1

Introduction

Materials Chemistry as a Means to an End(o) – The Invisible Foundation

Brian W. Darvell

School of Dentistry, Institute of Clinical Sciences, College of Medical and Dental Sciences, University of Birmingham, Birmingham, UK

TABLE OF CONTENTS

1.1 Introduction

In the last 70 years or so, our understanding of dental materials has progressed from the more or less purely pragmatic to a more structure–function design-based science. This process is not yet complete. That is, despite the currency of 'evidence-based dentistry' – which has its own Wikipedia entry and an eponymous journal – there remains much work to be done to make everyone appreciate the value of the science of those materials. Inadequate teaching and dogmatic schools of thought are also manifest in endodontics to no lesser extent. It is my understanding that this book represents an attempt to begin the essential process of modernization in this field. Accordingly, I shall attempt to provide some foundations for the necessary insight.

Once the vitality of the dental pulp becomes compromised, endodontic intervention is necessary to preserve a functional natural dentition, with natural alveolar (as opposed to ankylosed) bone attachment, and thus the preservation of that very bone. More, perhaps, than in some other areas of dentistry, the materials used in endodontic work have an intimate relationship with tissues. Most obviously, the dentine is subject to exposure to a variety of more or less aggressive irrigants as well as fillers and (putative) sealers, often involving calcium hydroxide. Another possibility is of a strong oxidizing agent in the form of hypochlorite. Whilst the need for microbial elimination is not disputed, it is appropriate to be aware of the implications of such treatments: the chemistry demands that if a reaction is possible, it will occur, whether you like it or not, whether you meant it or not, and whether you are aware of it or not. Of course, apical extrusion of almost all materials can have very unfortunate consequences. Such intimacy is quite undesirable.

Endodontic Materials in Clinical Practice, First Edition. Edited by Josette Camilleri.

At the least, a foreign body reaction will be elicited; at the worst, destruction of periapical bone – but the risk of infection is always high, with potentially wider implications.

1.2 The Substrate

Dentine has a complex composite structure whose matrix is largely proteinaceous, but it also has an inorganic component, biological apatite. As such, it is vulnerable to hydrolysis (whether acid- or base-catalysed), even at pH 7 – although this may then be at a very low rate [1]. Since the mechanical properties of a composite structure are dependent on the integrity of the matrix, any such hydrolysis must be considered detrimental. In this light, the frequent finding that root fracture is associated with the use of calcium hydroxide, or materials containing it, is a predictable outcome for inevitable chemistry. The increased risk has to be treated as a necessary sequela of such a treatment, with the unhappy implication that the life of the remaining tooth may be limited (bearing in mind that the loads experienced by such teeth depend on a number of circumstances). Indeed, the use of oxidants such as sodium hypochlorite (which also deliberately has a high pH) must likewise contribute to such deterioration, because all organic material must be subject to oxidation, and indiscriminately. Add to this the penetration and diffusion of fluids and the effect can be seen to be not necessarily local. We therefore need to recognize that all such treatments involve compromise, a trade-off between immediate benefit and longer-term failure risk.

Disruption of the dentine matrix has further implications. As is discussed in Chapter 3, many biologically important molecules become bound within it during its development. Should these molecules be released through matrix breakdown, they may become once again biologically active and thus be important in reparative or regenerative processes. Such release through mechanical processes has little implication for that activity. Likewise, demineralization under mild conditions, such as with ethylene diamine tetra-acetic acid or 'EDTA' (what is used in dentistry is actually closer to the trisodium salt, in order to provide enough solubility at around pH 7–8), may be considered in the same context. Such demineralization can be presumed to offer an easier diffusive path through the now much more porous tissue, and so may release these molecules without detriment to them, although perhaps the larger ones – proteins, for example – may emerge more slowly. It is, however, worth considering whether the more aggressive media at high pH cause any destruction of such molecules: proteins of whatever kind are still subject to hydrolysis. Are any of the other important matrix components capable of reaction, and thus damage and inactivation, under those conditions? Naturally, this is not necessarily an all-or-nothing kind of event – the kinetics of the reaction determines how much survives. It would follow, though, given that these molecules are believed to be of value in the course of treatment, that finding more benign means of release than the presently documented range of products would be of value for a more reliable effect of full efficacy. It would be wrong to assume, again, that the chemical reaction that destroys the matrix and releases these substances is selective. For example, urea may solubilize (that is, make soluble, as opposed to merely releasing) the matrix protein, but at the risk of unfolding, and therefore inactivating, enzymes of interest. There will probably not be a perfect resolution of this problem, but the means may conceivably be designed or selected for specific targets. It should be apparent that oxidizing agents are liable to destroy any and all biologically active molecules more rapidly than high pH alone. What appear to be needed are assays of the sequestered substances for comparison with release rates and survival in an active form after the various possible treatments.

The use of demineralizing and matrix-destroying agents has an important implication. If bonding to collagen is intended, it must be left intact. If interaction with the calcium or phosphate of the mineral is contemplated, that must remain available. It is clearly illogical to use a treatment that removes an essential component of a subsequently intended process.

