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An Investigation into the History, Science, and Future of Dental Filling Materials

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AN INVESTIGATION INTO THE HISTORY, SCIENCE, AND FUTURE OF DENTAL FILLING MATERIALS

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Chapter 1: Introduction

You take a bite of a sweet toffee bar. Instantly, you feel a sharp pain in your back molar. You continue chewing in excruciating pain, trying to use the sensations of the delicious treat to distract you from the ache in your tooth. To no avail, you put down the rest of the sweet treat. "Not again," you think to yourself. "I take such good care of my teeth. Why is this happening to me?"

If this experience has befallen you, it is likely that you, like 92% of Americans age 20-64, have had dental caries in one of your teeth.[1] The main cause of dental carries, more commonly known as cavities, are caused by bacteria "feeding on the sugars in the foods and drinks we consume to grow – then leaving behind the waste, in the form of a biofilm known as dental plaque."[2] Eventually, the bacteria produce acids from living on the plaque, which wears down the tooth enamel and causes cavities.[2] Toxic products that are also formed enter gum tissues, causing gingivitis, producing a new set of issues, which can lead to periodontitis, the loss of bone and tissue around the teeth.[2]

Sugary foods are the main culprits when it comes to producing cavity-causing bacteria. However, starches can lead to plaque production as well.[2] The production of these bacteria can be depleted "through good oral hygiene practices, healthy diet and dental checkups. Brushing after meals, using antimicrobial mouthwash, and flossing at least once per day."[2]

When a cavity is present in a tooth, a filling is usually required to correct it, if only a small portion of the tooth has been affected by the decay. There is a plethora of factors that influence the choice of dental fillings used for a dental cavity. Some main aspects include affordability for the patient, durability, and the health risks linked to the materials of the filling.

Two main fillings are commonly used throughout dental practices today: silver amalgam and composite resins. Silver amalgam is a mixture of soft metals that is used to fill a cavity. This material is malleable, affordable and requires an easy application process, yet it is not the first choice of many patients because it lacks a pleasant aesthetic. It is visible in the mouth when a patient smiles, laughs, speaks or chews. The more common filling of the two is a composite resin. This type of filling has transformed over the last few decades, improving in areas such as affordability, durability and aesthetic look. A composite resin material can last longer because of its binding to the patient's tooth through a light-curing chemical process. It is also possible to match the color of the material to the color of the patient's tooth, which heightens its aesthetic appeal. It is not visible in the mouth, such as the silver amalgam.

Other filling materials of notable importance, which are not as common, are gold and porcelain fillings. The gold filling is an alloy of gold and other soft metals. Since gold is more expensive than other metals, this filling was used for patients of upper classes in the eighteenth, nineteenth, twentieth, and even twenty-first centuries. It was also more malleable than the current silver amalgam filling, which decreased its durability and sustainability. The porcelain filling is used when a large portion of the tooth is decayed, and requires removal of a substantial amount of tooth for its placement. This highly invasive procedure is not common because the goal of a dental filling is to fill in, or seal, the cavity with as little damage and invasiveness to a tooth as possible. If a significant amount of tooth is decayed, the dentist may opt to remove the entire tooth and replace it with an implant, which will not be discussed in this thesis.

Another, more modern direction of dental caries restorative materials is rapidly developing. This procedure includes taking stem cells from a different part of a patient's body, storing them until needed, and differentiating the cells to replace the damaged and decayed portion of the tooth. Another branch of this form of restoration is three-dimensional printing, in which a specific portion of the tooth is 3D printed using biomaterial mimicking the tooth itself. This developing technique is still in its beginning stages. It is difficult to pinpoint exactly which direction this technique will follow. Even though it is in its early development, it is worth studying if developing a new technique for restoring dental caries is truly necessary. The current materials are durable, affordable, and the composite resins are aesthetically pleasing. There may be benefits in exploring existing composite resin materials, and potentially revolutionizing them to meet the demands and desires of patients and dentists alike. Even if the development of stem cell tooth regeneration were to emerge, it would take many more years of trials and studies to determine if this filling would be an overall better replacement than the fillings used today.

Chapter 2: History of Dental Medicine

"That dentistry in some form has been practiced from the most ancient times, there seems to be but little doubt, since considerable fragmentary evidence still exists as to the general methods used by the ancients. If we stop to inquire who first extracted teeth, made plates or filled carious cavities we shall find that all such information is shrouded in the mists of antiquity along with the history of the pyramids and other relics of early civilization." – J. A. Taylor, D. D. S.

Dentistry has revolutionized from a form of ancient medicine, to an expansive practice with many subdivisions. The first descriptions of cavities in history books dates back to 5000 BC, where "a Sumerian text of this date describes 'tooth worms' as the cause of dental decay."[3] Since there were no scientific explanations for tooth decay and no dentists during those times, the Sumerians assumed that some external organisms were causing teeth to decay. The Sumerians wrote a poem where they acknowledged these tooth worms:

After Anu had created heaven,
Heaven had created the earth,
The earth had created the rivers,
The rivers had created the marsh,
And the marsh had created the worm—
The worm went, weeping, before Shamash,
His tears flowing before Ea:
"What will you give me for food?
What will you give me to suck on?"
"I will give you the ripe fig and the apricot."
"What good are the ripe fig and the apricot?
Lift me up, and assign me to the teeth and the gums!
I will suck the blood of the tooth,
and I will gnaw its roots at the gum!"
Because you have said this, O worm,
May Ea strike you with the might of his hand![4]

They believed that these worms created holes in the teeth and hid inside the cavities in the teeth. Toothaches were believed to be caused by the worms moving around in the teeth.[4] These assumptions likely initiated the fascination with dental treatments.

The first known medical treatise dates back to 3,000 B.C. and is named the Edwin Smith Papyrus, after the dealer who bought it in 1862. This medical text is an ancient Egyptian manuscript which gives instructions on "how to heal and treat wounds in the mouth"[5]. Even though the causes of oral problems, such as cavities or decay, were not discovered in these early ages, the introduction of oral medicine is evident throughout ancient civilizations. For example, the Ebers Papyrus, an ancient Egyptian papyrus on herbal knowledge, contains eleven dental prescriptions. The hieratic characters explaining the prescriptions can be seen in Figure 1:

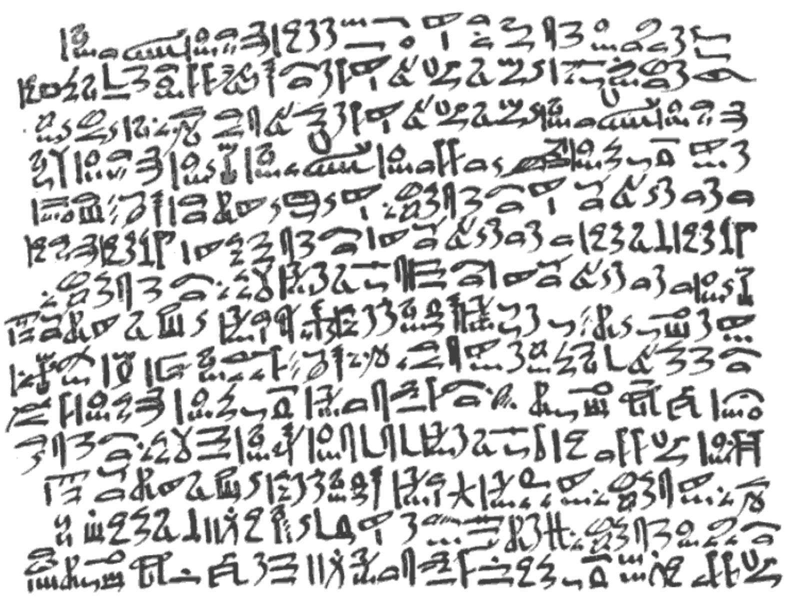

Figure 1: Eleven dental prescriptions written on the Ebers Papyrus in Egyptian hieratic characters.

In addition to ancient civilizations including written remedies on oral medicine, they also graphically depicted the treatment of oral obstructions, in paintings such as the one presented in Figure 2 below[5]:

Figure 2: A painting on an ancient Egyptian papyrus scroll indicating the treatment of the mouth.

In Figure 2, an Egyptian (center) is depicted with a probe inserted in the oral cavity of a human specimen (right). On the left side of the painting, another servant is present, etching characters into a column. In this situation, it can be concluded that the Egyptian is performing some sort of oral procedure on the seated servant, while the other servant simultaneously takes notes on the procedure. This form of exploration paved the wave for the future of dentistry. At the time, in 2600 B.C., an Egyptian scribe by the name of Hesy-Re was dubbed as the first dentist. His tomb contained an inscription that read "'the greatest of those who deal with teeth, and of physicians"[3].

Although many ancient Egyptian manuscripts and papyrus scrolls have been uncovered, it is estimated that much of the information and history of dentistry was destroyed when the Saracens invaded Egypt and destroyed the library at Alexandria[6]. This library was the largest one in Egypt, containing a large majority of written work from the area at the time.

One important piece of conserved dental literature from the library of Alexandria, mentioned above, is the Ebers papyrus, written between 1700-1550 B.C. It was discovered in 1872 by Prof. George Ebers, hence the name, at Thebes, an ancient city in Greece. It provides remedies for toothaches and 'blisters in the teeth,' which in modern terminology, are defined as cavities. The remedies were instructions to mix ingredients such as honey, oil, various seeds, onions and incense to create a paste and apply it to the problem area of the tooth[6]. They would use this paste to scrub their teeth to prevent oral decay, just as we do with toothpaste today. This was most likely the early precursor for the modern toothpaste used in today's society.

