Back to the egg: An evidence-based endo-implant algorithm (Part II)

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The laws of nature are but the mathematical thoughts of God.
—Euclid of Alexandria

Four thousand years ago, a number of Babylonian legal decisions were compiled in what came to be known as the Code of Hammurabi. The decision with reference to the construction of dwellings and the responsibility for their safety begins: If a builder engineers a house for a man and does not make it firm, and the structure collapses and causes the death of the owner, the builder shall be put to death. We are all builders or engineers of sorts; we calculate the path of our arms and legs with the computer of our brain and we catch baseballs and footballs with greater dependability than the most advanced weapons system intercepts missiles. In our professional lives, however, in contradistinction to the paradigm of evidence-based dentistry, our efforts as builders often rely solely upon personal experience, intuitive cognition and anecdotal accounts of successful strategies.

The challenges posed by implant-driven treatment planning mandate vigilance of the interaction between those involved in research and development, manufacturing and distribution and the leaders of ideologically diverse disciplines. Temporal shifts and trends in the service mix are part of the evolution of the art and science of dentistry; to some degree, the implant-driven vector has captured the hearts and minds of those who seek to nullify preservation of natural tooth structure in the oral ecosystem and deify ortho-biological replacement. The corporate entities from which we derive our tools too often fail to distinguish the point at which science ends and policy begins.

By positioning advocates and acolytes at the vanguard of their marketing campaigns, they effect change; however, their support for education is directed towards dissemination of product, not the fundamentals and rudiments of biological imperatives. Prospective large cohort clinical trials with clearly defined criteria for survival, with and without intervention, quality of life information and economic outcomes are essential to comparing alternative foundational treatments. These studies will require expertise, time and financial support from the various stakeholders, professional and corporate alike.

Table I. As reported by Chugal et al., the most significant vector relevant to post-op healing is the presence and magnitude of pre-op apical periodontitis.17

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The authority of those who teach is often an obstacle to those who want to learn.
—Marcus Tullius Cicero
The prosthodontic pundits maintain that the spiralling costs of saving endodontically retreated teeth, for which extraction may well prove to be the common endpoint, bring into question whether such teeth should be sacrificed early. Ruskin et al. concluded that implants have greater success than endodontic therapy, are more predictable, and cost less when one considers the 'inevitable' failure of initial root-canal treatment, retreatment and peri-apical surgery. Is it responsible therapeutics or irresponsible expediency that justifies the removal and restoration of such teeth from the outset with an implant-supported restoration? Can one ethically argue that extraction is warranted because the financial cost of orthodontic extrusion/soft-tissue surgery, endodontic retreatment and post/core/crown fabrication is greater than extraction with an implant-buttressed restoration, and in all likelihood, more predictable? Jokstad et al. identified over 220 implant brands in the dental marketplace. With variability in surface, shape, length, width and form, there are potentially more than 2000 implants for any given treatment situation. A systematic review by Berglundh et al. assessed the reporting of biological and technical complications in prospective implant studies. Their findings indicated that while implant survival and loss were reported in all studies, biological difficulties, such as sensory disturbance, soft-tissue complications, peri-implantitis/mucositis and crestal bone loss, were considered in only 40 to 60% of studies. Technical complications such as component/connection and superstructure failure were addressed in only 60 to 80% of the studies. Are we as a profession standing idly by and watching marketing pressures force treatment decisions to be made empirically, with untested materials and techniques? There is an unsettling similarity between these events and the early days of implant development.

The endodontic pundits argue that major studies published to date suggest there is no difference in long-term prognosis between single-tooth implants and restored root-canal treated teeth. In fact, regardless of the similarity of treatment outcomes, the preponderance of post-treatment complications favours endodontic therapy. Therefore, the decision to treat a tooth endodontically or to place a single-tooth implant should be based on criteria such as restorability of the tooth, quality and quantity of bone, aesthetic demands, cost-benefit ratio, systemic factors, potential for adverse effects and patient preferences. A review of endodontic treatment outcomes by Friedman and Mor used radiographic absence of disease and clinical absence of signs and symptoms as the defining parameters for success. They suggested that the chance of having a tooth extracted after failure from initial endodontic treatment, retreatment and apical surgery collectively would be roughly 1 in 500 cases.

