Lithotripsy

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Abstract: Shock wave lithotripsy (SWL) is the process of fragmentation of renal or ureteric stones by the use of repetitive shock waves generated outside the body and focused onto the stone. Following its introduction in 1980, SWL revolutionized the treatment of kidney stones by offering patients a non-invasive procedure. It is now seen as a mature technology and its use is perceived to be routine. It is noteworthy that, at the time of its introduction, there was a great effort to discover the mechanism(s) by which it works, and the type of sound field that is optimal. Although nearly three decades of subsequent research have increased the knowledge base significantly, the mechanisms are still controversial. Furthermore there is a growing body of evidence that SWL results in injury to the kidney which may have long-term side effects, such as new onset hypertension, although again there is much controversy within the field. Currently, use of lithotripsy is waning, particularly with the advent of minimally invasive ureteroscopic approaches. The goal here is to review the state of the art in SWL and to present the barriers and challenges that need to be addressed for SWL to deliver on its initial promise of a safe, effective, non-invasive treatment for kidney stones.

Keywords: lithotripsy, shock, acoustic, urolithiasis, kidney stone

1 INTRODUCTION

During extracorporeal shock wave lithotripsy (ESWL or SWL; it is noted that ESWL is a registered trademark and therefore in this article the acronym SWL will be employed), usually 1500–3000 shock waves are focused upon a renal or ureteric stone at a rate of one or two per second (so that the treatment usually lasts for 30 min). The shocks are generated outside the body by a source which is coupled to the patient by a water path (Fig. 1). The objective of SWL is to reduce the stone into fragments that are small enough to be passed naturally from the body or dissolved by drugs [**1**].

The costs associated with kidney stones appear to be growing. For example, the expenditure for individuals with claims for a diagnosis of urolithiasis was almost US$2.1 billion in the USA in 2000, representing a 50 per cent increase since 1994 [**2**]. The costs appear to be increasing despite a shift from inpatient to outpatient treatment, and away from open surgery (which now accounts for less than 1 per cent of stone procedures in the USA). This increased cost might be linked to an increased prevalence in stone disease. Currently it is expected that around 13 per cent of men and 7 per cent of women in the USA will be diagnosed as having a kidney stone during their lives [**2**, **3**].

The following article reviews the current mature state of the technology and the implications of that (section 1). Section 2 describes the two key physical environmental factors in this process, namely the acoustic field (section 2.1) and the stone (section 2.3), and in addition the monitoring environment (section 2.2). The mechanism of fragmentation is still unresolved, in part because of the variety of complicated interactions which take place between the shock wave, the soft tissue, and the stone (section 3). Unwanted effects, including soft-tissue damage (morbidity), can also occur (section 4). Section 5 discusses the challenges and opportunities facing clinicians, researchers, and manufacturers.

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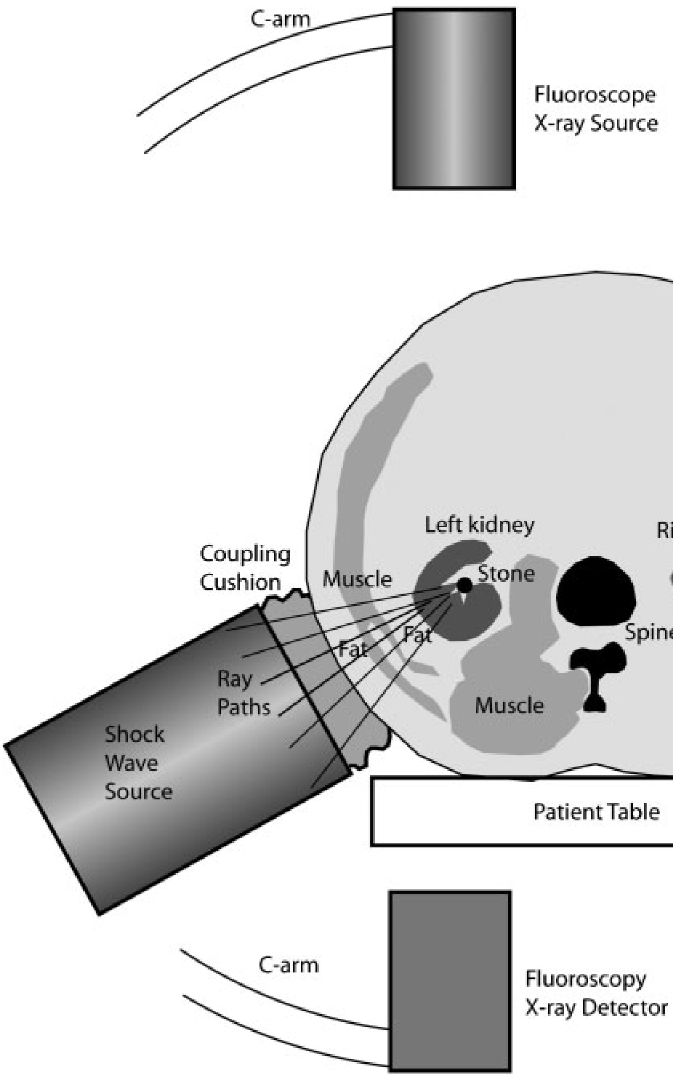

Fig. 1 A schematic diagram showing the basic components of a lithotripter. The patient is positioned on their back on a table. The shock wave source is placed in contact with the patient by means of a water-filled coupling cushion with a gel or fluid employed to ensure good coupling. The stone is targeted by means of fluoroscopy (as shown) or by means of in-line or out-line ultrasound (not shown). The focused shock wave has to pass through layers of fat and tissue before it reaches the kidney stone

After the first patient was treated in Germany in 1980 [**4**, **5**], SWL quickly became the preferred modality for the non-invasive treatment of renal and ureteric stone disease. By 1989, reports from clinics in Europe and the USA indicated that around 85 per cent of patients were treated with SWL without the need for open procedures [**6**, **7**]. However, the numbers have steadily declined since then, such that approximately 50 per cent of stones are treated by SWL today [**8**], with anecdotal reports that the proportion can be as low as 10 per cent in teaching hospitals (S. P. Dretler, personal communication, 2008). The rate of SWL use is typically lower for urologists in metropolitan settings, which is attributed to the fact that those urologists are comfortable with the greater technical challenges associated with endoscopic procedures [**9**]. If this trend continues, SWL may no longer be a treatment modality 15 years from now.