Another way in which the Egyptians aimed to prevent tooth decay, which seems bizarre by today's standards, was to use mice. In their religion, the mouse was "considered to be protected by the Sun and capable of fending off death."[4] They would kill a mouse and apply half of its warm, dead body to the aching tooth. They believed the powers of the mouse would expel any decay or death of the tooth from the affected individual.

In addition, there have been preserved lower jaws found in Egypt, dated to be from 2900 to 2750 BC by experts. One jaw had two holes drilled through the bone, which could have been part of a procedure to drain an abscessed tooth.[4] Other ancient Egyptian dental procedures included fillings using a handmade mineral cement, using gold wire to bind loose teeth together, presumably teeth with decaying roots, and tooth extraction using a dentist's actual fingers[4], which eventually gave rise to the invention of modern dental instruments.

There were different ranking ancient Egyptian dentists. The lower-class dentist, called a *iryw-ibew,* treated the ordinary common man. The elite dental specialist, referred to as the *ir-iryw-ihew* treated the royal court and other high-ranking individuals. Regardless of rank, the dentists were more focused on research and recording their observations rather than treating patients, who "suffered from extensive, severe and painful dental disease which the available treatments of the time can have done relatively little to alleviate."[4]

The next significant contributions to dentistry were recorded by the famous Greek physicians Hippocrates. Hippocrates is credited as the "Father of Medicine," and all who wish to practice medicine still have to take his famous "Hippocratic Oath." One of the oldest known oaths in recorded history. Hippocrates was born in 460 B.C. and studied medicine under his father, but later turned to study the medical texts in the temple of Cos.[6] Much of his recorded literature covers dental diseases and their treatments. He included detailed instructions on how to extract teeth and invented dental forceps, as well as other dental instruments.[6] He also cauterized teeth that were painful, but not loose or falling out. He instead recommended binding loose teeth to healthy teeth using gold wire, like the ancient Egyptians, or with linen thread. An example of these procedures is depicted below, in Figure 3. The development and history of bridges is beyond the scope of this thesis, but are necessary to demonstrate the development of dental treatment options throughout history.

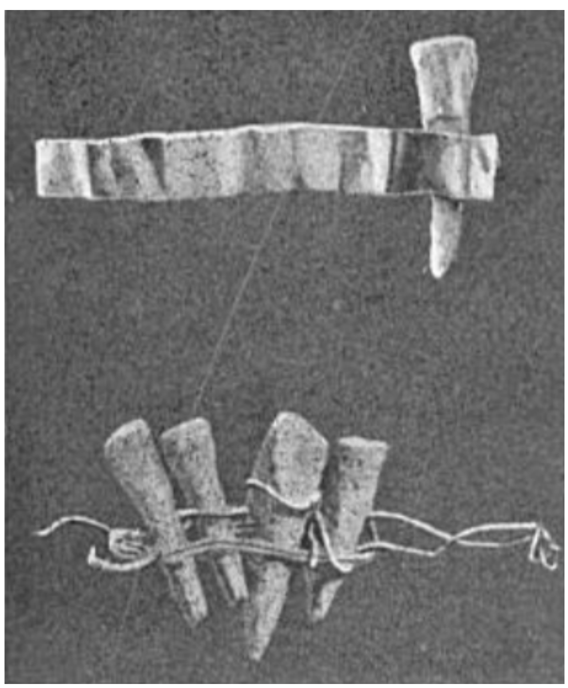

Figure 3: A photo of Hippocrates' gold wire and linen thread procedures for securing loose teeth.[6]

About six hundred years after Hippocrates, a noted Roman anatomist by the name of Galen commented on Hippocrates' work. He classified teeth as bones, but noted that they were different than any other bones.[6] He was the first researcher to discover nerves in teeth, and recognized seven cranial nerves in his work. In addition, he hypothesized that teeth grow and self-repair themselves on the assumption that teeth growly independently; without the interreference of other teeth, the teeth were able to grow longer.[6] He advised people with dental decay or toothaches to rub their gums with "the milk of a birch or the brains of a hare"[6] to assist the teeth in self-repair.

The Romans made significant improvements in dentistry around 100 B.C. They made advanced gold crowns, which were discovered at the excavation of Satricum. These crowns can now be found in the museum of Pope Julius in Rome. They were composed of two gold plates stamped to "represent the labial and lingual surfaces of the lower central incisor, and were then soldered together to form the crown of the tooth."[6] They were soldered to "a narrow strip of gold which is contoured in such a manner as to encircle the neighboring teeth, which act as support for the appliance."[6] These crowns are shown below in Figure 4:

Figure 4: Roman gold crown of lower incisor, found at Satricum (left) and the same crown, as seen from below (right).

A few hundred years later, between the years 166-201 AD, "the Etruscans practice[d] dental prosthetics using gold crowns and fixed bridgework."[3] The Etruscans were the early Italians who inhabited a part of Italy known as Etruria. A dental crown is a synthesized tooth that is placed onto a dental implant; dental bridges are similar to dental crowns, but they span over numerous teeth. In both cases, the goal is to remove decay from the oral cavity and treat the patient with the most minimally invasive procedure possible. The Etruscans “used bridges made of gold rings holding ox teeth for the purpose of replacing lost dental organs.”[6] A example of their work is pictured below in Figure 5:

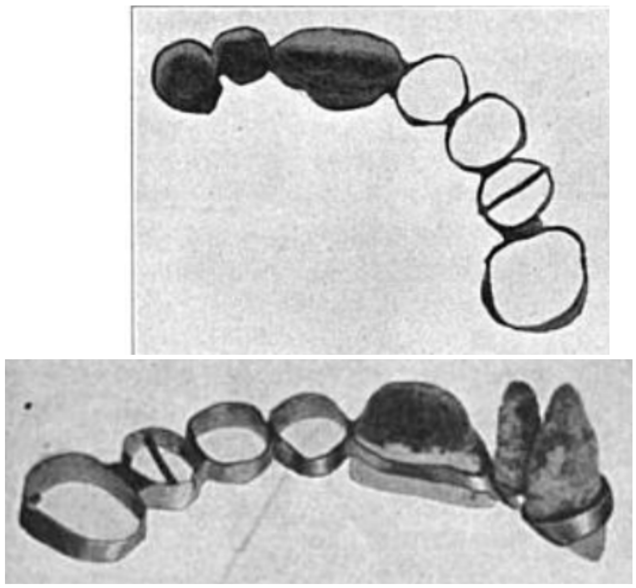

Figure 5: Etruscan appliance for supporting three artificial teeth, two of which were made of one tooth (left) and the same appliance, reversed (right).

However, much recorded literature from the Etruscans is yet to be translated because no code has been discovered that can allow scientists to decipher their writings.

The long-recorded history of dentistry and its treatments gave way to advancements across the world during the Middle Ages. The first uses of amalgam (a mercury/soft metal mixture) to fill in caries were recorded in 659 AD in China, where “a medical text in China mention[ed] the use of ‘silver paste’”[7], which is one of the common types of amalgam. This medical text titled *Xinxiu bencao* was written by Su Gong, during the Tang Dynasty in China. The silver amalgam filling would eventually evolve into a modern dental filling, still in modern dental practice today.

For the next century, techniques were being refined and information was shared and standardized. Advancements across the globe, most notably in Europe and Asian, gave rise to the acceleration of dentistry in the sixteenth century.

In 1530, German Artney Buchlein published the *Little Medicinal Book for All Kinds of Diseases and Infirmities of the Teeth.* It was the first book of its kind, devoted entirely to dentistry and written for barbers and surgeons who treated the mouth. It covered "practical topics such as oral hygiene, tooth extraction, drilling teeth, and placement of gold fillings."[3] A few decades later, in 1575, Ambrose Pare, a French man known as the Father of Modern Dentistry, published *Complete Works*. His medical text included information about dentistry, including tooth extraction and treatment of jaw fractures and tooth decay.[3] He worked his way up the dental practice ladder, initially starting off as a barber, then a surgeon-barber and eventually the chief surgeon to the French court.[6]

In 1723, Pierre Fauchard, a French surgeon dubbed the Father of Modern Dentistry, published *The Surgeon Dentist, A Treatise on Teeth* describing "a comprehensive system for the practice of dentistry including basic oral anatomy and function, operative and restorative techniques, and denture construction."[4] This was a major step in the standardization of dental practices. He researched several improvements in prothesis and commented on the preconceived ideas of tooth worms. He stated that he had never personally seen the "worms", and if they did exist, did not cause caries. He believed that the if old folklore was true, the eggs of insects could have entered the cavities, laid their eggs there, and therefore produced the worms. Fauchard also further explained the anatomy of the tooth, including "their structure, position, origin, growth and … body, root and neck."[6] In addition, he suggested using small sponges to clean the teeth daily, and dipping the sponges in tepid water prior to brushing. In terms of caries, Fauchard explained the draining of the pus from the cavity, then inserting a cotton-wool swab soaked in oil and cinnamon, and leaving it for several weeks. He then filled the cavity with fine tin, lead, or gold; that was the order of his preferences. He stated that gold did form well enough to the cavity, but admitted that not everyone could afford it.[6] As an alternative, he cauterized the tooth to diminish the caries and relieve toothaches; this method destroyed the nerves within the tooth. Some of his tools for cleaning caries out are pictured below in Figure 6:

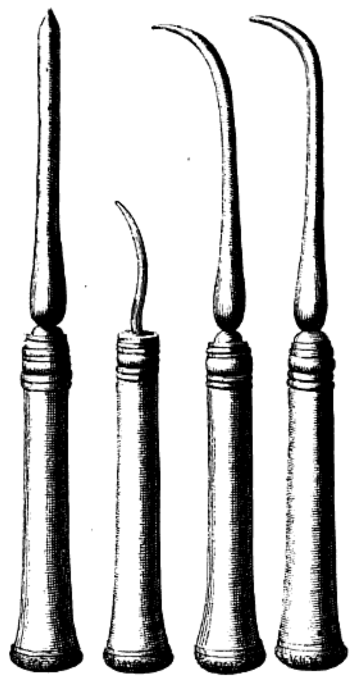

Figure 6: Fauchard's instruments for scraping caries, which were precursors to modern dental cleaning implements.