The dialogue comparing endodontic treatment to implant therapy jarringly overlooks the crucial fact that it is often the calibre of the restoration and its prognosis, and not the endodontic prognosis per se, that is the determinant of the treatment outcome. The primary biological mandate of any dental procedure is the retention of the orofacial ecosystem in a disease-free state. Surgical and non-surgical endodontic therapies...
special _ endo-implant algorithm

have historically been key modalities in the attainment of this foundational goal. Friedman noted that “the patient weighing one ‘success’ rate against the other may erroneously assume their definitions to be comparable and select the treatment alternative that appears to be offering the better chance of success.”

The conundrum with which researchers and clinicians alike wrestle increasingly includes the non-science of emotion as well.

This publication will address non-surgical and/or surgical resolution of failing primary endodontic treatment outcomes and the historical and ongoing efforts of the dental industry to engineer the biomimetic replacement of natural teeth successfully and replicate the structural predicates that comprise the substitution algorithm of bone, soft tissue and tooth. There are many levels to the accrual of ‘best evidence dentistry’. The purpose of this paper is to ensure that all variables in the treatment planning equation of foundational dentistry are understood and given equal weight in the decision-making process for comprehensive care.

Whenever possible, the treatment choice should be an attempt to salvage a tooth using a multidisciplinary team approach, putting aside preconceived notions and biases. Finances should not dictate the advice proffered. Furthermore, it is advisable to forego being clinically ‘conservative’. Treatment should not be initiated in the absence of a critical evaluation of the potential for all contributing factors to equate to a positive outcome. When needed, care must be taken to carry out every diagnostic procedure available, even those of a more invasive nature (Fig. 1). Before arriving at a definitive diagnosis and treatment plan, the clinician should obtain consent from the patient to remove any restoration in order to analyse the residual tooth structure and assess the potential to carry out reliably predictable treatment. The patient must understand in detail, the feasibility of and margin for success of each treatment option presented.

There are few studies in the endodontic literature analysing the reasons for extraction of endodontically treated teeth. Root-filled teeth are invariably prone to extraction due to non-restorable carious destruction and fracture of unprotected cusps. Tamse et al. found that mandibular first molars were extracted with greater frequency than maxillary first molars; the most significant causal difference was the incidence of vertical root fracture (VRF—1.8% maxillary molar, 9.8% mandibular molar). Teeth not crowned after obturation are lost with six times the frequency of those restored with full coverage restorations.

Procedural failure, iatrogenic perforation or stripping, idiopathic resorption, trauma and periodontal disease all contribute to a lesser degree. The major biological factor that influences endodontic treatment outcome failure with the possibility of extraction appears to be the extent of microbiological insult to the pulp and peri-apical tissue, as reflected by the peri-apical diagnosis and the magnitude of peri-apical pathosis (Table I and Figs. 2a–c).

Fig. 3 Two different retreated teeth; two different potential treatment outcomes. The root-canal system of both teeth has been re-engineered in its anatomic entirety; however, the treatment outcome after restoration for both is unlikely to be the same. Regenerative technologies incorporating mesenchymal stem cells derived from dental tissues may one day obviate the concern.

Fig. 4 Less porous, less hydrated and highly mineralised outer dentine (a); pulp canal space (b); more porous, more hydrated and less mineralised inner dentine (c); water in the dentinal tubules and pulp space is held in a confined environment under hydrostatic pressure (d).
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Dentine is the most abundant mineralised tissue in the human tooth. In spite of this importance, over half a century of research has failed to provide consistent values of dentine’s mechanical properties. In clinical dentistry, knowledge of these properties is pivotal to any number of variables, ranging from innovations in preparation design to the choice of bonding materials and methods. The Young’s modulus (the measure of the stiffness of an isotropic elastic material) and the shear modulus (modulus of rigidity) are diminished by viscoelastic behaviour (time-dependent stress relaxation) at strain rates of physiological (functional) relevance. The reported tensile strength data suggests that failure initiates at flaws. These flaws may be intrinsic, perhaps regions of altered mineralisation, or extrinsic, caused by cavity or post-channel preparation, wear, or damage. There have been few studies of fracture toughness or fatigue.18 Finally, little is known about the biomechanical properties of altered forms of dentine subsequent to decay, the influence of irrigants and chemicals, and the choice of curing techniques used for bonded restorations.19

Mechanisms for energy dissipation and crack growth resistance present in young dentine are not present in old dentine. Restorative methods and techniques, particularly regarding ferrule creation for endodontically treated teeth, may need to be amplified to address the fact that fatigue crack growth resistance of dentine decreases with age (Fig. 3).21