This decline is due to a number of factors, some of which are real and some perceived. The factors include the following.

1. SWL is not as effective as it was 25 years ago. Despite marketing claims to the contrary, the clinical results from the first commercial lithotripter (Dornier HM3) are generally accepted not to have been bettered by any other lithotripter

[**10**], although there is not consensus on this point [**11**]. This is remarkable given the advances in most other technologies over the same time period.
2. Competing technologies, and in particular ureteroscopy, have advanced significantly [**12**] (see section 5.6).
3. There is a growing body of evidence that the tissue damage induced by SWL leads to chronic complications [**13**], e.g. hypertension (see section 4). Although there is dispute in the community, some clinicians are cautious about using SWL on these grounds, and to date an equivalent body of evidence has yet to accumulate for the competing technologies.
4. The patient population, at least in the USA, has changed, with higher obesity rates resulting in longer propagation paths to the stone, which in turn makes stone fragmentation by SWL more difficult [**14**].
5. The established nature of the technique can stifle innovation (see section 5.1) [**15**].

Such perceptions on the future of an established technology can be self-fulfilling, in that they cause a decrease in research and development. Researchers, clinicians, and sponsors are attracted to ultrasonic therapies (e.g. high-intensity focused ultrasound and sonoporesis) which have yet to enter a corresponding stage of maturity to that in which SWL now resides; where its clinical use (at least for renal and ureteric stone treatment) is perceived to be routine; where sales opportunities for the established manufacturers (at least in developed nations) are limited, as the market is saturated; and where there is limited investment in research, as there appear to be few opportunities to enhance revenue or to benefit patients or practitioners. These factors have contributed to a loss of research interest in SWL.

2 THE ENVIRONMENT

2.1 The acoustic field

Much of the research into the bioeffects of clinical ultrasound has focused on avoiding side effects. While the avoidance of anatomical or physiological changes is desirable in a diagnostic procedure, in therapeutic uses of ultrasound (such as physiotherapy) some changes would be required for any non-placebo benefit. However, for many years, any such changes were marginal in all the routine uses of clinical ultrasound (with the exception of dentistry, which does not involve the same propagation issues [**16–18**]). Ultrasonically induced changes were avoided during diagnostic procedures and were so indistinct during physiotherapy that the mechanism for benefit has never been elucidated and indeed has been difficult to distinguish from placebo effects [**19**]. The advent of SWL in 1980 changed this situation. Here the change to tissue was clear, with stone fragmentation and accompanying soft-tissue damage (section 4). Previously, the major mechanism for an adverse bioeffect had been hyperthermia (tissue heating), with cavitation as an important secondary consideration. Indeed, today all modern diagnostic ultrasound scanners have real-time on-screen indicators which inform the clinician of the likelihood of generating both these effects *in vivo* during a given procedure. In SWL, each pulse has a short duration (a few microseconds) and they are fired at a low rate (one or two a second), and so any temperature elevation is negligible [**20**]. However, within a few years after the introduction of the first commercial units, cavitation was perceived to be important to stone fragmentation (section 3.2) [**21**]. Although SWL pulses were not intentionally designed to promote cavitation, they have properties which do just this [**22**]. SWL employs pressure pulses with a peak positive pressure of the order of 60 MPa and a 1 μs duration, followed by a longer tensile tail about 5 μs duration with a peak negative pressure of around -10 MPa (Fig. 2) [**23**, **24**]. The trailing negative pressure, which has a higher amplitude and longer duration than occurs in diagnostic ultrasound, results in the explosive growth of cavitation bubbles (section 3.2).

In the late 1980s, manufacturers increased the size of the aperture of the source to reduce pain by increasing the area over which the shock wave interacted with the skin. This was done to allow the procedure to be carried out with sedation instead of general anaesthetic. However, increasing the aperture had the secondary effect of decreasing the size of the focus [**25**]. Once recognized, this secondary effect was assumed to be beneficial, in that a smaller focus would constrain the high pressures to the region of the stone and so reduce the collateral damage to soft tissue. However, as will be discussed in section 5, the SWL community is divided as to whether this is a good strategy or not.

Three types of shock wave source have been used: electrohydraulic, electromagnetic, or piezoelectric sources [**23–27**]. In electrohydraulic sources (Fig. 3(a)) a high-voltage (10–30 kV) capacitor is discharged between two electrodes immersed in water. The discharge results in growth and collapse