The preceding discussions are essentially of simple chemistry. It is curious then that in the historical focus on sterility and its maintenance in the present context, there has been little consideration of the inevitable effects of some of the agents used. Ignorance of the chemistry is no excuse, and to claim, for example, that a particular effect is not required is a chemical absurdity: as already stressed, if a reaction is possible, it will occur; if a pathway exists, it will be taken. The only debate is about relative rates. Materials science – and no less in endodontics than anywhere else – must recognize the chemistry of systems and design accordingly. The dogma mentioned must be designed out of dentistry. Again, though, compromise is inevitable; perfection is – at best – unlikely. Rational assessment is not optional, it is essential.

1.3 Nomenclatural Hype: 'Bioactivity', 'Bioceramics'

It is clear that substances released unaltered from the dentine matrix must retain their biological function and activity, although whether the balance that originally obtained during development in the many complex interacting pathways is effectively and usefully maintained remains a matter for investigation. Nevertheless, it is proper to argue that this is indeed biological activity – bioactivity, to use the current jargon – because these are natural substances involved in entirely normal biological processes. Unfortunately, the field of dentistry is heavily trampled and muddied by the indiscriminate use of the term in any context where a biological response is elicited. That is, in the absence of those natural biological substances, any action, process, or material that provokes a response of any kind is automatically labelled 'bioactive'. Such responses fall for now into just two classes: simple chemical and challenge defence.

Simple chemical responses typically involve the provision of a species that perturbs a chemical equilibrium, such as by changing the local pH. To take an ordinary example, adding sufficient calcium ions to a tissue fluid (by dissolution of a component of a material, say) must locally drive the precipitation of a calcium phosphate, assuming nucleation can occur. Because this is inevitable simple chemistry, with no sign of the involvement of a biological process, there is no logic or sense in labelling the source material 'bioactive', yet this is commonplace. We may note in passing that a frequently-used test of 'bioactivity' involves immersing the test material in a metastable supersaturated solution of calcium and phosphate, the criterion being the appearance in due course of an apatitic precipitate on that material. The fact is that almost everything produces that effect, due to the ease with which apatitic material nucleates under those circumstances – there are many papers reporting such an outcome. It is worth remembering that tissue fluids are not, in general, supersaturated with respect to apatites. Simplistic calculations based on analytical values without taking into account speciation (and, especially, binding by many specialized protein systems) fail to give sensible results. Whilst hypercalcification (heterotopic ossification) is a real and distressing disease, we do not as a matter of course calcify promptly and locally in response to cuts and bruises, which effect would otherwise be expected. To make this point more clearly, highly supersaturated calcium phosphate solutions can be prepared that can stand for days without doing anything. Yet, merely shaking the flask can result in the prompt and massive precipitation of the excess: any seed is enough. There is no discernible chemical

difference between such a system and the 'bioactivity' test. There is simply no biology involved.

Challenge defence responses are elicited by anything that represents a foreign body, toxicity, osmotic imbalance, boundary layer disturbance (*via* zeta potentials or surface chemistry), pH change, or merely an unusual ion – that is, a chemical challenge, an insult to the tissue. The body's natural reaction is to mount a defensive response such as encapsulation and immune reactions, if outright apoptosis and necrosis does not occur. When calcification (*e.g.* dentine formation) is involved, it is greeted with pleasure. But then, such an effect occurs with low-level challenges such as caries anyway. It does not seem to be sensible to label materials that provoke a defensive response, however natural or normal, as 'bioactive'. On that basis, formaldehyde is bioactive, zinc oxide-eugenol is bioactive, and calcium hydroxide is bioactive.

By extension, then, it is a puzzle how materials that cause disruption or degradation of the dentine matrix can be labelled 'bioactive' simply because in the course of that damage some truly biologically active substances happen to be released, and quite regardless of the fact that such substances may have local beneficial effects. What we see is a creeping inflation of titular importance that bears no relation to underlying processes. It is one of the worst examples of the hijacking of a term to make the products it is attached to seem more valuable and useful. There are many such in dentistry. The problem is that, in the absence of understanding by the general user of the products' actual chemistry, their use and effects are misunderstood. We do not serve patients' best interests by such exaggeration and misinformation.

All that said, there is a conceptual class of material that can truly be described as bioactive, and although there is nothing at present on the market, it has been demonstrated in principle. That is, the incorporation of a naturally occurring biological substance or substances that may stimulate or trigger a natural process that leads to a suitable outcome, such as bone growth or dentine deposition. By definition, this is a substance that is normally involved, but whose artificial provision enables, facilitates, or amplifies the pathway. One would expect that the vehicle for such a delivery would be otherwise benign, not representing a challenge in itself – for example, a resorbable, noninflammatory material.

We must be careful, though, not to stray into the realm of pharmaceutical products (which incidentally has all kinds of implications for marketing and promotion, never mind supply and use). That is, pharmaceuticals are intended to be biologically active in that they may, for example, modulate or trigger natural processes. The question is whether a material that is the vehicle for a substance not normally involved in the usual biochemistry of repair can be considered 'bioactive'. Imagine a material carrying, say, aspirin: it would be wrong to say this is bioactive. Thus, salicylate-based cements and liners are not. Whether the provision of a normal, human, biological substance in such a fashion is pharmaceutical is for others to debate and decide. Ponder the taking of vitamin D, or melatonin, for example. Antibiotics clearly cross the line.