Fauchard also advised that a dentist be included in the board of examiners and insisted that a school of surgery where the theory and practice of dental surgery could be taught. He also noted that few dental texts were published before his time because the authors did not want their findings to be plagiarized and profited off of by someone else.[6]

The first German to write a treatise on dentistry was Philip Pfaff, who was dentist to Frederick the Great. His work, titled *Treatise on The Teeth of the Human Body and Their Diseases* (1756) is the first recorded practice of "capping an exposed nerve before placing a filling in the cavity."[6] Pfaff also described constructing artificial teeth with ivory and bone/tusks of hippopotami. In addition to these materials, he recounted using silver to fill teeth, which gave rise to the modern silver amalgam filling.

Shortly thereafter in 1789, Nicolas Dubois de Chemant received the first patent for porcelain dentures, the first recorded use of porcelain in dentistry.[3] However, this was not the first time where porcelain teeth were revealed in history. In 1710, Guillemeau "suggested a formula for paste for artificial teeth composed of white wax, softened with a little gum elemi, to which was to be added a powder of white mastic, of coral, and of pearl."[6] In addition, Fauchard mentioned the idea of porcelain teeth in his work, *Le Chirugien Dentiste,* although there is no proof that he ever made any.[6] This opened the door for further advancements in dental materials, revolutionizing the treatment options for dental caries.

All of the dental advancements prior to the nineteenth century gave rise to what is today known as modern dentistry.

Robert Arthur was an American-born dentist who was a member of the first graduating class of the Baltimore College of Dental Surgery in 1841. He revolutionized the treatment for dental caries by abandoning "the old method of filing a separation between the teeth to prevent or arrest caries" and instead providing "a small shoulder at the gum, presumably for its protection, but at the same time allowing a free excursion of the food over the filed surfaces."[6] Continuing advancements allowed Arthur to develop the cohesive gold foil method in 1855, which inserted gold into a dental carie after drilling, with minimal pressure,[3] thus offering an alternative to silver amalgam. In *A Treatise on the Use of Adhesive Foil,* Arthur published his method to claim the discovery, even though many claimed to have used this method before his publication.[6]

A major innovation that changed the practice of dentistry was the formulation of the local anesthetic procaine in the twentieth century. Procaine was later marketed and produced as Novocain. It was developed by German chemist Alfred Einhorn in 1905. Prior to this invention, all dental procedures were done without strong anesthetics. Some herbal-based medicines were applied to the treatment areas dating back to the ancient origins of dentistry to help mildly numb pain. However, after Novocain, dentistry developed into a more standard area of health care because the procedures were less painful and people were more willing to receive dental treatment.

Another revolutionary advancement was achieved by Oskar Hagger in 1949, where the Swiss chemist developed the "first system of bonding acrylic resin to dentin."[3] This adhesive was acidic and thus bonded to the tooth on the molecular level. Physical and chemical bonds between the tooth and bonding resin held the filling in place. This idea was further developed when new materials began emerging, launching dentistry into a promising industry.

A little over a decade later, in 1962, Rafael Bowen developed bisphenol A-glycidyl methacrylate, or Bis-GMA, which is used in "most modern composite resin restorative materials."[8] He mixed bisphenol A and glycidylmethacrylate thinned with triethylene glycol dimethacrylate to create this hardened and robust resin.[7] Leading up to this time, there were disadvantages of each of the materials used in restorative dentistry. Some issues include that they were visible in the mouth as silver, gold, or off-colored tooth fillings, in addition to price and health risks. Bowen's contribution to the dental world aided in the change of dentistry from an undeveloped practice to an esthetic that was desired by many. It helped to minimize the appearance of dental fillings in the mouth, while creating a longer-lasting adhesive.

In 1990, "new tooth-colored restorative materials"[3] were introduced, creating an advancement in aesthetic dentistry. Since then, there has been a continued rush to create even more effective and appealing dental fillings to meet the demands of not only dentists, but also of patients.

Chapter 3: Chemistry of Modern Dental Caries

A healthy tooth is composed of multiple layers. The layer that is visible to the naked eye is called the enamel. This makes up the crown, or the part of the tooth that protrudes from the gums. Underneath the enamel is dentin, which is a hard, light yellow and porous layer of tissue. It is the largest portion of the tooth and consists of 70% inorganic matter and 30% organic matter and water.[9] Directly underneath the dentin is the pulp cavity, which is the central cavity of a tooth, which contains dental pulp and is composed of the root canal and pulp chamber.[10] The root canal contains the nerves and blood vessels that are located inside a tooth, and are found in the root of the tooth. In between the crown and the root is the neck of the tooth, which rests between the layers of exposed and hidden gum tissue.

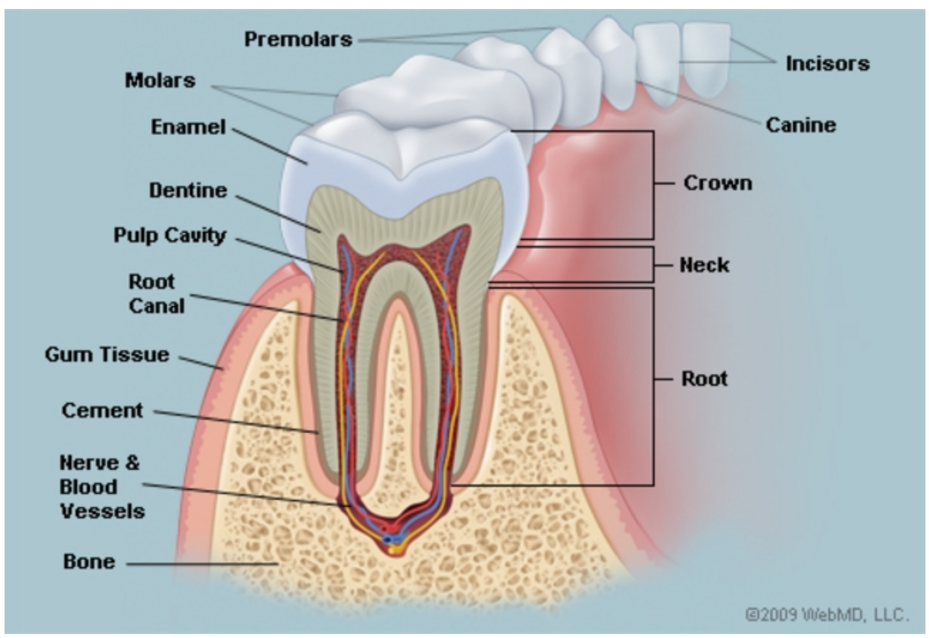

Figure 7: A cross section diagram of a typical healthy tooth rooted in gum tissue. The primary structural features of the tooth are indicated.[11]

The formation of dental caries is caused by many factors, but chemistry is intertwined in each instance. At a macroscopic level, sugar, saliva and bacteria contribute to the acceleration of cavity formation. The ingestion of the main component of typical table sugar, sucrose, accelerates the formation of sticky glycoproteins, which are composed of a combination of carbohydrates and proteins.[12] Glycoproteins attach to teeth and are the basis of the formation of plaque on teeth.[12] *Streptococcus mutans*, the only bacteria found in the mouth which contributes to cavities, sticks to the glycoproteins.[12] These bacteria contain an enzyme called glucosyl transferase, which accelerates the polymerization of glucose on the sucrose from the sugary food, releasing fructose, shown in Figure 8.[12]

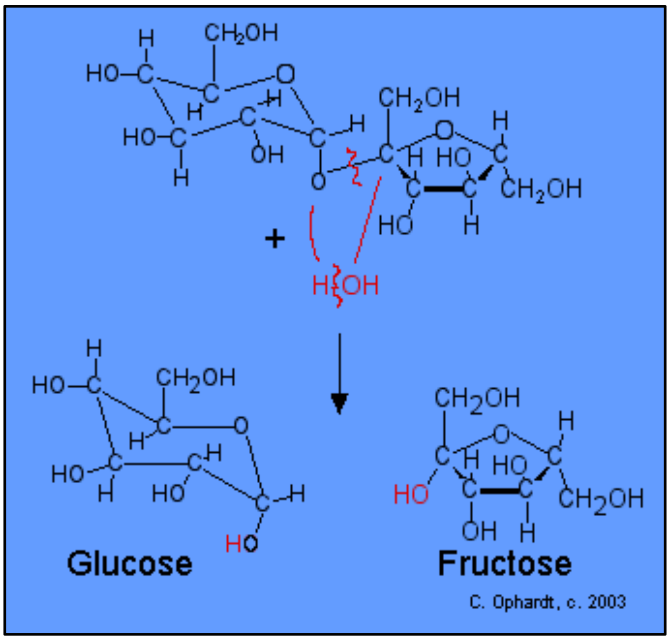

Figure 8: The hydrolysis reaction of the decomposition of sucrose into glucose and fructose. See text for discussion of reaction mechanism.[12]

Glucosyl transferase also polymerizes glucose molecules, creating dextran, a starch with similar structure to amylose.[12] Dextran also attaches to the tooth enamel, leading to the formation of plaque; this step is the first of cavity formation.[12] The bacteria metabolize fructose through glycolysis to obtain energy.[12] The end product of anerobic glycolysis is lactic acid, shown in Figure 9, which contributes extra acidity and lowers the pH of the mouth, leading to the dissolution of calcium phosphate, one of the main components in tooth enamel:[12]