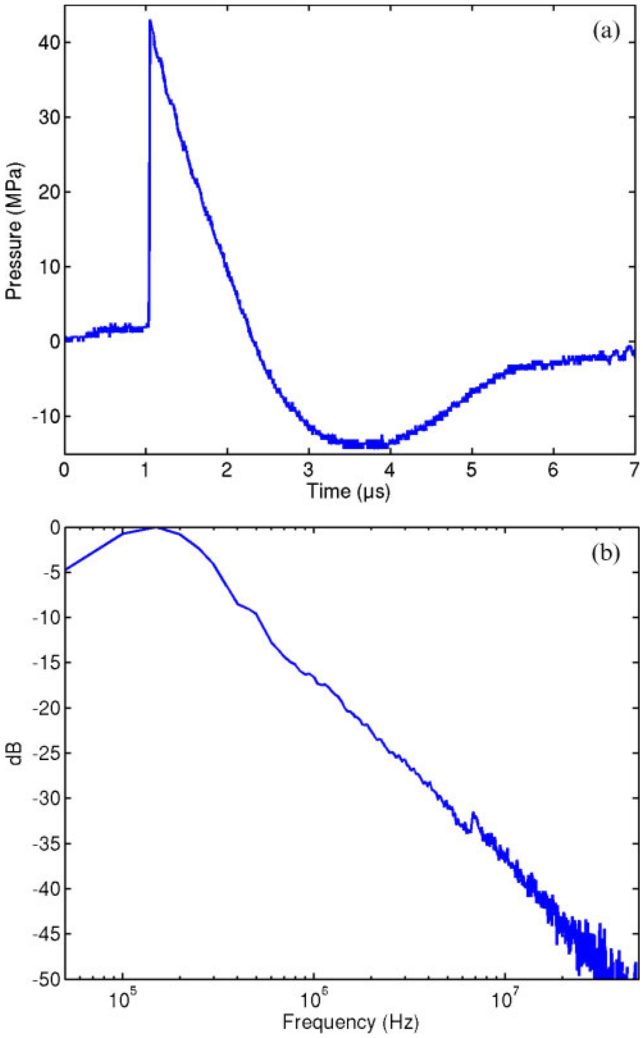

Fig. 2 Shock wave from a Dornier HM3 operating at 24 kV, as measured in degassed deionized water by a poly(vinylidene fluoride) membrane hydrophone (Sonic Industries, Hatboro, Pennsylvania, USA). (a) Pressure–time trace showing a leading positive pressure with peak of 42 MPa and duration of 1 μs. The trailing negative tail is lower in amplitude (−12 MPa peak) but longer in duration (3 μs). (b) Amplitude spectrum of the waveform in (a) (normalized to spectral peak). The spectrum peaks at around 150 kHz and more than 90 per cent of the energy lies below 1 MHz. The higher-frequency components are important in determining the structure of the shock front

of a vaporous 'gas globe', which generates the main lithotripter pulse in the form of a spherically spreading shock front (subsequent decaying oscillations of the gas globe may generate smaller pulses which are not significant for stone fragmentation) [**28**, **29**]. In order to focus the spherical shock wave, the spark is placed at the interior focus of a hemi-ellipsoidal reflector. The reflector focuses the spherically spreading shock wave to the second focus of the ellipse, commonly referred to as F2. It is at F2 that the stone is positioned. One drawback of electrohydraulic sources is that, except for two clinical lithotripters that are now marketed with long-life electrodes [**30**, **31**], the spark source needs to be replaced at regular intervals (1000–2000 shock waves, which is less than one typical treatment) owing to their vaporization and erosion by the spark [**32**].

Most current lithotripters use electromagnetic sources which consist of a coil of wire placed against a thin metal membrane. The other side of the membrane is in contact with water. A high-voltage capacitor is discharged through the coil. The subsequent current pulse through the coil induces a repulsive force on the metal membrane which deflects and generates a pressure pulse in the water. In this case the leading positive pressure sharpens to form a shock through non-linear effects [**22**, **27**, **32**, **33**] as it propagates and is focused by means of an acoustic lens (Fig. 3(b)) or a paraboloidal reflector [**34**]. These sources have lifetimes in excess of one million shock waves [**34**].

Piezoelectric shock wave sources consist of an immersed array of hundreds or thousands of ceramic elements placed on the inner surface of a spherical bowl which, when simultaneously excited by the discharge of a high-voltage capacitor, produce waves that converge at the focus (Fig. 3(c)) [**27**]. These shock wave sources have very limited market presence, particularly in the USA, and there is a perception that the fragmentation efficiency is poor [**35**]. They have lifetimes of up to five million shock waves [**34**], but over time the ceramic elements suffer mechanical damage and electrical breakdown [**27**].

In the first commercial lithotripter, the electrohydraulic shock wave source was in the bottom of a water-filled tub, and the patient was immersed in the water to remove the acoustic impedance mismatch that would occur if air was present in the propagation path between source and tissue. In subsequent designs, so-called 'dry lithotripters', the shock source is placed in a sealed unit with a flexible membrane which is placed against the patient's skin with a coupling gel used to facilitate transmission into the body (Fig. 1). However, methods for assessing the reliability of the coupling are not typically available and *in-vitro* experiments have indicated that stone fragmentation is reduced by 50 per cent for the case where 6 per cent of the surface area has visible air pockets [**36**]. Furthermore, this report