Overall, then, the key is that we must inspect the chemistry to ascertain what is going on. If it is a simple chemical effect that does not involve any biology as such, or if it is a chemical challenge that results in a defensive (albeit normal) response, it is quite improper to apply the term 'bioactive': it is an advertising malfeasance. If – or, perhaps, when – materials are available that are the vehicles for any of the many biologically active substances that offer the possibility of true reparative or regenerative responses, the label will be fully justified and accurate. Until then, it is suggested that much more careful thought is required, which goes beyond the allure of advertising hype and wishful thinking. Mere repetition does not make it so. Believing one's own propaganda is not scientific.

A similar abuse occurs in the term 'bioceramic'. A ceramic material is, in simple chemical terms, anything that is not metallic or organic polymeric. The prefix 'bio' only seems to refer to the context in which it is used: in a medical or dental application. This is pretentiously misleading. It does not automatically confer special properties on the material in question, which has in any case been chosen (one hopes) on grounds of its general inertness and suitable mechanical properties. There are no classes of materials that in any sense earn the label, except possibly those of bone, dentine, and enamel – natural hard tissues – and even then, it serves no real purpose. Can it be applied to mollusc shells? Quite possibly. But how does that help us understand the value of marketing hype? Its extension to setting cements and sealers is incomprehensible [2].

Chemistry is frequently a weak point in other areas. Take 'MTA' as perhaps the most egregious example: this is the trade-name abbreviation for what is described as 'mineral trioxide aggregate'. Try as one might, this phrase makes no sense whatsoever: it does not inform in any way at all – it does not even describe the material itself – yet it is bandied about as if it were a meaningful label. It is inorganic, admittedly, but as the Oxford English Dictionary has it: 'Mineral: A naturally occurring substance of neither animal nor vegetable origin; an inorganic substance. (Not now in technical use.)'. MTA plainly does not qualify.[1] The only 'mineral' present as such is gypsum, possibly – but not originally. Then again, 'mineral aggregate' is a term for 'rock' that has fallen out of fashion. This kind of product is not a rock, nor derived as such from one. Otherwise, 'aggregate' ordinarily means the rough granular material used in concrete, for example, such as pebbles, crushed rock, slag, and so on – the first thing that springs to mind – but that is clearly not what is meant (where it is in fact the core or filler in that composite material).

The first publication to refer to 'MTA' claims that one of the 'principle [sic] compounds present' is 'tricalcium oxide silicate oxide' [3]. This is not an identifiable substance; indeed, it is chemical nonsense. There are no details given whatsoever of provenance, processing, or analysis. The next paper says, 'The principle compounds present . . . tricalcium oxide, and silicate oxide', which speaks of a lack of understanding and an earlier failure to proof-read (and of very poor reviewing on both occasions), but quite simply neither compound exists, nor can the labels be parsed in a chemically meaningful fashion [4]. Later, we find: 'All MTA was divided into calcium oxide and calcium phosphate' – this was for the set material [5]. Calcium oxide cannot survive contact with water, and no calcium phosphate has been seen since. There is not a trioxide anywhere claimed, not does one exist in either the initial or the reacted powder. The word 'aggregate' seems merely to have been used as a synonym for 'mixture'. Can it be that 'MTA' simply stands for 'mixture of three solid oxides'? Even that is quite untrue. (The later-incorporated so-called 'bismuth trioxide' does not exist as such – the Bi(III) oxide actually used would better be called 'sesquioxide', which would be accurate if not currently the standard term). The point of all this is to say that accuracy and precision are required for science and proper communication – to understand what is being done and what might be expected to happen.

It is, of course, necessary to identify products fully and accurately in recording and reporting work, whether clinical or experimental. However – and especially given the number of products subsequently sold – it is clear that the continual use of the trade name as a generic is both wrong and misleading. Genericization, or 'trademark erosion', is commonly viewed as detrimental to (and by) the owners of trademarks, but in the contexts of teaching, research, insurance, and standardization, too, it plainly has severe drawbacks. It is proper

1 The irony of having to refer to the 'mineral' of tooth tissue is not lost on me.

then to use a label that conveys the essential information succinctly, for a class of materials. It was on the basis of this argument that the term 'hydraulic silicate cement' (HSC) was proposed [6]. The qualifying 'hydraulic' is necessary and sufficient to distinguish such materials from the now-obsolete silicate cements which relied on reaction with phosphoric acid (*i.e.* a type of acid–base system): water is the reactant for the setting of an HSC. The persistence of 'MTA' might reflect chemical ignorance, again, but certainly it represents an unthinking adherence to habit.

The term 'hydraulic' is also applied in another context: so-called 'hydraulic condensation', or the technique of forcing a fluid material to fill the space of a root canal by means of, say, a gutta-percha cone pushed into it. The relationship of the term to hydraulic machinery is obvious: transmission of pressure using a liquid. In that physical sense, it is legitimate [7] (but then a syringe is also 'hydraulic'). The difficulty seems to be in prevention of extrusion (*v.s.*) – simple hydrostatics says that this is likely, and promotional material seems to imply that it is expected. It is for others to decide whether the use of such techniques is appropriate.

