link between enamel and cementum formation is, e.g., illustrated by the fact that a great number of herbivorous animals have cementum on top of the enamel. It is emphasized that the three tissues of the periodontium are dental tissues and that growth and maintenance of the alveolar bone are regulated by cells at the root surface. Regeneration of the root surface by means of enamel proteins will thus result in regeneration of the cementum as well as of the periodontal ligament and alveolar bone.

**References**

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