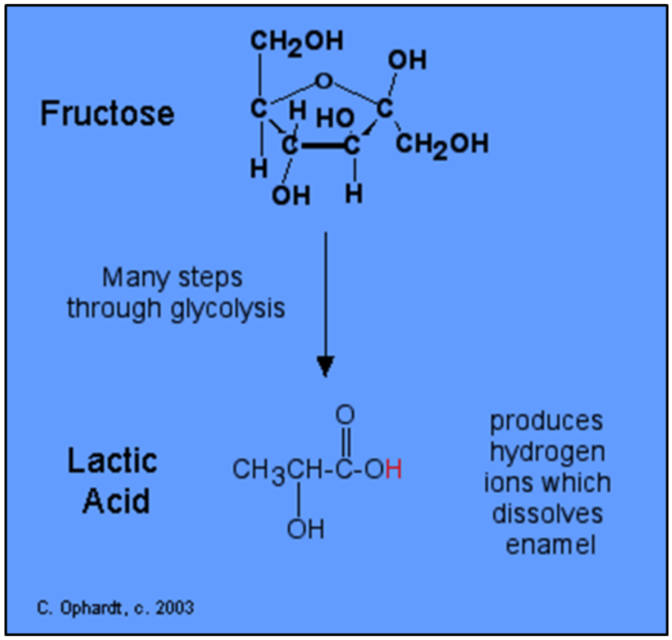

Figure 9: The formation of lactic acid from sucrose/fructose through anerobic glycolysis. The lactic acid dissolves and erodes the calcium phosphate of teeth.[12]

This dissolution is the second step of cavity formation. These steps are summarized in Figure 10:

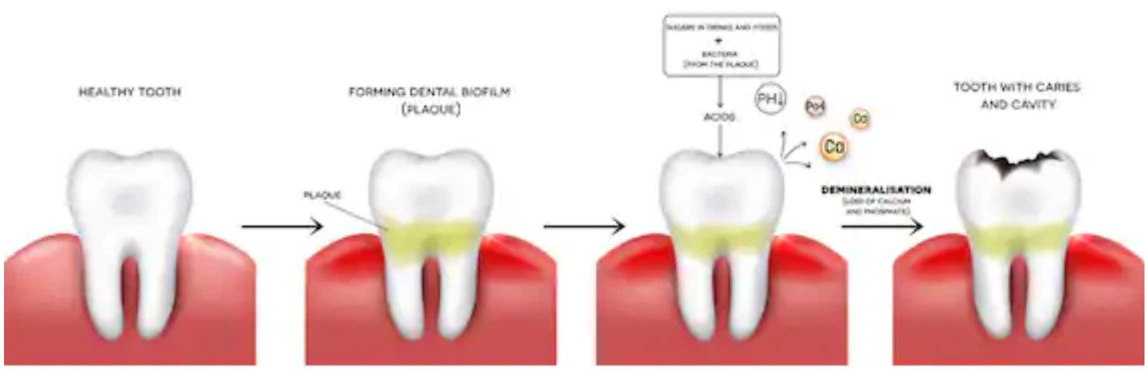

Figure 10: The stages of tooth decay, which result in cavity formation. In step one, a healthy tooth exists. Step two is indicative of the initial formation of plaque. Step three shows that the acid production of bacteria directly attacks the tooth, with results in the dissolution of the calcium phosphate. This results in a cavity formation, shown in step four. (shutterstock.com, image 324724157)

The formation of a dental cavity may seem like a simple process: plaque is deposited on the teeth as a byproduct of food consumed, bacteria create acids that dissolve the calcium phosphate on the teeth, and a cavity is formed. However, looking at the chemical level of the tooth and oral cavity, there are a lot of chemical reactions occurring that lead to the degradation of enamel, that begins the formation of cavities. The definition of dental caries is "the destruction/demineralization of the tooth's calcified tissues by acid generated in oral 'plaque biofilms.'"[13]

Dental caries can be classified as a disease; several factors make it a unique one. Tooth enamel is acellular because it does not contain living tissue, so the formation of caries occurs without the participation of host cells.[13] In addition, changes in oral acidity continually affect tooth enamel, so constant reparative or preventative measures are required to maintain a disease-free oral cavity.[13] The oral cavity can naturally repair some damage to enamel through remineralization, but usually, by the time a cavity is formed, this disease is beyond self-repair.

Dental caries exist in the enamel of a tooth, so it is beneficial to describe the microstructure of enamel by looking at the crystallography of the tooth. As mentioned previously, enamel is "an acellular tissue comprised 80-90% by volume of carbonated calcium hydroxyapatite… the remaining 10-20% consists of fluid and organic, usually proteinaceous material."[13] The crystals are approximately "50 nm wide by 25 nm thick, extending from the dentin toward the enamel surface."[13] The crystals exist in bundles of approximately 1000 crystals, called enamel prisms. Their cross-sections vary in size, ranging from circular to keyhole shaped.[13] The crystals are arranged with their long (c-) axes parallel to the long axes of prisms, but can deviate from this orientation, producing an interface with space in between; this space offers diffusion pathways within the acellular tissue, which is an important feature for the formation of caries because it allows acid and plaque buildup to enter into the tiny pores in the enamel of the tooth.[13]

The carbonated hydroxyapatite that comprises enamel has a structure of ions arranged around the central hydroxyl column, as shown in Figure 11.[13] Its stoichiometric formula is $Ca_{10}(PO_4)_6(OH)_2$.

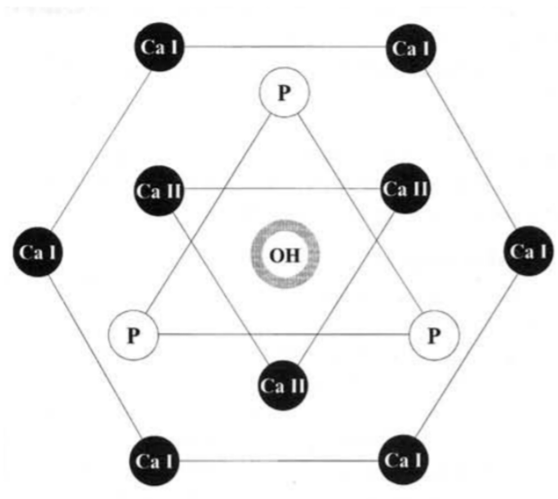

Figure 11: The crystal structure of hydroxyapatite, consisting of a planar hexagonal shape and the arrangement of calcium and phosphorus ions around the central hydroxyl column. This is an aerial view, looking down the C-axis of the structure.

As shown in the figure above, the hydroxyl ion is enclosed by a triangle of calcium ions, which is in turn surrounded by a triangle of phosphate ions, rotated by 60º, which are surrounded by a hexagon of calcium ions. The entire crystal structure consists of these hexagonal planes stacked on top of each other and rotated by 60º.[13] However, calcium and hydroxyl ions can be missing in enamel and replaced by extraneous ions such as carbonate, fluoride, sodium and magnesium.[13] Therefore, a more realistic chemical formula could be $[Ca]_{10-x-y}$ $[HPO_4][PO_4]_{6-x}$ $[CO_3]_w$ $[OH]_{2-x-y}$ where $v + w = x$.[13] The average composition for enamel apatite has been determined to be $Ca_{9.8}Mg_{0.18}Na_{0.11}(PO_4)_{5.67}(CO_3)_{0.45}(OH)_{1.54}(H_2O)_{0.46}$.[13]

Despite these deviations in enamel composition, there is no significant change in apatite's solubility at low pH. The solubility product for enamel mineral (7.2×10^{-53} to 6.4×10^{-58}) is actually higher than that of stoichiometric apatite (3.04×10^{-59}).[13]

When cavities are in their early stages of formation, the most soluble material in the enamel is removed from the prism's periphery; it is not known if this represents preferential dissolution of crystal surfaces or dissolution of a separate mineral phase.[13] It can be predicted that the lower crystal packing at the surface of the tooth permits the easier diffusion of acids and protons into the tissue and subsequent removal of mineral ions. After this initial step, successive steps track across prisms at their junctions, followed by the dissolution of the prism bodies themselves.[13]

In order to understand the severity of dental caries, it is important to look at the different zones of enamel, shown in Figure 12. Starting at the deepest zone of enamel, called the translucent zone, a loss of 1-2% of mineral indicates the first development of caries.[13] This zone is composed of a small number of large pores. Protein removal and mineral loss comprise the first step of decay. The next zone is the positively birefringent (dark) zone, which contain large pores of the translucent zone and smaller pores.[13] These smaller pores exist because the "occlusion of some larger spaces in the initial translucent zone ha[ve] occurred."[13] The following zone is the body of the lesion, which is caused by further demineralization (at about 25-50% porosity).[13] These pores enlarge until mechanical destruction of the tissue, called cavitation, occurs. The enamel visible to the eye, called the surface zone, is the last to persist until cavitation is performed. This surface is between 1-2% porous.[13] These four zones are depicted below in Figure 12:

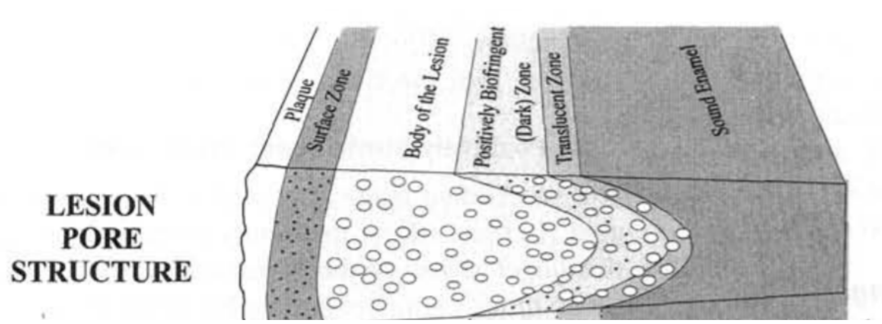

Figure 12: Relative pore structure of the four zones of a caries lesion in enamel.[13]

As mentioned above, enamel is nonhomogeneous, both structurally and chemically, with chemical gradients existing within the tissue from the surface towards the dentin.[13] The enamel's microporosity affects the diffusion of materials in and out of the tissue, which could be an explanation for the low diffusion constants for enamel. The changes in pore sizes at different zones allow for the entry of foreign materials, but pore reduction and chemical changes can hinder demineralization. [13]

Kinetic analyses have suggested that "demineralization may, to a large extent, be surface-controlled."[13] However, it can be difficult to create a general model of the chemistry of enamel caries because of the large variations in enamel composition, local concentrations of mineral ions, and variety of endogenous organic material.[13] Consequently, it is best to compare the relationship of changes in enamel pore structure during carious attack to chemical change in order to best discuss chemical changes in enamel during the formation of caries.