Understanding the mechanical properties of teeth is essential in order to address the most common clinical problem affecting all endodontically treated teeth, fracturing, which in spite of even minimal loss of tooth structure may be severe enough to necessitate removal.22–24 The hypothesis that dentine brittleness increases with diminished moisture content has been debunked; conserving bulk dentine is the *sine qua non* of fracture prevention. Kuttler et al. reported that dentine thickness correlates inversely to post-space diameter in the distal roots of mandibular molars.25 A size #4 Gates-Glidden drill caused strip perforations in 7.3% of canals studied. The authors recommend that Gates-Glidden drills no larger than a size #3 be used. After endodontic treatment, dentine thickness on the furcation side was less than 1mm in 82% of the distal roots studied (Fig. 4).

There are primary causes that predispose teeth to fracturing and secondary causes that predispose teeth to fracturing after a period of time (Fig. 5). Endodontics is a component of an interdisciplinary process and a chain is only as strong as its weakest link. Subsequent to any endodontic procedure, intensity of stress concentration and tensile stresses within an endodontically treated tooth will depend upon:

1) the material properties of the crown, post, and core material chosen;
2) the shape of the post;
3) the adhesive strength at the crown–tooth, core–tooth, core–post, and post–tooth interfaces;

Fig. 6. Flat field peri-apical radiograph (left); small focal field CBCT (right; Kodak 90003D, Kodak Dental Systems). The differential in visualisation of peri-apical pathology from a 3-D to a 2-D image is as much as 2:1.14

Fig. 7. The initial endodontic treatment procedure was inadequate and failing. Re-engineering (inclusive of interim calcium hydroxide therapy) ensured optimal eradication of microflora from the root-canal space, and the obturation produced definitive closure of the apical termini. Surgery was performed to redress persistent symptoms.
in endodontics have been egregiously abused by those surgical retreatment, and treatment outcome studies imply in infection cannot be ruled out. Time constraints or indications in these cases, especially when intra-canal treatment.33 Non-surgical retreatment may still be root-canal system, surgery is the most beneficial of the root-canal space. It should therefore be limited may isolate, but not eliminate, the residual microflora to situations in which non-surgical retreatment is contained within an idealised shape that is structurally enhanced by the use of a precise friction-fit connection.

Kvist and Reit39 have shown that while surgical cases demonstrated higher healing rates than non-surgical retreatment cases initially, four years after treatment there was no difference between the two modalities, owing to ‘late’ surgical failure. The failure rate for surgical therapy appears to be analogous to the failure rate for retreatment as a function of the size of the lesion treated.40 Levels of apical resection41 and the type of root-end filling material make a difference to surgical treatment outcome success;42 however, the dentine-bonded composite technique and the use of compomer materials has not been widely reported on. As these techniques dome the resected root face, sealing off the cut tubules, they may prove to be the 4) the magnitude and direction of occlusal loads; 5) the amount of available tooth structure; and 6) the anatomy of the tooth.

Any combination of vectored stress concentration and high tensile stresses will predispose these teeth to fracturing without an adequately engineered restorative design.

_Re-engineering_

Re-engineering negative treatment outcomes is a significant part of the contemporary endodontic oeuvre. The presence of apical periodontitis may affect the outcome of initial endodontic treatment;26 however, there is general consensus that apical periodontitis is the most important variable that influences a positive outcome with non-surgical and surgical retreatment.27–29 Positive treatment outcomes may be more likely in certain teeth with a combination of both procedures, rather than with one or the other alone (Fig. 6).

The premise that non-surgical retreatment improves the outcome of peri-apical surgery has been supported by both historical and current studies.30–32 Apical surgical ‘correction’ of intra-canal infections may isolate, but not eliminate, the residual microflora of the root-canal space. It should therefore be limited to situations in which non-surgical retreatment is judged impractical. With the range of sophisticated equipment and material in the conventional endodontic armamentarium, this is a remote consideration at best. When the aetiology is independent of the root-canal system, surgery is the most beneficial treatment.33 Non-surgical retreatment may still be indicated in these cases, especially when intra-canal infection cannot be ruled out. Time constraints or financial pressures should never be a factor in making surgery the first treatment choice (Fig. 7).