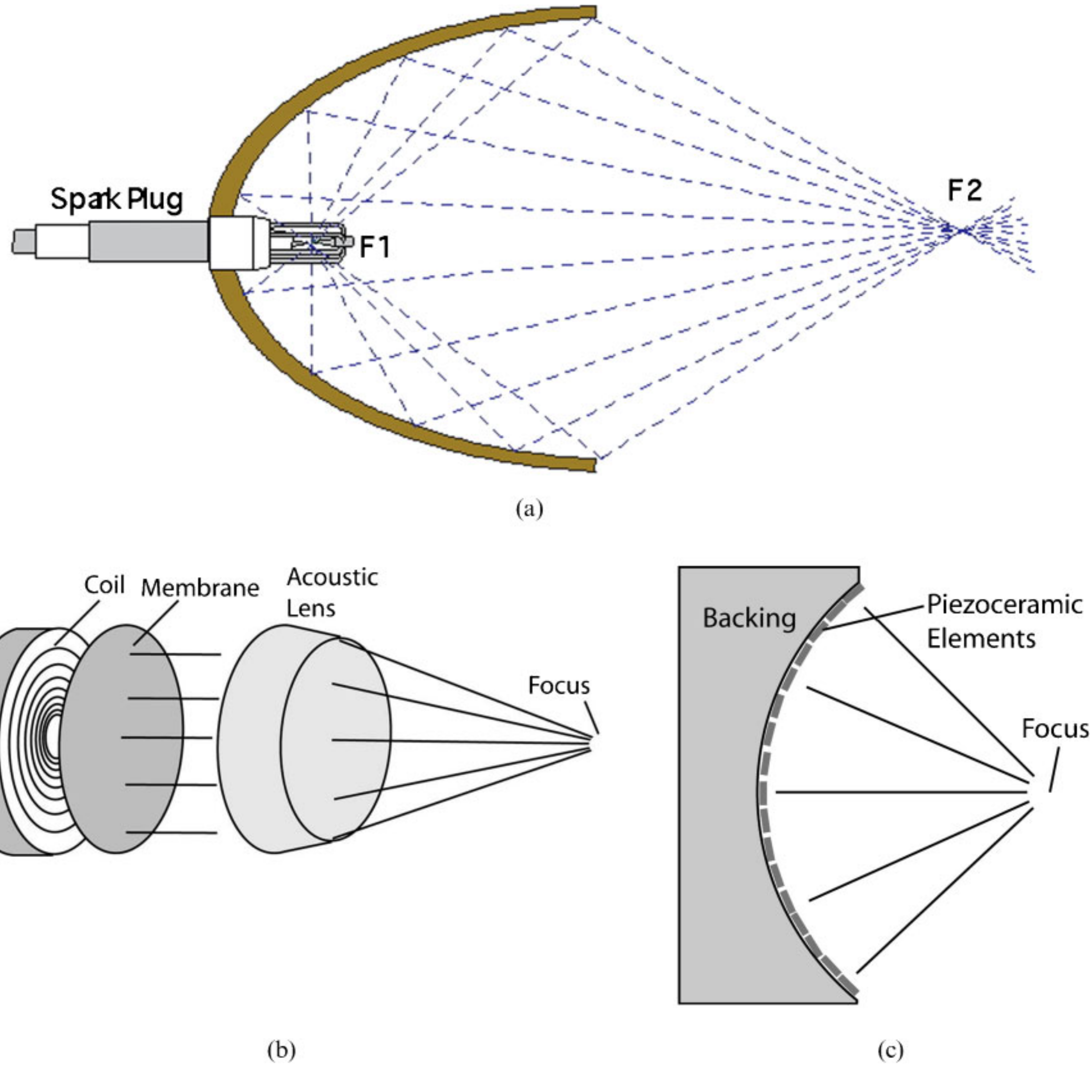

Fig. 3 Schematic diagrams of (a) an electrohydraulic source with a spark plug at the interior focus F1, hemi-ellipsoidal reflector, and the ray paths to the exterior focus F2; (b) an electromagnetic source showing the coil and metallic membrane which generate a quasi-planar wave, and the lens that is used to focus the wave to the stone; and (c) a piezoelectric source where the piezoelectric elements are placed on the concave surface of a spherical bowl. The wave focuses onto the centre of the radius of curvature of the bowl

indicated that variability in stone fragmentation performance increases as coupling degrades.

2.2 Monitoring

The focus of the lithotripter is aligned with the stones using ultrasonic imaging and/or X-ray fluoroscopy, with the former being more widespread in Europe, and the latter more common in the USA. However, retreatment rates are high, with reports of 30–50 per cent [**37**, **38**], and some patients undergo more than three treatments for the same stone [**26**, **39**]. These high retreatment rates suggest that the imaging methods mentioned above are not completely effective at maintaining targeting or assessing whether sufficient stone fragmentation has occurred (section 5.4). The assessment of the success of an SWL procedure is complicated by the differing criteria used to measure success (see section 5). Even a simple phrase such as 'stone-free rate' could in fact be based on a range of definitions. It could refer to the proportion of patients (so that a success is a success regardless of the number of treatments). This is the most common usage and will be employed in this article. However, an alternative interpretation is that it refers to the number of treatments (so that, if a patient requires three treatments to become 'stone free', two of those treatments count as unsuccessful and one as successful). Furthermore, variation exists in assessing the stage at which a patient is 'stone free' [**40**].

Early studies with the Dornier HM3 (water-bath-based electrohydraulic lithotripter) reported success rates in excess of 90 per cent [**6**, **41**]. The clinical performance of the HM3 is considered to be the gold standard by many (but not all) urologists. The 'progress' towards electromagnetic dry lithotripters, which have the advantages of longer life, no water bath, and small focus, has also meant poorer outcomes [**10**, **42**]. In its 1997 guidelines the American Urological Association (AUA) panel presented a meta-analysis of published data on SWL treatment that indicated that SWL resulted in stone-free rates of 83 per cent for stones in the proximal ureter and 85 per cent in the distal ureter [**43**]. In their more recent 2007 guidelines [**44**], jointly published with the European Association of Urology (EAU), a meta-analysis showed 82 per cent stone-free rate for stones in the proximal ureter but only 73 per cent for the mid-ureter and 74 per cent for the distal ureter. They comment that the data for the mid-ureter and distal ureter are statistically worse than in 1997 but were unable to identify a cause. It is reports such as this that contribute to the perception that SWL is less effective now than when it was first introduced [**45**].