In addition to the chemistry occurring in tooth enamel, there is chemistry present in the material that is used to restore cavities after decay has been removed after cavitation. The best dental restorative material should be well-suited to the oral environment and fulfill the following criteria:

- easily mixed and placed as an unset paste
- short working and setting times
- rapid buildup in mechanical properties on setting
- match of thermal and expansion properties with the tooth
- high resistance to erosion and degradation by oral
- fluids/saliva, brushing, and flossing
- biologically inert or bioactive
- achieves a hermetic seal with the surrounding tooth tissue
- color and translucency to match the tooth
- high strength (tensile and compressive)
- inexpensive. [14]

The most common dental filling is a composite resin. They are composed of "bulky methacrylate monomers, which set by a free-radical polymerization and are heavily filled with a finely divided ceramic... The organic resin matrix is bonded to the inorganic filler by means of coupling agents, which are typically organosilane compounds."[14]

An example of a large dimethacrylate is bisGMA and urethane dimethacrylate, which are used to ensure minimalization of polymerization shrinkage. [14] However, these monomers have high viscosities, making it difficult for dentists to incorporate the filler into cavities.[14] A solution to this problem is to use smaller monomers that have lower molecular weight and therefore lower viscosities; an example of such a monomer is ethylene glycol dimethacrylate (EGDMA), which is added as a diluent in the formulation of the resin.[14] In turn, the addition of these extra monomers causes a larger polymerization shrinkage, introducing a tradeoff between viscosity, incorporation ease, and polymerization shrinkage.[14] Examples of these monomers as shown in Figure 13:

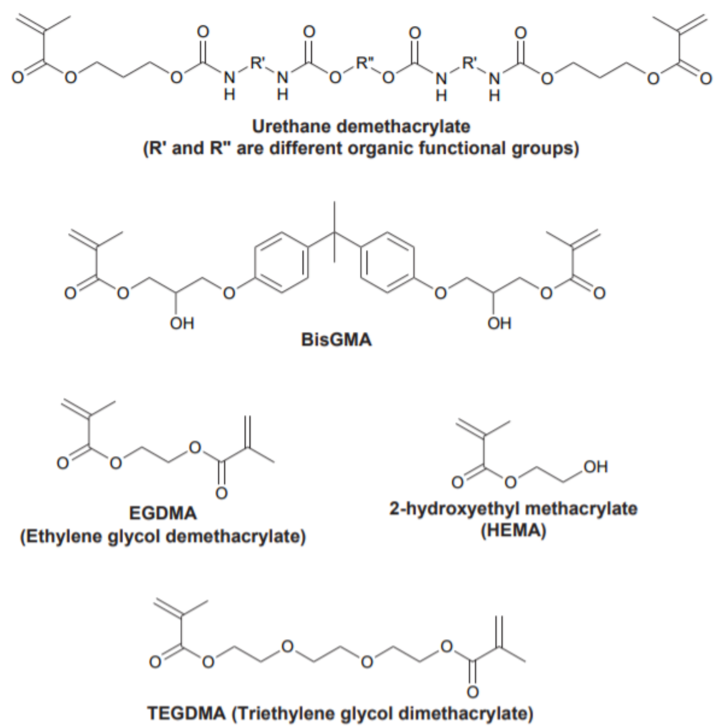

Figure 13: Common organic monomers that are used in composite resin filling materials. These monomers will be joined together during the UV curing process.[14]

Composite resins are characterized by their filler type, which influence the properties of the resins. The main categories are "conventional," "microfilled," or "hybrid."[14] In conventional resins, the filler can be composed of glass or quartz, with the particle size ranging from 1 to 50 µm. This type of resin is composed of 60-80% of filler, by volume.[14] The next category, microfilled composites, use a 0.01-0.1 µm colloidal silica filler. The advantage of the small particle size is that "the restoration can be polished to a good surface finish."[14] The increase in surface area of filler increases the paste's viscosity, making it difficult to have a large concentration of filler. The solution to this viscosity increase it to mix the filler with resin, polymerize the filling to form a highly loaded material, break blocks of the material ranging in 10-40 μm in size, and then combining with more resin to form a cement paste.[14] This cement has a filler loading between 30-60% by weight. The final category is the hybrid resin, in which the aim is to create a balance of conventional and microfine particle sizes.[14] The resin is composed of 75% large-particle-sized glass and 10% colloidal silica, both by weight. The variations in particle sizes allows for efficient packing, which results in high strength of the cement.[14] In addition to its strength, this resin can be polished, has an appearance that matches the color of teeth, and experiences minimal wear.[14]

The next category of dental fillings is the glass-ionomer cement (GIC), which is a translucent filling developed in the 1970s. It is composed of a water-soluble organic polymer and a solid powdered base, made from reactive aluminosilicate glasses.[14] Setting this filling involves an acid-base reaction and the set cement consists of metal polyacrylates formed by calcium and aluminum ions derived from the glass.[14] There is also an inorganic matrix present in the resin, formed by "reaction of ion-depleted species from the glass."[14] The completed cement is composed of unreacted glass particles embedded in this matrix.

As soon as the components of the cement are mixed, the setting reaction begins. Initially, the acid groups are ionized, causing an extension in polymer chains, increasing viscosity and resulting in the stiff cement paste.[14] The first product of this reaction is calcium polyacrylate, but eventually, aluminum polyacrylate is recognizable because the inorganic network forms for months after the initial mixing of the cement at the time of the cavity filling. [14] This reaction is sensitive to both moisture and desiccation because the glass ionomers and inorganic matrix can be washed out in the initial step in the presence of moisture, and since water is needed for the following neutralization reaction, the loss of water can lead to a less strong final cement product.[14]

The glass ionomer filling has a high compressive strength, is resistant to acid and aqueous attacks in the oral cavity, and it releases fluoride. In addition to these advantages, it forms a strong bond to the tooth, thought to be due to the formation of salt bridges to the minerals in the tooth.[14] This compact filling allows for minimal cavity excavation and prevents leakage surrounding the filling. The fluoride released from the filling is found in the glass. Fluoride ions can inhibit dental decay, with two proposed explanations: the fluoride ions replace hydroxyl ions in the mineral content of the tooth, or the formation of fluoride salts is favored in demineralization with the fluoride ions present, rather than the dissolution of the tooth.[14] This leads to the theory that the glass ionomer filling acts as a fluoride store by taking in fluoride from toothpaste and other fluoride-containing products, which it can release later to prevent further cavity formation.[14]

Fluoride has been added to community water supplied for the past 60 years, with its optimal levels for preventing tooth decay ranging from 0.7 to 1.2 parts per million. Water fluoridation can reduce dental decay in children by up to 60%.[15] Because of its dental cavity preventative properties, fluoridation of water supplies has been endorsed by the American Dental Association since 1950.[15] The Center for Disease Control and Prevention has "recognized the fluoridation of drinking water to prevent dental decay as one of 10 great public health achievements of the 20th century.[15] Water fluoridation is a powerful tool to prevent dental decay because it is accessible to all people, regardless of income level of dental care availability.

One disadvantage of the glass-ionomer filling is its inability to maintain its structure with heavy load bearing activities in the mouth. As a solution, metal has been added to some of these fillings to maintain higher strength and wear properties.[14] Two applications of the metal into the filling comprises including finely divided alloy particles in the cement or fusing the glass with either gold or silver prior to mixing the components, which is then used in the cement-forming reaction.[14]

They have also been suggested as an alternative for amalgam because of their increased strength and wear properties.

The development of the resin-modified glass-ionomer cement was due to the problems with brittleness associated with the pure glass ionomer filling, but with the goal of maintaining the other properties. This was executed by adding water-miscible monomers to the cement, resulting in two setting reactions, a neutralization and polymerization, as opposed to the one-step reaction of the glass ionomer filling.[14] These fillings have been created as a non-light-cured version, where the polymerization reaction is induced by a chemical generation of free radicals "brought about by mixing a peroxide initiator with an amine accelerator"[14] instead of using light to initiate polymerization. In another form of the resin-modified glass ionomer, the polyacid itself has been modified by replacing some of the carboxylic acid groups by methacrylate species, resulting in unsaturated groups pointing outwards from the backbone of the species.[14] The new polyacid is involved in the neutralization and polymerization reactions, which still involve a monomer to ensure a steady cross-linking reaction.