There are a myriad of variables associated with non-surgical retreatment, and treatment outcome studies in endodontics have been egregiously abused by those wishing to diminish the value of re-engineering natural teeth. Many studies have categorised teeth with caries, fractures, periodontal involvement and poor coronal restorations as negative endodontic outcomes.34,35

Prior procedural errors,36 occlusal considerations,37 material choice for the restoration38 and design of the full coverage component all suggest that success is a function of comprehensive treatment planning as much as technical expertise. Evidence-based or controlled best evidence studies should conclude that these are non-endodontic causes of failure and that the success of endodontic treatment itself is high and predictable.

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Fig. 9 An arch eliminates tensile stresses in spanning an open space, as all forces are resolved into compressive stresses. It requires all of its elements to hold it together, thus making it self-supporting. The incorporation of platform switching into the design of an implant abutment simulates three oblate spheroid shapes—one vertical, two horizontal. The objective is to ensure that axially vectored compressive stresses are contained within an idealised shape that is structurally enhanced by the use of a precise friction-fit connection.

Fig. 10a Foundational dentistry mandates that the impact of an ortho-biological replacement unit be commensurate with the biological objectives and functional requirements of the natural tooth.

Fig. 10b As the number of implant-supported single-tooth replacements increases, implant-abutment connection design should ensure that occlusal table replication displays equivalency in both dimension and cuspal inclination with the surrounding natural dentition.
most effective retrograde surgical protocols of all. The literature is unclear concerning peri-apical re-surgery. Gagliani et al. compared peri-apical surgery and re-surgery over a five-year follow-up period. Using magnification and microsurgical root-end preparations, the positive outcome for primary surgery was 86% and 59% for re-surgery. While others have shown positive outcomes for re-surgery, the decision remains highly case specific. In spite of our best efforts, negative endodontic treatment outcomes occur and ortho-biological replacement of teeth and their surrounding anchoring structures is an integral part of contemporary foundational treatment planning.

A recent article by Assuncao et al. describes engineering methods used in dentistry to evaluate the biomechanical behaviour of osseointegrated implants. Photoelasticity is used for determining stress-concentration factors in irregular geometries. The application of strain-gauge methodology to dental implants provides both in vitro and in vivo measurement strains under static and dynamic loads. Finite element analysis can simulate stress using a computer-generated model to calculate stress, strain, and displacement. An analysis of the impact of mechanical/technical risk factors on implant-supported reconstructions is beyond the scope of this publication; however, the replacement of lost teeth by implants should, without exemption, provide a feeling of restitutio ad integrum. The means by which the restoration of the original condition at the crown-root interface is idealised is detailed in this article.

The structure and composition of teeth is perfectly adapted to the functional demands of the mouth, and are superior in comparison to any artificial material. So first of all, do no harm. —Anonymous

Back to the egg

An increased uniform amount of coronal dentine significantly amplifies the fracture resistance of endodontically treated teeth regardless of the post system used or the choice of material for the full coverage restoration. A recent article by Coppede et al. demonstrated that friction-locking mechanics and the solid design of internal conical abutments provided greater resistance to deformation and fracture under oblique compressive loading when compared to internal hex abutments. These two 'seemingly' disparate observations define the inherent continuum between natural tooth engineering and the principles of engineering necessary to ortho-biologically replicating the native state.

The use of a ferrule or collet and a bonded or intimately fitted post-core to restore function and form to an endodontically treated tooth is analogous to the use of a long, tapered friction-fit interface with a retaining screw (Morse taper) to secure an abutment to a fixture. In both cases, the role of contact pressure between mating surfaces in generating frictional resistance provides a locked connection. This has been shown to effect long-term stability of crestal bone support for the overlying gingival tissues and maintain a healthy protective and aesthetic periodontal attachment apparatus.

The Roman architect Vitruvius’ (Marcus Vitruvius Pollio) description of the perfect human form in geometrical terms was a source of inspiration for Leonardo da Vinci, who successfully illustrated the proportions outlined in Vitruvius’ work De Architectura. The result, the Vitruvian man, is one of the most recognised drawings in the world and is accepted as the standard of human physical beauty. Vitruvius theorised that the essential symmetry of the human body with arms and legs extended should fit into the perfect geometric forms: the circle and the square. Da Vinci recognised that the circle and the square are only tangent at one place, the base. Observe the insert in Figure 8. The stabilising platform for the human form outlined begins at that tangent; the intersection is graphically analogous to the structural configuration of platform switching.