2.3 Tissues and stones

The shock wave requires a soft-tissue path to the kidney, and the usual approach is through the back or flank. The soft-tissue path to the stone consists of skin, subcutaneous fat, muscle, perirenal fat, and then the kidney. The acoustic properties of tissue are similar to those of water, which is why a water bath was used for coupling in the initial lithotripter [**4**]. On average, the speed of sound in soft tissue is 1540 m/s, and most tissue types lie within about 20 m/s of this value. One notable exception is fat, which has a sound speed of approximately 1450 m/s [**46**]. This slower sound speed results in refraction of the sound waves as they pass into and out of the fat. This can cause the focus to broaden and shift position. Within the kidney, the shock wave passes through the parenchyma to the urine in the collecting system in which the stones reside. The motivation for insonification of the patient through the back or flank is to deliver the shock waves along a path which avoids bones (in particular, spine and ribs) and gas (in the intestines and lungs). Such avoidance eliminates the attenuation which would be caused by the impedance mismatch between soft tissue and either bone or gas, and furthermore reduces possible hazards associated with the interaction of shock waves with gas bodies in, for example, the lung [**47**].

Kidney stones that are considered to be candidates for SWL are typically greater than 3 mm in diameter and may be up to 10–20 mm [**44**]. For sizes beyond this, the amount of fragmented stone produced is too great to be passed naturally [**44**]. The aetiology and pathogenesis of kidney stones are active research topics in their own right [**48**, **49**]. Although the initial pathway by which stones form is still debated, it is generally accepted that, once a crystal nucleation site occurs in the collecting system of the kidney, then it will grow into a stone depending on the conditions of the urine (e.g. pH or supersaturation of calcium salts) [**48**, **49**]. The sources of high levels of calcium in urine are intestinal hyperabsorption and reduced renal reabsorption of calcium, and calcium release from bone (which may be associated with low bone mass and increased fracture risk) [**50**]. The recurrent nature of stone formation in some patients indicates that these problems are chronic. Nearly 80 per cent of kidney stones are mainly calcium oxalate but contain some calcium phosphate, with 10 per cent of stones mainly calcium phosphate with some calcium oxalate [**51**]. A typical calcium oxalate stone has a core of apatite [**52**], and can contain an organic matrix of mucoproteins, mucopolysaccharides, inorganic material, and bound water [**53**]. Other stone types are dominated by uric acid, struvite, cystine, or less common components, and this characterization through composition (determined on passed, removed, or fragmented stones using infrared spectroscopy or X-ray crystallography) is extremely useful [**49**]. However, composition alone gives insufficient discrimination for assessing the susceptibility of a stone to SWL, which could be significantly influenced by variations in the stone shape and volume, the crystal formation, the size and distribution of flaws, the microhardness, the surface features, the fracture strength and the elasticity [**51**, **54–59**].

Some *in-vitro* stone phantom tests have used the same material as *in-vivo* stones, although it is more convenient to use plaster of Paris in place of struvite [**60**, **61**] and a dental plaster to substitute for a calcium oxalate monohydrate stone [**60**]. When excised stones are tested *in vitro*, it is important to recall that many material properties, such as the hardness, can be strongly dependent upon the immersion and storage conditions [**52**, **62–64**].

Soon after the introduction of SWL to treat kidney stones, attention was turned to using SWL to treat biliary stones, or gallstones, which have a higher incidence than kidney stones. There are two types: cholesterol gallstones (which are usually yellow) and pigment gallstones (which are usually black) [**64**]. While most gallstones have a hardness of about one order of magnitude lower than kidney stones [**64**], they are more difficult to fragment *in vitro* than kidney stones [**64**], suggesting the importance of other factors. Although SWL was used to treat gallstones in Europe, it never received acceptance in the USA. SWL has also been used to treat salivary stones but this is an uncommon treatment [**65–67**].

3 INTERACTION BETWEEN THE SHOCK WAVE, TISSUE, AND STONE: MECHANISMS OF FRAGMENTATION

As the shock wave passes through tissue on the way to the stone, it suffers amplitude loss due to the attenuation of tissue (which is about 1000 times higher than water at the frequencies used in SWL), and refraction due to sound speed changes. Measurements of the sound field *in vivo* are challenging, but they indicate that the peak positive-pressure amplitude is reduced by approximately 30 per cent and the peak negative-pressure amplitude by substantially less [**68**]. This is consistent with the fact that the high-frequency components of the wave contribute strongly to the peak positive pressure, and the low-frequency components to the peak negative pressure (Fig. 2(b)).

The shock wave that interacts with a stone is therefore similar to what might be measured in water. There is at present no consensus on how shock waves fragment stones. There are a number of mechanisms that are likely contributors to the fragmentation and these can be broadly divided into *direct stress* and *cavitation*. Direct stress refers to the impact of the shock wave on the stone and the subsequent evolution of stress inside the stone. Cavitation refers to small bubbles and cavities that grow in the urine surrounding the stone because of the large negative-pressure tail of the acoustic pulse.

3.1 Direct stress

The urine (and to a first approximation the tissue) surrounding a stone is a fluid and therefore can only support acoustic waves. Kidney stones, on the other hand, are elastic solids and therefore can support both compressional and shear waves. When the shock wave is incident on the stone, it will couple into both compressional and shear waves in the stone. Early work suggested that spallation, also known as the Hopkinson effect, may play a role in fragmentation [**69**]. The spall effect occurs when the shock wave couples into a compressive wave in the stone, which subsequently reflects from the rear of the stone. The stone–urine interface inverts the large positive-pressure pulse, resulting in a large tensile stress. This stress is added to the tensile stress of the (still incoming) negative-pressure tail, resulting in a very large tensile stress near the back wall [**1**, **58**, **69–71**]. Most solids are much weaker in tension than in compression and so the large tensile stress near the rear of the stone can be expected to make the material fail.