Neutralization of a mixed resin-modified glass ionomer starts when the cement is mixed, yet the rate of the reaction is reduced due to the presence of the organic species.[14] Polymerizations occurs simultaneously with neutralization, which gives this resin its strength. There are believed to be two interpenetrating matrices in this resin: an ionic matric and an organic one, from the neutralization and polymerization reactions, respectively.[14] An example of this setting reaction is shown in Figure 14:

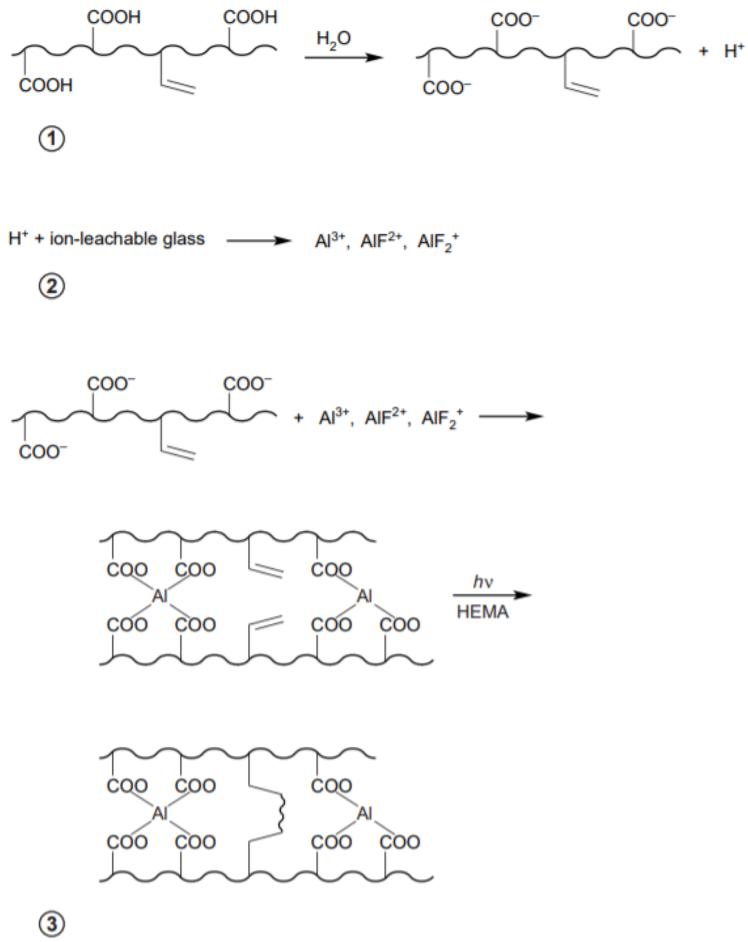

Figure 14: The setting reaction of Vitrebond, a specific resin-modified glass ionomer. In step 1, the resin is deprotonated, releasing a proton. In step 2, the proton binds to the glass filler to produce aluminum ions. In the subsequent step, the positively charged ions bind to the deprotonated resin. Then, light is applied to cure the resin, resulting in the complete binding of the resin. [14]

Another advantage of the resin-modified glass ionomer is that it is more esthetically pleasing because of their greater similarity to tooth color. They include all the advantages of the glass ionomers, including adhesion and fluoride releases, in addition to being able to withstand tougher conditions. However, one disadvantage includes that these fillings can undergo polymerization shrinkage and exhibit a setting exotherm.[14]

The most recently-developed dental fillings are the acid-modified composite resins, more commonly known as compomers. The goal of this resin is to combine properties of both the composite resins and glass ionomer cements. Compomers are composed of inert filler, bulky methacrylate monomers and photoinitiators, with the addition of a lightly carboxylated monomer and basic glass powder, like those used in glass ionomers.[14] These carboxylated resins are not soluble in water, unlike the acids in glass ionomers, so neutralization is not a necessary step in this setting process, which is controlled entirely by polymerization.[14] Once set, they can intake water from saliva, activating the acidity of the carboxylic acid group in the new monomer, leading to a reaction with the glass filler that ultimately results in the production of a small salt matrix which releases fluoride ions. [14]

Compomers have received positive feedback from dentists over their esthetic qualities, and good clinical performance, but have also raised concerns over their wear and bonding techniques, which are similar to that of the original composite resins

A summary of the compositions of the discussed resins are shown below, in Table 1.

Material	Components
Composite resin	methacrylate monomers nonreactive glass and/or silica filler initiator system
Glass-ionomer	acid-degradable glass polymeric acid water
Resin-modified glass-ionomer	acid-degradable glass polymeric acid (often modified with pendant unsaturated groups) water various methacrylate monomers initiator system
Acid-modified composite resin	methacrylate monomer acidic monomer acid-degradable glass initiator system

Table 1: Composition of common dental cements in the four major resin types.

Chapter 4: Comparison of Modern Dental Fillings

There are two main categories of dental fillings used in modern dentistry practice. One type is the silver amalgam filling, which dates back over 100 years. The other type is the composite filling, which was introduced in the 1970s. Although the composite filling is the most popular material in use, the silver amalgam is still used in some instances. In this section, the two types will be compared and contrasted.

Section A: Silver Amalgam

According to the American Dental Association, dental amalgam is composed of "a combination of metals that include mercury, silver, tin, and copper."[16] Specifically, it is created by "mixing elemental mercury (43-54%), and an alloy powder (46-57%), composed mainly of silver, tin and copper."[17] This long-lasting filling is more cost efficient when compared to composite resins because it requires less time to apply to a cavity and the material itself is cheaper.[16] Silver amalgam is also more durable, and is often used in molars because those are the teeth that experience the most pressure when masticating, or chewing. Silver amalgam hardens faster than composite resin, so it is useful in places that are difficult for the dentist to reach or that are hard to keep dry during application, such as cavities below the gum line. It is also a more effective filling to use for children or people with special needs because of its quick application.[16] Generally, it only takes one visit to the dentist to successfully insert a silver amalgam filling; since the material is self-sealing, and minimal to no shrinkage occurs once placed in the tooth, follow-up visits are typically not required.[17]

The main disadvantage with silver amalgam is its appearance. Because of its metal composition and color, it is extremely visible in the mouth. This becomes an aesthetic problem if the filling is present towards the front of the mouth; the further back in the mouth the filling is, the less likely it is to be seen in the mouth when a person is talking or laughing.[16] The amalgam may also darken over times because it can undergo corrosion in the mouth, which can lead to the staining of the sealed tooth over time.[17] One additional disadvantage of silver amalgam is the size of the area around the cavity that is required to secure the filling. This type of filling entails the removal of more tooth structure around the cavity itself because it needs to completely seal the affected area. The dentist cannot simply fill the cavity with the silver amalgam filling, but must rather seal, or clean and cover the area of and around the cavity with the silver amalgam filling.[16] This can weaken and even fracture the remnants of the underlying tooth.[17] In addition, the metal component of the amalgam filling are not as thermal insulating and can conduct hot and cold temperatures more easily. A tooth with an amalgam filling may experience a hypersensitivity to hot or cold fluids or solids in the mouth.[17] One unique disadvantage is that the metal may conduct electricity when exposed to other metals, which can be present in the saliva.[17] This electrical flow is not strong, but may still cause discomfort in the patient or cause unintended redox chemistry in the mouth.

One controversial topic involving silver amalgam is its traces of mercury in the material. This mercury can be emitted in a vaporous form when reacted with the saliva in the mouth.[17] However, the American Dental Association states that “when combined with the other metals, it forms a safe, stable material.”[16] In addition, the U.S. Centers for Disease Control and Prevention, U. S. Food and Drug Administration, and the World Health Organization agree that dental amalgam is a safe and effective cavity restorative material.[16] A visual reference for an amalgam filling is shown in Figure 15.

Figure 15: A visual representation of a silver amalgam filling. Note the size and invasiveness of the material. (serenitydentalcenter.com)

Section B: Composite Fillings

Composite resins, more commonly known as tooth-colored fillings, have good durability and can withstand moderate pressure from the stress of mastication in small and mid-size fillings.[18] These types of fillings can be used on both the front and back of teeth, which is appealing to those who do not want their fillings visible in their mouths. Composite fillings can be color-matched to the color of the patient's teeth, making them appealing to those searching for a more aesthetic alternative. They also preserve the maximum amount of tooth possible because their application is not as invasive as in other treatments.[17] Composite resins also do not corrode because they are both chemically bonded to the tooth and virtually chemically inert when cured. Composite fillings are therefore more likely to resist decay, so they do not require frequent repair.[17]

One disadvantage of a composite filling is the large cost. They are pricier than silver amalgam fillings, and are not always covered by insurance plans.[18] In addition, some studies have been conducted that conclude that a composite filling does not last as long as an amalgam filling. It also takes longer to seal a cavity with a composite filling because of the chemical reactions that need to occur to bind the filling to the tooth, harden the composite, and because the tooth must be kept clean and dry during the application process. Multiple visits may be required when the restoration precedes another application of a dental restoration or implant.[17]

The material can also shrink when it hardens which can lead to decay and slight sensitivity. Another disadvantage, or specifically a possible health risk, is that "some composite resins include crystalline silica, which is on the State of California's Proposition 65 list of chemicals known to the state to cause cancer."[17] However, there has not been any extensive research on if the amounts of this chemical present in a composite filling can lead to cancer and any silica is trapped inside of the cured composite. An image of a composite filling is shown in Figure 16.

Figure 16: An example of a composite filling. Note the lack in color difference between the restorative material and the tooth.