1.4 Chemical Interactions and Irrigation

Another weakness is found in the use of irrigants. It is perhaps well known that chlorhexidine reacts with EDTA-containing products, precipitating material that will clog tubules and canals. But reaction also occurs between chlorhexidine and various other irrigants, producing with NaOCl various chlorinated substances and precipitates, which may be coloured [8]. Hydrolysis to produce 4-chloroaniline, a toxic substance, has also been suggested [9]. Essentially, the possible chemical interaction between all substances used in any sequential treatment should be considered for adverse effects as a matter of routine. Neither independence, nor complementarity, nor synergy may be assumed. It makes sense to ensure that some rinsing occurs between each irrigant used to minimize risks. Even so, since diffusion into tubules and accessory canals must occur, the efficiency of that rinsing cannot be very great. Reactions in the deeper tissue must be expected. In fact, that is how staining occurs in the first place. Indeed, even a mixture that is advocated (Chapter 5), HEDP-NaOCl, clearly has an oxidation reaction proceeding fairly rapidly, although the speculated details appear not yet to be verified [10].

A related issue arises in respect of the formulation of products. It is incumbent on researchers to know what they are working with, the composition of materials, and all setting, mechanical, and physical properties and subsequent degradations. Failure to do so can be considered a lapse. However, it is often singularly difficult to get such information: it does not appear in full in product literature, it does not appear in Material Safety Data Sheets because only known or expected hazardous materials need be declared, and it is often denied to enquirers by the manufacturer on grounds of trade secrets. We are owed full declaration of ingredients in manufactured foodstuffs, even if the wording is obfuscated by industry jargon, so that we can avoid adverse reactions or belief violations. We expect to know what is in cosmetics, perfumes, and anything else we put on our bodies, for similar reasons. Likewise with pharmaceuticals. So why, then, is it permissible to sell products that will be implanted in patients without a full list of ingredients and components? The possibility of direct adverse effects is certainly of great concern (especially because we differ widely in our sensitivities). Given that many materials are used in sequence or are contiguous on completion, that concern is raised to an imperative. It is surely inappropriate, if not arrogant, for a manufacturer tacitly to imply that we do not need to know because they have decided it is safe, and that no regulation is thereby contravened. The regulations must be addressed.

The word 'activation' is also frequently misapplied in chemical contexts. Thus, so-called 'electrochemically activated water' is in fact a solution of various substances produced by electrolysis. The water as such is not 'activated' in any sense whatsoever. The word is used outside dentistry in a variety of similar contexts, similarly vacuously. The most relevant meaning is the switching of a system into a new state or condition, as for example the electronic transition in a photosensitizer, making it capable of the next step in a reaction. Simply raising temperature, for example, often has clear chemical rate effects – but that is not 'activation' (such an approach of course ignores the detrimental effect on vital tissue of temperatures above 42 °C and cannot be recommended for that reason anyway). Likewise, (ultra)sonication cannot 'activate' anything in this switching sense. Although it does have some remarkable effects in what is termed 'sonochemistry', outcomes in the present context can be attributed simply to mechanical actions, including stirring through induced flow: no specific chemistry is known to have been demonstrated. Care must be taken, of course, when discussing the standard chemical term 'activation energy': what is required to overcome an energy barrier to a process. Sonication may well provide that for some chemical processes by means of cavitation effects, but as far as can be ascertained, this does not apply here (cavitation is also mechanically destructive). Laser-based techniques also appear to be purely mechanical in effect. 'Activation' is likewise unhelpfully applied to mere agitation of a reactive solution by stirring or pumping, such as moving an irrigating solution with a gutta-percha point or the like. Whilst this may allow faster bulk reaction, overcoming the limitation of reliance on diffusive processes to some extent, the actual chemical kinetics of the reaction are totally unaffected. Such magic is not scientific.

Whilst on the subject of irrigation, it is often said that a solution is applied specifically to remove the smear layer resulting from instrumentation. That smear layer must, of course, be composed of the same proportions of matrix and mineral as the underlying tissue. It follows that no single solution can achieve such removal: mineral can be dissolved, and matrix oxidized, but not by the same agent. Likewise, there can be no selectivity on the part of the agents: chemically, smeared material is essentially indistinguishable from its source. Diffusion ensures that an acid or chelator, say, will reach underlying material in due course (and, of course, reach more remote areas than the canal being treated via accessory canals and so on). Very often, one sees references to so-called 'appropriate concentrations', which supposedly avoid overextended reaction, without recognizing that both time and concentration – to say nothing of temperature – affect rate, whilst the extent of dissolution depends on the relative amounts of smeared material and reactant (volume × concentration), assuming that factors such as flow and streaming are not involved. Even then, one cannot assume uniformity of thickness or of any of the relevant factors over the entire space, most especially because it is tapered. Always, there is a compromise – in particular because the extent of the smeared material is unknown and progress cannot be monitored. Protocols based on the mean behaviour of a laboratory series cannot inform on the status of the individual case – an example of the fallacy of averages: sample means convey no information on distribution and thus on behaviour in the tails [11].