However, more recently it has been suggested that shear waves generated at the outer surfaces of the stone may contribute more to the maximum tensile stress in the stones [**58**, **59**, **72**]. The shear waves are generated by two mechanisms: the passage of the shock wave in the fluid outside the stone, which can be thought of as squeezing the stone [**59**], and the internal wave that interacts with the surface [**58**]. The shear waves propagate from the surface of the stone to the centre of the stone where they result in large tensile stresses. *In-vitro* experiments [**72**] demonstrate that both types of shear wave are important in the production of fracture in artificial stones.

It is noted that many materials are weak in shear, particularly if they consist of layered structures, as the bonding strength of the glue often has a low ultimate shear stress. It is also likely that, in stones with a strong lamellar internal structure, the shear stress may play an important role in fragmentation [**73**].

The rich set of phenomena that occur when a lithotripter shock wave is incident on a kidney stone is illustrated in Fig. 4. This figure results from a computer simulation which incorporates much of the important physics associated with the stress waves resulting from the passage of a lithotripsy shock wave through a stone. The code uses the same principles described in reference [**58**] but calculates the solution in three dimensions using the geometry and material properties of a human kidney stone [**74**]. The images show regions of high tensile stress and shear stress within the stone and indicate that shear waves are responsible for the highest tensile stresses in this particular stone.

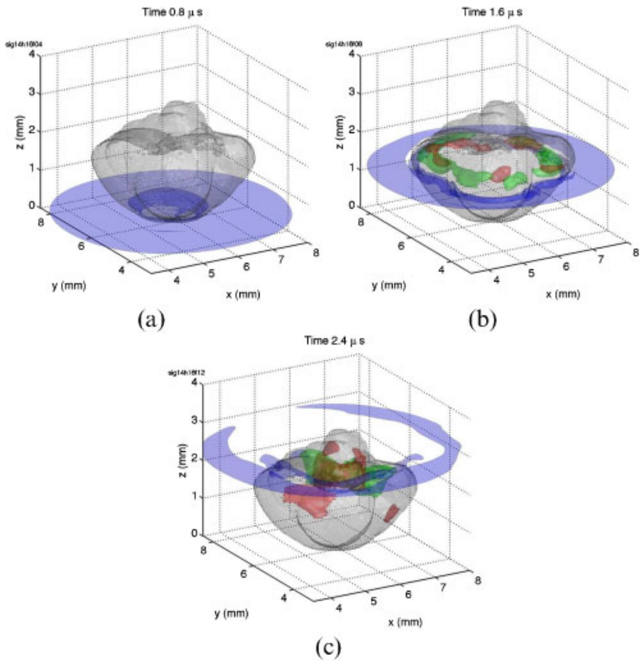

Fig. 4 Snapshots from a numerical simulation of the stress waves in a natural stone where the stone is surrounded by fluid. The blue areas are isobar surfaces for a compressive stress above 20 MPa and show the incident shock wave coming from below. Inside the stone, the red areas are the isobar surfaces for the principal tensile stress to exceed 60 MPa, and the green areas are the isobar surfaces for the maximum shear stress to exceed 40 MPa. The shock wave was incident from below and was modelled after the shock wave shown in Fig. 2(a). (a) This snapshot shows the stress field when the shock wave is just incident on the proximal surface of the stone. (b) This snapshot was chosen at the point where spall should be a maximum as it corresponds to the time that it takes for the shock front to propagate through the stone and to reflect from the distal surface as a tensile wave. The absence of tension indicates that spall would not significantly contribute to the tensile stress. Rather, it can be seen in (b) that the compression wave that rings the equator of the stone is generating shear (green) and tensile (red) stresses at the edge of the stone. (c) This snapshot shows a region of high tension near the distal surface; this is predominantly due to the presence of the shear waves generated in the snapshot (b) that have propagated to the centre of the stone

3.2 Cavitation

At the focus of a SWL, the pulse can generate 'inertial acoustic cavitation' in the liquid (not to be confused with the pulsations of the 'gas globe' at the spark source of an electrohydraulic lithotripter). The term 'inertial acoustic cavitation' encompasses a range of behaviours [**75**]. The shock pulse usually acts upon some pre-existing microscopic gas bubble in the liquid; this may be left over from the passage of previous shock waves (estimated to be around 40 μm in radius [**76**, **77**]), or, for the first shock wave, formed by the presence of natural weak spots at biological interfaces. Provided that the bubble is initially neither too small that surface tension hinders its growth, nor too large that it responds insufficiently quickly to the SWL pulse [**22**], then it can nucleate inertial cavitation when subjected to the SWL pulse [**76**]. The nucleation bubble is compressed by the compressive part of the pulse and then expands (through a complicated series of processes [**78**]), emitting a spherically spreading shock wave which is intense, close to the bubble. This first compression is labelled α in Fig. 5. It then expands under the tension to many times its original size (β in Fig. 5), and then collapses (χ in Fig. 5) to emit a second shock wave as it begins its next expansion. Subsequent decaying pulsations (ϕ in Fig. 5) and emissions occur, but these are probably insignificant to stone fragmentation. Note that, in the idealized simulation in Fig. 5 on which this description is based, the bubble is assumed to remain spherical and intact at all times. While in broad terms this description is useful, the details of the bubble pulsations may include loss of spherical shape and bubble fragmentation on collapse (which can be reversed through coalescence during bubble expansion [**79**], maintaining the usefulness of the above broad description). One particular category of non-spherical bubble behaviour is the involution of the bubble wall on collapse, which can lead to the formation of a high-speed liquid microjet [**80**]. (A movie of this effect can be found at the online version of reference [**78**].) The impact of jets on solid surfaces can erode them directly. However, the impact of the jet on the bubble wall towards which it has travelled can generate a blast wave [**81**] which, close to the bubble, can be very much greater than the pressures in the SWL pulse [**78**, **82**, **83**] (a feature which is missed by those simulations that are required to stop prior to the moment of liquid–liquid impact [**84–88**]). The strong pressure and flow features which occur following the jet impact may significantly influence stone erosion and also intensify the collapse of neighbouring bubbles. Cavitation therefore includes a range of phenomena which could potentially damage a stone surface, including microjetting (through direct solid impact and through a blast wave), the individual spherically