The relative simplicity of this construct reinforces the obvious. When we compare design in living things to the artificial designs they inspire, a striking parallel emerges. Almost all the products of man’s technology
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tripod experiments from grade school in which an egg acts as one of three supporting legs of a square section of wood that bears books as the load. The structure could support over sixty books, almost twenty pounds (9 kilograms), before breaking the supporting egg. One need only look at the root trunk and coronal egg structure of a multi-rooted teeth and it becomes apparent that strength of the tooth form is dependent upon an arch form for its integrity (Figs. 8 & 9).

Is it possible for this natural feat of engineering to be biomimetically replicated to the design parameters of osseointegrated implants? There are a number of paradigms that continue to fuel debate in the dental clinical and scientific communities that pertain to the optimal engineering predicates for implant design. These include smooth versus rough surfaces, submerged versus non-submerged installation techniques, mixed tooth-implant versus solely implant-supported reconstructions, Morse taper abutment fixation versus a butt-joint interface, and titanium abutments versus aesthetic abutments in clinical situations in which aesthetics are of primary concern.

The cone-screw abutment has been shown to diminish micro-movement by reducing the burden of component loosening and fracture. This enables the identification of the effects of the parameters such as friction, geometric properties of the screw, the taper angle and the elastic properties of the materials on the mechanics of the system. In particular, a relation between the tightening torque and the screw pre-tension is identified. It was shown that the loosening torque is smaller than the tightening torque for typical values of the parameters. Most of the tightening load is carried by the tapered section of the abutment, and in certain combinations of the parameters the pre-tension in the screw may be reduced to zero. This tapered abutment connection provides high resistance to bending and rotational torque during clinical function, which significantly reduces the possibilities of screw fracture or loosening.

Biomechanics

The seed of a tree has the nature of a branch or twig or bud. It is a part of the tree, but if separated and set in the earth to be better nourished, the embryo or young tree contained in it takes root and grows into a new tree.

—Isaac Newton

Pressure on the cervical cortical plate, micro-movement of the fixture-abutment interface (FAI), and...
microflora leakage and colonisation at and within the FAI are some of the pathological vectors associated with osseous remodelling, both crestal and peripheral to dental implants.\textsuperscript{46} Ocular considerations engineered into fixture design should enable optimum load distribution for permanent load stability during functional loading, reduce functional stress transfer to the interfacial tissues, and enhance the biological reaction of interfacial tissues to occlusally generated stress transfer conditions.\textsuperscript{47} Future modifications to implant biomechanics should focus on designs wherein the osseous trabecular framework that retains the fixture will adapt to the amount and direction of applied mechanical forces, cope with off-axis loading, compensate for differences in occlusal plane to implant height ratios, as well as adjust to mandibular flexion and torsion.\textsuperscript{52} In this new era of implant-driven treatment planning, fixtures should be engineered to support single crowns with cantilevers instead of implant–implant or implant–teeth connections for a span of any degree. These engineering design iterations will minimise high-stress torque load at the implant–abutment interface and obviate areas with degrees of bone insufficiency. The goal should be to biomimetically replicate the natural state to the greatest degree with regard to load bearing capacity (Figs. 10a \& b).

Stable crestal bone levels are the yardstick by which treatment success and health are measured in the orofacial ecosystem, whether success and health relate to natural tooth retention or restorative and/or replacement rehabilitation. It is therefore surprising that the treatment outcome standards for osseointegration accept crestal bone remodelling and resorption of up to 1.5 to 2\,mm in the first year following fixture placement and prosthetic insertion.\textsuperscript{51}

The concept of biological width outlines the minimum soft-tissue dimension that is physiologically necessary to protect and separate the osseous crest from a healthy gingival margin surrounding teeth and the peri-implant environment. A bacteria-proof seal, the lack of micro-movement associated with a friction grip interface and a minimally invasive second-stage surgery (where indicated) without any major trauma to the periosteal tissues are also important factors in preventing cervical bone loss. The literature suggests that the stability of the implant–abutment interface may have an important initial role to play in determining crestal bone levels.\textsuperscript{52} Tarnow’s seminal study on crestal bone height support for the interdental papillae clearly demonstrated the influence of the bony crest on the presence or absence of papillae between implants and adjacent teeth.\textsuperscript{53} Twenty years later, logic dictates that anticipated early crestal bone loss and diminished, albeit continual, loss in successive years of function ought to have been engineered out of the substitution algorithm for peri-implant tissues.\textsuperscript{54}

Platform switching: By default or by design

There is no logical way to the discovery of elemental laws. There is only the way of intuition, which is helped by a feeling for the order lying behind the appearance.