Following irrigation, it is necessary to dry the canal. This makes sense in that free liquid as such could interfere (mechanically) with subsequent processes, or even chemically via dilution or dissolution. However, it is wrong to imagine that water (as a substance) can be removed and then excluded from tooth tissue: desiccation is neither achievable not desirable. Dentine matrix, being proteinaceous, is hydrated. Removal of that water would be detrimental to its structure and properties. However, all tooth tissues are permeable, both

grossly through patent canals and tubules and diffusively through soft and hard tissues, including enamel and cementum, and the vast majority of materials (solid ceramics and metals excluded). Water is therefore always available, everywhere, always. What matters, chemically, is its activity, not its concentration. That is, the equilibrium condition to be expected is that the activity of the water in all diffusively contiguous regions – that means everywhere in the mouth and surrounding structures – is the same. This is a thermodynamic condition that cannot be gainsaid. 'Humidity' is therefore 100%, always (although this really is not the proper term, except in a void, where it refers to the relative saturation of the vapour – 'wet' is preferable). How long it takes is a separate matter: diffusivity depends on the medium (we assume close enough to constant temperature). Even so, approach to equilibrium can be expected within a couple of weeks at most in the majority of materials and relevant circumstances [12, 13]. Any reactions that are possible (including absorption, and thus swelling) are therefore necessarily going to occur, but the extent in a given timeframe – the rate – depends on the availability of the water: gradients, diffusivity, and reaction kinetics. Avoidance of 'leakage', meaning actual liquid flow or diffusion through liquid pathways, may properly be the goal, but exclusion of water as a reactive substance is not possible.

In the context of leakage, there is clearly much interest in how well a material may be attached to tooth tissue. Commonly, this is referred to in terms of 'bond strength', yet it is acknowledged that for many materials this is ordinarily attributable only to a mechanical key – the result of the interlocking of the cast asperities of the material on those of the substrate [14]. It would seem preferable in such cases simply to refer to 'retention', as then it is accepted that there is nothing else going on. This thought raises an interesting point: on what is actual bond strength measured? Most systems of interest in dentistry involve a carefully prepared rough surface, whether through instrumentation, grit-blasting, or etching, seemingly acknowledging that this is the main source of interaction. Would it not be sensible to test the adhesive qualities of materials using a smoothly polished, unetched substrate? That way, the true bond strength could be ascertained; that is, the benefit of any chemical interactions could be measured directly, instead of being confounded by the mechanical key. Proper efforts could then be directed to improving the chemistry, even if the key was to be used to augment the retention in normal service.

In passing, we may note that there is no such thing as a meaningful shear test in dentistry, as has been shown several times. Its continued use – in numerous highly idiosyncratic and ill-controlled forms – is both pointless and bemusing: the results are uninterpretable, and certainly of no clinical relevance. Whilst that leaves axial tension as the only viable method, no material in any dental context is known to fail in that mode either: the service interpretability of all such results is problematic, therefore. A related problem occurs with 'push-out' tests. The assumed interfacial shear is confounded by parasitic stresses and distortions that vitiate intent and thus interpretation. The absence of appreciation of the mechanics of such systems is disappointing.

A distinction also needs to be drawn between adhesion and seal. The latter can arise from a coating that has no specific bonding beyond the van der Waals (*i.e.* simple wetting) or from a material that expands (for whatever reason) and is sufficiently plastic to conform to the surface. It might help to ponder the way in which an O-ring seal works: a purely elastic system that has no bond requirement of any kind. Quality of 'seal' is plainly not related to 'bond strength' in any fundamental fashion, although in a dental context its continued existence might be. There are evident dangers in expanding materials in what are unavoidably weakened roots, but thought must be given to what scale of gap might be considered appropriate: does it matter

at the molecular scale, say of water (the answer has to be no, since this is probably unavoidable), or is it just that of bacteria that is required? Perhaps somewhere in between is acceptable. This needs thinking through.

Lack of thinking is also evident in the use of methods taken from dental International Standards (ISO) documents, showing both a misapprehension of their purpose and unfamiliarity with the subtleties – indeed, outright difficulties – of testing, especially for mechanical properties, which is an exacting field [15]. Such 'standardized' methods are to be understood as economically sensible means of ascertaining safety and efficacy; as quality-control (QC) methods. To call them quick and dirty is perhaps going too far, but they cannot necessarily represent the last word for scientific studies, because the manufacturer, for example, would not be prepared to pay for such accreditation testing, and they make their views known in the drafting committees and national bodies. It is essential to give a full appraisal of a proposed method, refining and elaborating it as necessary, to avoid pitfalls and increase the value of the results in terms of clinical relevance and interpretability. The fact that there are no universally recognized methods of unimpeachable protocol speaks of the difficulties of doing a good job, but also imposes severe requirements on those doing any testing. That severity is rarely even acknowledged, let alone honoured. Crude methods are taken from the literature simply because they have been used before (sometimes for many years), and that precedent is the only defence – there is no science. But on top of that, modifications are made without justification, seemingly for convenience. Comparability between papers evaporates.