Part C: Comparisons

Putting both amalgam and composites side by side helps dentists and patients to compare and contrast multiple factors. The principal use of amalgam is to aid in heavily loaded molar restorations, while composites are used for a more aesthetic filling and as a precursor to other implants.[19] There is potential for leakage of foreign liquids, such as those present in the mouth, in both materials once they have been set, but the leakage in amalgam is moderate and decay is not more prevalent than in other fillings, while composites have a low leakage when they are properly bonded and decay depends on the maintenance of the bond between the tooth and filling.[19] Both fillings have good overall durability, but amalgam is excellent in load-bearing areas of the mouth, while composites are excellent in small or moderation restorations.[19] The preparation of the cavity for the filling is not comparable between the two because amalgam requires more removal of the area around the decayed portion of the tooth for "adequate retention and thickness of the filling" while composites do not require the removal of as much tooth structure.[19] Amalgam is highly resistant to wear, but is slightly brittle and can chip. However, it has great resistance to both in high load situations, while composites are moderately resistant to wear and fractures in high-load restorations.[19] Both these materials are biocompatible and have rare occurrences for allergic responses.[19] Sensitivity with amalgam can result from exposure to hot or cold substances, but sensitivity with composites depends on the quality of the bond between the material and the tooth.[19] An obvious physical difference between the two is the color: silver or gray for amalgam and natural tooth or translucent color for the composite. Amalgam costs are generally lower than that of composites, but the relative cost to the patient is dependent on the size and technique of application of the filling.[19] Both filling require one visit to complete the application and bonding of the filling, but multiple visits may be necessary in the case of a composite, where future implants or restoration such as crowns are expected. [19]

When comparing the longevity of the two most common dental fillings, silver amalgam and composite resins, there are multiple factors that affect their survival rates. Dental amalgam can survive twice as long in the mouth when compared to a composite filling. "Polymerization shrinkage, deficient marginal adaptation, higher wear rates, defective contact points leading to food impaction, [and] insufficiently converted composite at the bottom of the cavity" are problems that can arise when applying a composite resin to a cavity.[20] However, this does not mean that amalgam does not have disadvantages of its own: "the need for retentive cavities at the cost of healthy tooth substance, weakening of the tooth's strength by cutting through the tooth crown's ridges, the risk of fracture of remaining tooth substance (mostly buccal and lingual surfaces) as the result of the cavity design, and the lack of adhesion between amalgam and tooth substance."[20]

These disadvantages are comparable to those of composite fillings, but other factors have made composite resins more attractive to patients and dentists alike.

Ultimately, the use of one dental material over another is up to both the patient and the dentist, and whatever is best for a given cavity situation. Even though composites have become increasingly popular, "there is still a place for dental amalgam in modern restorative dentistry when plastic filling materials are used for the direct tooth repair or restoration."[20] A side-by-side visual comparison of amalgam and composite fillings is shown in Figure 17.

Figure 17: A comparison of amalgam and composite fillings (Michael Bentz Dentistry). Note the difference in visual appearance of the two different filling materials.

Chapter 5: Outlook of Carie Restoration using Regenerative Dentistry

New technologies for the treatment of dental caries are emerging. One such treatment is three-dimensional (3D) bioprinting, or tissue engineering. The format of this technique is also referred to as solid freeform fabrication and additive biomanufacturing; it "enables precise positioning of cells and biomaterials in 3D with finely tuned internal and external architectures, while being customizable to patient-specific needs."[21] Three-dimensional printing also "allows for on-demand and scalable fabrication of complex designs, while being compatible with various scaffold materials and cell sources... it represents a powerful approach for engineering biomimetic craniofacial tissue constructs."[21] In addition, tissue engineering "is a science based on fundamental principles that involves the identification of appropriate cells, the development of conducive scaffolds, and the understanding of the morphogenic signals required to induce cells to regenerate a tissue or organ."[22] Although this is not the same technique currently used to treat dental caries, it can be applicable in the future when technologies advance, since 3D printing of all the components of a tooth, including the living cells in the root of the tooth, is in its early stages. An example of this technology is shown in Figure 18.

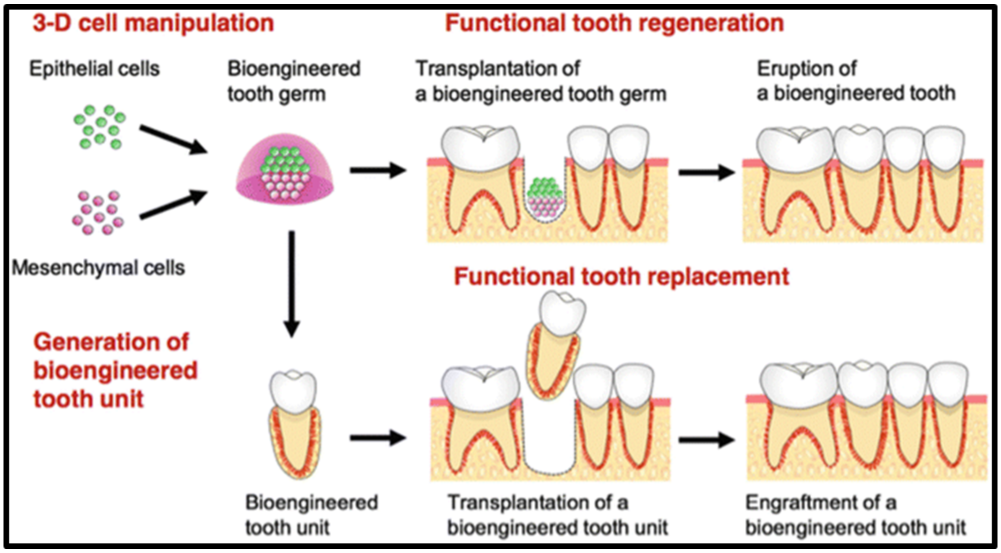

Figure 18: Regenerative strategy of whole-tooth replacement. Fully functioning teeth can be regenerated in vivo by transplanting bioengineered tooth germs reconstituted from epithelial and mesenchymal cells via the organ germ method or by transplanting bioengineered tooth units with a periodontal ligament and alveolar bone that developed from bioengineered tooth germs.[23]

The aim of this technology is craniofacial regeneration, which seeks "to mimic or promote oral development processes using biomaterials and growth factors to induce tissue formation via stimulation of specific cellular function, both in vitro and in vivo."[21] Teeth and their fundamental building blocks, such as blood vessels and nerves, "form complex systems responsible for a number of critical functions…these structures work synergistically to ensure physiologic respiration, speech, digestion and craniofacial support… these tissues are organized with complex heterotypic 3-dimensional (3D) architectures, specific cell-cell interactions, anisotropic mechanical properties, and heterogenous distribution of growth factors."[21] However, there are still obstacles in this technique, since "conventional regenerative strategies still largely fail to mimic the 3D complexity and the multicellular interactions occurring in native craniofacial tissues."[21]

In order to better understand the capacity of the possibility of this technique, it is necessary to break the tooth down into its components. The tooth is composed of "buccal epithelial cells that form the enamel organ [which form the enamel] and the mesenchymal cells that form the dental papilla…the dentin is formed by the dental papilla."[24] These cells originate from the nervous system, where they "migrate to the maxilla and mandible [and] interact with mesenchymal cells to form the enamel organ and the dental papilla."[24] Mesenchymal cells are stromal cells that can differentiate into various cell types, such as osteoblasts in this case.

The dental pulp tissue is found within the pulp chamber and is the only smooth tissue in the tooth.[24] It originates in the embryonic dental papilla, yet is the mature form of the papilla. [24] In addition to the papilla, the dental pulp tissues contains "fibroblasts, undifferentiated mesenchymal cells or stem cells, macrophages, and lymphocytes."[24]

The periodontal ligament (PDL), is a soft connective tissue that surrounds the teeth and connects the root to the hard sheet of alveolar bone.[24] Most cells in PDL are fibroblasts, which synthesize and maintain the extracellular matrix; they contain a cytoskeleton of microtubules and actin microfilaments that aid in cellular motility.[24] In addition, the PDL contains other cells, including "osteoblasts, osteoclasts, cementoblasts, macrophages, and stem cells that are capable of generating fibroblasts, cementoblasts, and osteoblasts."[24] The PDL can be seen in Figure 19.

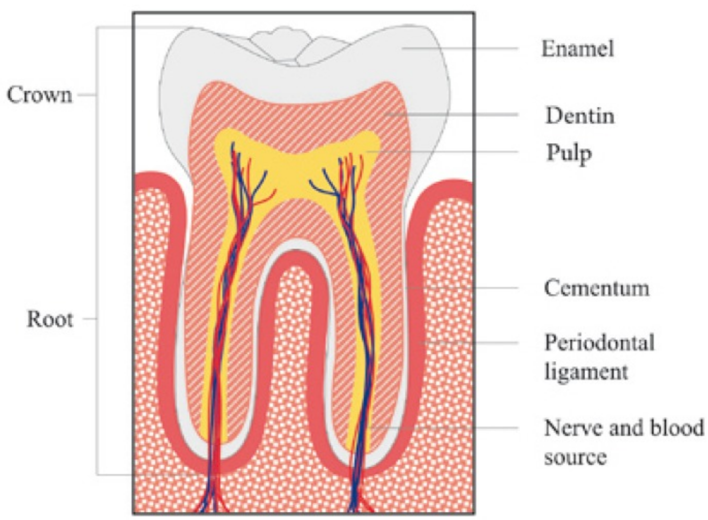

Figure 19: A cross section of a tooth, including the periodontal ligament (PDL). The PDL is an easy region to access stem cells in the oral cavity.

Stem cells are a type of cell that "constitute the source of differentiated cells for the generation of tissues during development, and for regeneration of tissues that are diseased or injured postnatally."[22] These cells are nonspecialized, continuously divide, have self-renewal abilities, and have the ability to generate complex tissues and organs."[22] In recent years, stem cells have been found in niches within the body and in dental pulp, which is rich in mesenchymal stem cells that are suitable for tissue engineering practices.[22] Dental pulp cells can differentiate into several cell types, are highly proliferative, and are arguably the most accessible source of postnatal stem cells.[22] These characteristics make dental pulp an accessible source of mesenchymal cells for tissue regeneration.[22]

Stem cells can be classified as either embryonic or postnatal. Embryonic stem cells are found in "the inner cell mass of the blastocyst during the early stages of embryo development"[22] and postnatal stem cells are found in various niches throughout the body at any stage in life. Embryonic stem cells have an unrestricted ability to generate new tissues because of their presence in early stages of embryonic development.[22] However, harvesting these cells requires the destruction of an embryo, posing ethical and legal arguments on the morality of their harvest.[24] Therefore, most research on tissue engineering focuses on postnatal stem cells.