—Albert Einstein

Platform switching theorises that by using an abutment diameter of a lesser dimension than the periphery of the implant fixture, horizontal relocation of the implant–abutment connection will reduce remodelling and resorption of crestal bone after insertion and loading. The concept implies that peri-implant hard tissue stability will engender soft tissue and papilla preservation. Maeda \textit{et al.} reported that stress levels in the cervical bone area peripheral to a fixture were greatly reduced when a narrow diameter abutment was connected, in comparison to a size commensurate with the fixture diameter.\textsuperscript{55} The authors concluded that the biomechanical advantage of shifting stress concentrations away from the cervical area will diminish their impact on the biological dimension of hard and soft tissue extending apically from the FAI (Figs. 11a–c). The inherent disadvantage is that this shifts stress to the abutment screw with the potential for loosening or fracture.

Ericsson \textit{et al.}\textsuperscript{56} detected neutrophilic infiltrate in the connective tissue zone at the implant–abutment interface. The facility by which platform switching/shifting reduces bone loss around implants has been investigated by Lazzara \textit{et al.}\textsuperscript{57} The authors hypothesised that if the abutment diameter matches that of the implant, the inflammatory cell infiltrate will be formed in the connective tissue at the micro-gap created at the FAI. If an abutment of narrower diameter is connected to a wider neck implant, the FAI is shifted away from the

Fig. 12a. The platform-switched design negates micro-motion and resultant crestal bone resorption. The goal of ortho-biological replacement is the idealised replication of the natural state.
outer edge of the implant, thus distancing inflammatory cell infiltrate away from bone. Hypothetically, less crestal bone loss is expected and an increased implant-abutment disparity allows more stable peri-implant soft-tissue integration.

Baggi et al. conducted a finite element analysis experiment to define stress distribution and magnitude in the crestal area around three commercially available implants: ITI Straumann (Straumann), Nobel Biocare (Nobel Biocare) and Ankylos C/X (DENTSPLY Friadent). Numerical models of maxillary and mandibular molar bone segments were generated from computed tomography images and local stress vectors were introduced to allow for the assessment of bone overload risk. Different crestal bone geometries were also modelled. Type II bone quality was approximated and complete osseointegration was assumed. It was concluded that the Ankylos C/X implant based on its platform switched and sub-crestally positioned design demonstrated better stress-based performance and lower risk of bone overload than the other implant systems evaluated.

Platform switching with a stable implant-abutment connection is increasingly accepted essential implant design features required to reduce or eliminate early crestal bone loss. A bacteria-proof seal, a lack of micro-movement due to a long friction grip tapered channel, and minimally invasive second-stage surgery without any major trauma for the periosteal tissues are also important factors in preventing cervical bone loss. A preconfigured platform-switched design has a significant impact on the implant treatment in aesthetic areas, as not only is the tissue biotype preserved, but it has also been shown to be enhanced by osseous generation over the collar of the fixture (Figs. 12a & b).55,60

The endo-implant algorithm parallels the question: Which came first, the chicken or the egg as an example of circular cause and consequence. It could be reformulated as follows: Which came first, X that cannot arise without Y, or Y that cannot arise without X? An equivalent situation arises in engineering and science known as circular reference, in which the parameter is required to calculate that parameter itself. This is the essence of foundational dentistry. If nature creates the ideal, are we as clinicians not responsible for replicating the ideal, should adverse conditions irrevocably alter nature and necessitate its elimination?

Nature wisely created a structure that could harmoniously interpolate hard and soft tissue, act as the portal of nutrition and communication for the body, and be the gatekeeper on guard and in function throughout our lifetime. Our role is to ensure that we re-engineer nature; we must adhere to its rules, its logic and fundamentals. This is not an easy task, as filtering out the best range of evidence from a wide range of sources, presenting clear, comprehensive analyses and incorporating patient experience is a Herculean task. In many ways, this is analogous to Alice’s Adventures in Wonderland, as so much of what we do grows curiouser and curiouser as each new innovation demands that we go through the looking glass and determine what Alice found there.

“There’s no use trying,” said Alice. “One can’t believe impossible things.” “I daresay you haven’t had much practice,” said the Queen. “When I was your age, I always did it for half an hour a day. Why, sometimes I’ve believed as many as six impossible things before breakfast.”

—Lewis Carroll

Editorial note: A complete list of references is available from the publisher.