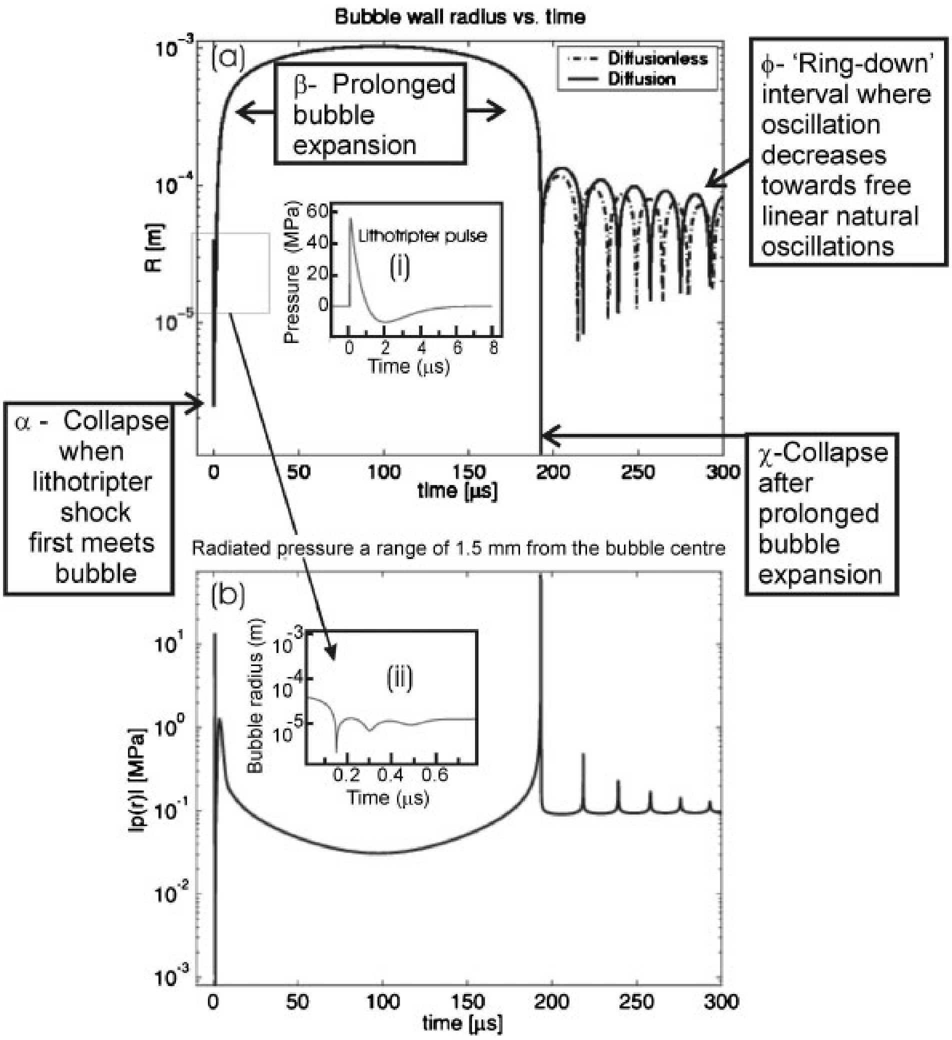

Fig. 5 An air bubble of initial radius 40 μm in water is subjected in the free field to the lithotripter pulse shown in inset (i) (peak positive pressure, 56 MPa; peak negative pressure, −10 MPa). (a) The bubble radius–time history, as predicted by the Gilmore model, is shown for conditions with (solid curve) and without (dashed curve) mass flux across the bubble wall. Note that the inclusion of diffusion [**75**, **76**, **78**, **136**, **216**] makes the final bubble size greater than the initial size, with a consequent slight increase in the period of the oscillations (i.e. a reduction in the frequency) at the timescales labelled ϕ. Inset (ii) shows the micro-rebounds that are visible in the fine detail of the collapse which occurs at around $t = 0$. Similar features are seen in the computational fluid dynamics predictions [**78**]. (b) On a common time axis with (a) and for the same bubble collapse, the pressure that would be measured 1.5 mm away from the bubble centre is shown. Two main emissions (at $t \approx 0$ μs and at $t \approx 190$ μs) are associated with rebounds in (a), subsequent emissions being smaller. Comparison of (a) with (b) suggests that the source of the first peak is the cavitational collapse which results when the lithotripter first meets the bubble (labelled α). After this collapse, the Gilmore model suggests that the bubble undertakes a prolonged expansion phase (labelled β), before collapsing again, at which time the second peak in acoustic emission and luminescence is generated (labelled χ). The bubble must remain spherical and intact in the Gilmore model, so that after this second collapse the bubble oscillates with gradually decreasing amplitude, with a frequency which tends ever more closely to its 'Minnaert' frequency as time proceeds (labelled ϕ). (Reprinted with permission from Leighton *et al.* [**136**])

spreading shocks if the bubble is close to the stone, and cloud cavitation effects when the shocks emitted by bubbles far from the stone cause a self-concentrating collapse of bubbles closer to the stone [**75**]. As a result, measurement of one effect (e.g. far-field acoustic emission) can, if interpreted carefully, be used to infer the quantitative degree of some other effect of cavitation (e.g. erosion, chemical processing, or luminescence) [**89–92**]. This approach has been exploited in SWL (see section 5.4).