1.5 Terminology

The history of the names of chemical substances is worth some study as it reveals the development of chemical thought from the earliest attempts to study the way the world works. Some old forms persist in literary contexts (*e.g.* brimstone), others are retained in common speech (*e.g.* acetic acid). The field of chemistry itself has endeavoured to standardize a systematic approach to a variety of areas on a number of occasions since the nineteenth century, culminating in the system of preferred names developed by the International Union of Pure and Applied Chemistry (IUPAC). The point of all this effort, of course, is to be able to communicate exactly, unambiguously, the substance involved. One can understand that the literature will show the progression over time as understanding and rigour develop, and it remains necessary to be able to decode old names. Yet, when perusing a list such as that for EDTA [16], several points emerge. Firstly, the use of trade names as if they were chemically meaningful (*v.s.* 'MTA'), when the cessation of the sale of the product would mean that decoding the reference might take some considerable effort in the future (and we have to assume and accept that trade products will at some point cease to be sold). Some products are the same but sold with different labels, such as the Endosequence, Totalfill, and iRoot ranges. Researchers can waste a lot of effort trying to compare these when it is not necessary. Secondly, the import of foreign-language versions without translation or checking can only confuse. Thirdly, the arcane terms used by manufacturers in their product information might seem intelligible, but you only have to read the ingredients of certain prepared foodstuffs or cosmetics to see how they would leave even a chemist stymied and bemused (part of the reason for the introduction of the E-number system by the European Food Safety Authority (EFSA)). Fourthly, there are several ways of being systematic. But then, looking at the dental literature, we can discern other problems. Manufacturers wish to obscure their formulations for commercial reasons, but the substance names used commonly convey very little to help understand their chemical, mechanical, or biological properties, such as

interactions and allergies – points that have already been made. For these to be parroted uncritically as technically correct labels betrays many things. The fact that there are documented instances of advertising copy-writers (presumably not chemists) garbling text in the manner we are used to from the press, only for this to be propagated by 'research' papers, is at best disappointing. We have a duty to communicate accurately. It is incumbent on us to check. We are obliged to review material critically, and report accordingly. In many cases, a preferable approach would be to identify a substance and state its IUPAC name, then be consistent in using a proper chemical term: the appearance of several names for the same substance in the same text underlines the complete absence of understanding. Reviewers should insist on clarity.

As we should appreciate, all materials used in dentistry represent compromise. It is simply not possible to obtain all desirable attributes (chemical, physical, mechanical, biological, economic, practical) simultaneously. We routinely trade off one thing against another, and accept some deficiency for some other benefit. There are commonly strong grounds for believing that ideality is unapproachable: physics is a hard taskmaster, and thermodynamics ineluctable. Nevertheless, it is proper to enquire as to the amelioration or refinement that might be possible. This should be on rational grounds, not guesswork or wishful thinking. We have seen such awkward proposals before in a number of instances, such as 'resin-modified' glass ionomer cement (GIC). If GIC has some good properties but is weak and moisture-sensitive, whilst light-cured materials are strong and insensitive, surely we can do both? No. Firstly, the one function replaces the other: in a given volume, something has to go to make space for something else. All too often, 'additions' are made that are not recognized as the replacements they are. Given that, something must be diminished even if something is gained. Secondly, by including competing reactions that have no chemistry in common, the trade-off depends on the relative rates and timings: it is a very fine balance, the probability of attaining which is low [17]. This is a complicated and messy system that falls between two stools. It is well recognized that 'compomers', where a GIC-type glass was used as the core in a resin matrix, failed to work as hoped [13, 18] – so why now do we see supposedly *light-cured hydraulic silicate* cement? Similar arguments apply, similar outcomes are to be expected. The triumph of advertising over substance? Wishful thinking is the bane of dentistry.

We see similar failures of appreciation in the seemingly random selections of additives regularly studied and proposed for many applications. For example, a material is too weak for a certain use, but a strong material is known that can be made as a powder – why not add this? Again, the replacement aspect of such a design is not recognized, but a key requirement of such composite structures is missing: bonding. Composite structures require a bond – that is, a chemical bond – between the matrix and the core (*alias* the 'filler', a term that betrays a less than honourable economic incentive in some contexts) for stress transfer to occur and the benefit to be realized. This is 'matrix constraint'. With it, there are remarkable improvements. Without it, the material behaves as if it were full of holes, with the obvious outcome. This was seen in the attempts to strengthen silver amalgam with (silver-plated!) sapphire whiskers, GIC with zirconia powder, and GIC with amalgam alloy powder ('miracle mix') to name but three egregious examples. Now we have 'microsilica' added to HSC. In fact, we should be careful to distinguish between materials that are included to do a job – such as reactants or bonded core – and those that have no other purpose than to dilute the system, which is all a true filler actually is. Of course, the inclusion of pharmaceutically active substances such as antimicrobials must also be treated rationally, because they are then part of the matrix (occupying volume) and therefore affect all its properties, always – poor discriminatory power experiments notwithstanding.