Postnatal stem cells are also capable of self-renewal, like embryonic stem cells. However, they are multipotent, meaning they have a "more limited capacity for differentiating into other cell types than embryonic stem cells."[22] These cells also present a lower risk of rejection by the immune system because of their use as autologous transplants.[22] Specific postnatal stem cells found in dental pulp have been named dental pulp stem cells (DPSCs).[22] Stem cells found in human exfoliated deciduous teeth (SHED), apical papilla, dental follicle progenitor cells and periodontal ligament stem stems have also been discovered.[22]

"The usefulness of stem cells in clinical applications depends on their proliferation rate, differentiation potential, and accessibility."[22] When compared to bone marrow stem cells, DPSCs presented favorable results for forming odontogenic tissue.[22] In addition, studies suggest that

"SHED and DPSCs are capable of generating a tissue that has morphological and functional characteristics that closely resemble those of human dental pulp,"[22] which could have significant implications for the future of regenerative dentistry. SHED cells are also easily accessible because they are retrievable from naturally exfoliated teeth, a "disposable" source of postnatal human tissue.[22]

Generating the cells necessary to restore decay in a tooth is one step of the future of regenerative dentistry. Another obstacle that must be overcome is the area of cell signaling. Two proteins that are prevalent in cell signaling are growth factors and morphogenic factors. Both of these proteins "bind to specific membrane receptors and trigger a series of signaling pathways that coordinate all cellular funcitons."[22] Growth and morphogenic factors help guide developmental processes that determine the fate of stem cells, and regulate the generation of all tissues and organs in a developing embryo.[22] As a result, these proteins are critical in tissue regeneration, in areas such as dental pulp responses to dental caries progression.[22]

Specifically, bone morphogenic proteins (BMPs) are used "sequentially and repeatedly throughout embryonic tooth "development, initiation, morphogenesis, cytodifferentiation and matrix secretion."[24] There are six different BMPs identified in human dental pulp cell cultures and have been successfully applied for the regeneration of periodontal tissue.[24] Other growth factors, such as PDGF, IGF-1, FGF-2, and TGF-β, have been utilized in tooth tissue engineering.[24] In a rat model, dentin matrix protein-1, which is involved in the mineralization process, induced "cytodifferentiation, collagen production and calcified deposits in dental pulp."[24] Other studies conducted studied the effect of dexamethasone on dental stem cell cultures, which resulted in differentiation into osteoblasts, adipocytes or chondrocytes.[24] An in vitro study on PDL fibroblasts presented "enhanced phosphatase activity and mineralized nodule formation when "17β-estradiol was added to the cell-culture medium."[24]

Once cell signaling molecules for tissue induction and responding stem cells are biologically engineered, a scaffold to maintain and preserve the microenvironment must be developed.[24] There is little current research on this topic because of the recent innovation of dental tissue regeneration, but scientists are actively trying to develop such a scaffold. Prior studies suggest that the ideal scaffold "should be biocompatible, non-toxic and have optimal physical features and mechanical properties."[24] Suggested research methods utilize cell-free scaffolds because of their easier handling, storage and shelf-life, cost, immunoresponse of the host and transmission of diseases.[24] Two disadvantages are present with this method: the cells may have low survival rates and may migrate to different locations in the body, leading to deviant patterns in mineralization.[24] To reduce these drawbacks, the collected stem cells may be applied within the scaffold to monitor their activity.

Scaffolds are most commonly composed of " natural and synthetic polymers or inorganic materials and composites, which have been fabricated into porous scaffolds, nanofibrous materials, microparticles and hydrogels."[24] Examples of natural materials include "collagen, elastin, fibrin, alginate, silk, glycosaminoglycans such as hyaluronan, and chitosan,"[24] which offer high structural strength, are compatible with cells and tissues, and are biodegradable. They can be difficult to process and can transmit pathogens, triggering an immunoresponse.[24] Synthetic polymers include "poly lactic acid (PLA), poly glycolic acid (PGA), and their copolymer, poly lactic-co-glycolic acid (PLGA),"[24] which provide excellent mechanical and chemical properties, and high control over characteristics such as molecular weight, polymer chain configuration, and functional group presence.[24] Newer technologies include hydrogels, which offer high biocompatibility, similar water content to tissues and similar mechanical characteristics to tissue.[24]

Future research can include how to control the same growth factors that guide physiological tissue regeneration, to guide stem cell regeneration toward specific cell roles and to coordinate cellular processes.[22] This could ultimately result in "the generation of a new tissue or organ via tissue engineering-based approaches."[22]

Applying this method to dental caries will likely be challenging. In a cavity, only a small portion of the tooth is decayed and therefore requires treatment. Most published studies focus on regenerating the tissues of the tooth that receive blood flow. Studies on dental tissue regeneration for calcified tissue, such as the kind present in enamel where cavities persist, could be revolutionary for the future of dental caries treatment. Or, in contrast, maybe tissue regeneration of dental pulp could lead to injections that terminate cavity formation in its initial stages below the crown of the tooth.

Chapter 6: Conclusion

Dental medicine has revolutionized over hundreds of years. As early as 5000 B.C., Sumerian texts described dental decay. Even though they did not have modern science to support their theories, their hypotheses became the foundation for the practice of dentistry. Generations after built upon their theories and helped dentistry evolve; therefore, the development of dentistry has been a steady process, rather than a rapid improvement. Every development surpassed a previous milestone and allowed for dentists and engineers alike to push the technology to a new level.

When looking at the last 50 years, modern technology has allowed for the revolution of dental resins and composites. From their first introduction in 1962 by Rafael Bowen, composite resins have overtaken the field of cavity restoration materials. Silver amalgam was popular throughout the nineteenth and twentieth centuries, but has since proven to be less appealing than the new composite fillings. Silver amalgam is visible in the mouth when the patient smiles, speaks or laughs. It also is more difficult to set this filling in the mouth because the oral cavity and decayed tooth region must be dry, or then there is a potential for bacterial growth and future decay underneath the set silver amalgam filling. Composite resins solve this problem because some do not require the oral cavity to be fully dry during application.

Two other fillings to note, that were not discussed in Chapter 4, are ceramic fillings and gold fillings. Ceramic fillings require that most of the tooth is removed in order to replace the damaged or decayed portion of the tooth. These are not as popular for cavity fillings, but are instead seen more throughout restorative dentistry where multiple teeth must be removed entirely or replaced, such as in bridges. Gold fillings were common before silver amalgam fillings, but typically, only patients of higher class were able to afford them. The fillings were more malleable than silver amalgam, which gave them appeal for application. However, this also led to problems where the gold fillings would change shape in the mouth from mastication or grinding teeth. As a result, gold fillings have been treated as not practical. Silver amalgam and composite resins are still the most common fillings used.

An enormous innovation has been the discovery of regenerative dentistry. Although this field is up and coming, there are different fields where regenerative medicine is actively used, such as in skin grafts for burn victims. It is more difficult to regenerate teeth because of their complex structure, nerve structure, cell signaling, and calcified tissue on the surface, as discussed in Chapter 5.

Since the use of embryonic stem cells raises both ethical and political concerns, most research is aimed at postnatal stem cells. These cells can be harvested at any point in an individual's life and can be found in various areas of the body. It is also easier to prevent rejection of these cells if they were injected into another area of the body because they come from the same individual from which they were taken. Stem cells can differentiate into other cells, which is why researching their potential differentiation into cells that make up teeth could be beneficial in the future.

Should the focus fall on diverting the path for current cavity filling materials onto new materials, or should current materials be revolutionized and potentially improved to fit what patients and dentists desire? Based on the research conducted in this thesis, it can be predicted that the current materials used in dental filling materials can be improved. It seems highly difficult to regenerate a specific portion of a decayed tooth to fill a cavity, which is the path that regenerative dentistry is leaning towards. This material would have to bind to the tooth and eventually fully form to the natural tooth, with both structure and cellular function.

It may be easier to fully replace the tooth with a 3D-printed tooth because there would be no discrepancy between the 3D-printed section and the preexisting tooth. However, this would be a highly invasive procedure and be counterintuitive to the point of sealing a cavity with the removal of as little of the healthy tooth as possible. The current method of cleaning the cavity and filling it with a composite resin or cement would be the better option if only a small portion of the tooth requires repair.

On the other hand, what if scientists and engineers were able to produce a biosynthetic tooth portion that could be inserted into a cleaned cavity? In the perfect scenario, the biosynthetic tooth would be accepted by the cells in the oral cavity and tooth, and grow to replace the removed decayed portion of the tooth. The result would be a tooth that looks as if it had no cavity initially: a "natural" tooth. Could future technology present such possibilities?

Although the research conducted in this thesis cannot determine the path for the future of dental restorative materials, it can advocate for this revolutionary path of dentistry as a practice. Looking back in time, the dentists of the eighteenth century most likely did not foresee the development of composite resin fillings. Similarly, two hundred years from now, it may be possible for the bioprinting of a small area of a tooth, even though it can seem like a far-fetched idea with today's technology.

There is no concrete conclusion for the future of the treatment of dental caries. Engineers could advance current dental restorative materials to minimize their drawbacks and produce an elite product, or they could turn a new page and aim to use stem cells to 3D print areas of a decayed tooth. There is no correct way of revolutionizing dentistry: it happens step-by-step, with the help of prior technology and history.

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