It is often the case that such an additive will be explored at a range of proportions (and, sadly, when it matters, not accounting for the consequent changes in other, more important, ratios). Then, through the sequential application of Student's *t*-test, the maximum amount that does not give a statistically significant result (*i.e.* a 'nonsignificant $P > 0.05$', 'N.S.') will be decided upon. This is fallacious in several respects. Firstly, anything that interferes with the setting reaction or the resulting structure must, by definition, cause a deterioration. Secondly, the 'failure to detect' is not the same as an assertion of no effect; it is the entirely expected consequence of the poor discriminatory power of testing with a small sample size, large scatter, and relatively weak effect. Whether it matters is not the focus of attention as it should be, but the claim is made that the addition is safe because 'nonsignificant' is enough. In fact, with a large enough sample size, you will always get a 'significant' result. In addition, the test is weak because it is piecemeal instead of looking for the covariance of the outcome with input, when the full power can be obtained. It is also wrong because it is trawling without multiple test protection. What is proper is to determine the size of the effect, then determine – from other considerations – how much is tolerable. If reviewers do not understand all this, what hope is there?

1.6 Classification of HSCs

As enthusiasm for this kind of material has grown, a range of variations has been produced, but many of them make reference to the original (nonsensical) labelling (*v.s.*). Consequently, there is a deal of confusion as to the nature of the various formulations and what behaviour might be expected from them. There are numerous products available now, and some systematic classification would be helpful to inform product selection. The chemistry is essential to understanding what

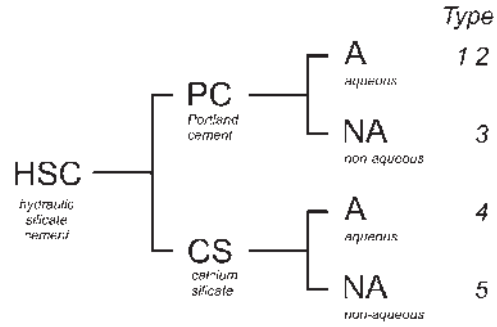

Figure 1.1 Fundamental classification of hydraulic silicate cements at the point of use. The types referred to for clinical purposes elsewhere in this book are shown. Type 1 is the original formulation of the class, without any additive. All others have one or more additives of various kinds, for various purposes [19].

is going on – how could it be otherwise? – and thus to enabling the statement of a simple, informative, and (most importantly) accurate classification. As already indicated, an HSC is defined by the reaction of a silicate system with water (a simple classification of HSCs based on their chemistry is shown in Figure 1.1). That silicate system might be a Portland cement-like (PC) complex mixture (regardless of its provenance, *i.e.* whether it is derived directly from a commercial PC or created in a similar fashion from less-contaminated feedstock) or a simpler calcium silicate (CS) or mixture of related compounds that has been synthesized for 'purity' (to avoid heavy metals) or for other reasons. We therefore have a very simple division into PC and CS. The main subdivision then is based on the water that is needed for the material hydration reaction. Some HSCs are to be mixed with water (*i.e.* they are an aqueous mixture at the point of application), and some are presented as a slurry or paste in a non-aqueous vehicle, which is subsequently lost entirely, diffusing away. In the latter case, setting is still specifically hydraulic, as it relies on water from the surroundings (*v.s.* re: drying) diffusing into the water-miscible liquid continuous phase: the setting chemistry is

essentially unaffected. (Incidentally, this gives the lie to the description of such products as 'pre-mixed' – quite clearly, they are not, as no reaction water is yet present. Such a presentation is a rather neat approach, so why is it trivialized by a nonsense label? This is advertising, not science.)

Whether or not a radio-opacifier is added to any of these does not affect the fundamental behaviour: the essential chemistry – hydraulic reaction – remains as the defining characteristic, whether or not that additive modifies the setting reaction rate or outcome in any way (whether deliberately or accidentally, and no matter how drastically) [20]. Indeed, whether any other additive is included or the formulation is tweaked for any reason (*e.g.* rate modification), the basic classification must remain if the key chemistry persists. Attempts to create 'generations' on a historical basis are as pointless as they are uninformative in the absence of logic, consistency, and relevance. There are no alternatives known at present for true HSCs, all of which are essentially based on CSs (as stressed elsewhere in this book).

The trouble is that what may reasonably be called 'fake HSCs' are also offered. Along the lines of compomer (*v.s.*), a PC material powder in a light-cured resin matrix has been produced: this is a filled (composite) resin (FR), no more, no less. It is simply irrational, and highly misleading (if not culpably misrepresented), to call this an HSC, or to imply that it is by association, irrespective of any beneficial effects, perceived or claimed, from a high pH at the surface, available calcium, and so on. If setting does not depend on water, it is not an HSC. In fact, water that does diffuse into the cured material (through the matrix, as is normal and expected for such resin systems, despite popular belief) must react with the PC material: such chemistry is unavoidable. Thus, one could reasonably expect this to expand (reaction product volume is necessarily greater than PC volume), with perhaps unfortunate results, albeit slowly – but this is not 'setting'. Similarly, a PC- or CS-containing material to be mixed with a salicylate-containing second paste, setting by the usual acid–base (AB), salt-formation process of many other proper cementitious materials, and not in the first place by reaction with water, cannot rationally be described as an HSC; to do so would be chemically false representation. Such a material is not fundamentally different from the old silicate cements that were mixed with phosphoric acid for setting, although they may be nearer to setting calcium hydroxide liners in the primary reaction. But here, again, water that must and will diffuse in must and will react in the usual way with any remaining core (and again cause expansion), but the setting mechanism as such is not at all that of an HSC. They may not be called HSCs, or suggested to be such.

1.7 Conclusion

It is possible to go on and dissect many more aspects of endodontic materials and treatments from a materials science perspective, most especially for the chemistry that is abused, ignored, or imagined. Were one not inured to a working life exposed to such, despair would follow rather promptly. Given that the role of all dentists, and thus of non-clinical teachers as well, is ultimately to ensure patient well-being, the plea now is for the underlying science (and its practitioners, therefore) to be respected, given credit, and adopted as the means of supporting that motivation.

Critical reading and informed thinking can reveal much about the dogma, unwarranted assumptions, and wishful thinking (despite perhaps the best of intentions) that pervade endodontics at least as much as anywhere else in dentistry. Challenge it all – *nullius in verba* – and in so doing, with an open mind and sound advice, take the subject forward: true evidence-based dentistry awaits your contribution.

References

1 Smith, R.M. and Hansen, D.E. (1998). The pH-rate profile for the hydrolysis of a peptide bond. *J. Am. Chem. Soc.* 120: 8910–8913.

2 Kohli, M.R. and Karabucak, B. (2019). Bioceramic usage in endodontics. Available from http://www.aae.org/specialty/2019/07/08/bioceramic-usage-in-endodontics (accessed 10 August 2020).

3 Lee, S.-J., Monsef, M., and Torabinejad, M. (1993). Sealing ability of a mineral trioxide aggregate for repair of lateral root perforations. *J. Endod.* 19 (11): 541–544.

4 Torabinejad, M., Watson, T.F., and TRP, F. (1993). Sealing ability of a mineral trioxide aggregate when used as a root end filling material. *J. Endod.* 19 (12): 591–595.

5 Torabinejad, M., Hong, C., McDonald, F., and Pitt Ford, T.R. (1995). Physical and chemical properties of a new root-end filling material. *J. Endod.* 21 (7): 349–353.

6 Darvell, B.W. and Wu, R.C.T. (2011). 'MTA' – an hydraulic silicate cement: review update and setting reaction. *Dent. Mater.* 27 (6): 407–422.

7 Fleisher, R.M. and Heintz, C.E. (1977). A plastic tube technique for direct vision of endodontic procedures. *J. Dent. Educ.* 4 (10): 630–632.

8 Prado, M., Santos Júnior, H.M., Rezende, C.M. et al. (2013). Interactions between irrigants commonly used in endodontic practice: a chemical analysis. *J. Endod.* 39: 505–510.

9 Basrani, B.R., Manek, S., Sodhi, R.N. et al. (2007). Interaction between sodium hypochlorite and chlorhexidine gluconate. *J. Endod.* 33: 966–969.

10 Zollinger, A., Mohn, D., Zeltner, M., and Zehnder, M. (2018). Short-term storage stability of NaOCl solutions when combined with dual rinse HEDP. *Int. Endod. J.* 51 (6): 691–696.

11 Welsh, A.H., Townsend Peterson, A., and Altman, S.A. (1988). The fallacy of averages. *Am. Nat.* 132 (2): 277–288.

12 Musanje, L. and Darvell, B.W. (2003). Aspects of water sorption from the air, water and artificial saliva in resin composite restorative materials. *Dent. Mater.* 19 (5): 414–422.

13 Musanje, L., Shu, M., and Darvell, B.W. (2001). Water sorption and mechanical behaviour of cosmetic direct restorative materials in artificial salvia. *Dent. Mater.* 17: 394–401.

14 Şanlı, S., Dündar Çömlekoğlu, M., Çömlekoğlu, E. et al. (2015). Influence of surface treatment on the resin-bonding of zirconia. *Dent. Mater.* 31: 657–668.

15 Darvell, B.W. (2020) Misuse of ISO standards in dental materials research. *Dent. Mater.* 36 (12): 1493–1494.

16 http://www.chemspider.com/Chemical-Structure.5826.html?rid=4a01b359-c38c-4e4a-9bce-487b6c2b5176

17 Yelamanchili, A. and Darvell, B.W. (2008). Network competition in a resin-modified glass-ionomer cement. *Dent. Mater.* 24: 1065–1069.

18 Ruse, N.D. (1999). What is a 'compomer'? *J. Can. Dent. Assoc.* 65: 500–504.

19 Camilleri, J. (2020). Hydraulic calcium silicate-based endodontic cements. In: *Endodontic Advances and Evidence-Based Clinical Guidelines; Section 2: Advances in Materials and Technology* (eds. H.M.A. Ahmed and P.M.H. Dummer). London: Wiley.

20 Camilleri, J. (2007). Hydration mechanisms of mineral trioxide aggregate. *Int. Endod. J.* 40: 462–470.