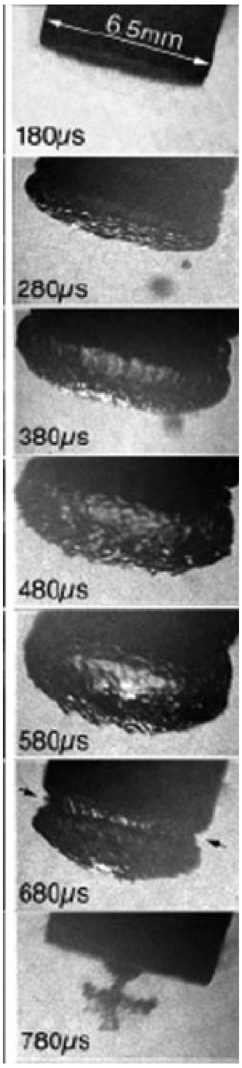

Fig. 6 High-speed movie images of the bubble cloud induced on the proximal surface of an artificial stone in response to a lithotripsy shock wave. The shock wave is incident from below and arrives at 180 μs. At 280 μs (100 μs after the arrival of the shock wave) a large bubble cloud grows on the stone. The bubble cloud grows for hundreds of microseconds. During the collapse the bubble cloud pinches in (arrows on the frame at 680 μs) and collapses to a jet on the surface. (After Pishchalnikov *et al.* [**94**])

Cavitation is principally a surface-acting mechanism, and experiments indicate that in SWL a cloud of cavitation bubbles is formed which acts most strongly on the proximal (shock wave incident) surface of the stone [**70**, **93**, **94**]. Figure 6 shows high-speed movie images of the bubble cloud induced on the proximal surface of a kidney stone in response to a lithotripsy shock wave. Numerous studies indicate that cavitation plays a role in stone fragmentation. There is evidence that it plays an important role in grinding up small fragments that may not be conducive to being fragmented by direct stress effects [**57**].

A drawback of having cavitation present is that the cavitation bubbles that are created by a lithotripter shock wave can take about 1 s to dissipate [**76**]. While a small number of remnant bubbles can be useful in nucleating the subsequent cavitation events, as described above, large numbers of remnant bubbles would in principle be effective at shielding subsequent shock waves [**22**, **95**, **96**]. The interdependence of the bubble cloud dynamics and the pulse with respect to the firing rate has been demonstrated *in vitro* [**97–99**]. The data indicate that delivering shock waves at a rate faster than 1 Hz results in unwanted shielding and the shielding increases as the rate increases. The clinical effects of this are discussed in section 5.3.1.

3.3 Fatigue

It should be commented that, regardless of the mechanism or mechanisms that contribute to SWL, it is likely that stones fragment through a fatigue process. *Fatigue* refers to the progressive development of cracks in a material over subsequent loading, which in this case is due to the thousands of shock waves delivered during a clinical SWL treatment [**100**, **101**]. The cracks are nucleated at sites of small imperfections that occur in almost all materials. The imperfections amplify stresses many times [**75**, **78**, **102**] and cause the imperfections to grow into microcracks. With an increasing number of shock waves the microcracks grow into macrocracks and eventually produce cracks large enough to induce failure. Any of the mechanisms discussed above could drive fatigue.

3.4 Aspects of the field which promote each mechanism

While the pulses used in SWL were not designed on the whole to promote any particular mechanisms, aspects of the field do act in this way. For example, a large focus (larger than the size of the stones) promotes the generation of shear waves at the outer edges of the stone, an effect which is predicted to contribute to the tensile stress inside the stone. Cavitation tends to be promoted by having longer periods of tension, since the bubble must have sufficient time to grow (even though it remains expanded long after the tension has ceased (Fig. 5)) [**22**]. As a result, the presence of energy in the range of hundreds of kilohertz (Fig. 2) associated with the tensile tail of the pulse promotes cavitation that would not occur if all the energy was at higher frequencies. A short interpulse time would mean that the shock wave would encounter remnants of previous cavitation which, depending on the specific circumstances, could nucleate further cavitation or shield the focal region from the incoming shock wave [**22**]. As consensus on mechanisms is reached, the manipulation of the acoustic field becomes a plausible pathway for innovation to be introduced into the next generation of lithotripter designs.

4 ADVERSE EFFECTS

Despite the widespread use of SWL, the treatment may induce some collateral damage (haemorrhages, thrombi, arrhythmias, vasoconstriction, hypertension, reduction of renal functionality, infections, alterations to the autonomous neural system, and the release of cell mediators and hormones [**103–110**]). Although, very occasionally, acute effects can be life threatening [**111**, **112**], after most treatment sessions for stones in the upper urinary tract, acute complications are not often reported and rarely require specific treatment [**110**]. However, when direct assessment could be made of collateral tissue damage (which usually implies the use of animal models), a clinical dose of shock waves has led to injury in most if not all subjects [**113**] and, in the absence of evidence to the contrary, the working assumption is that the same applies to human patients. Most treatments result in haematuria, indicating the breaking of blood vessels, although in most cases this appears to resolve naturally over a day or two or, at most, several weeks [**114**]. Inflammation and scarring can follow from such localized haemorrhage [**13**, **113–117**]. A dose-dependent loss of functional renal volume has been observed in the few laboratory studies that have followed the progression of a lesion after SWL [**13**, **113**, **118**]. Patients who receive multiple sessions of SWL may be at increased risk of long-term effects such as the transition from calcium oxalate stones to stones of calcium phosphate and brushite [**119**], and also hypertension [**120**]. Most recently there has been a report associating the onset of diabetes mellitus with SWL dose [**121**] although other studies contest this association [**122**, **123**]. However, assessment of these long-term effects is complicated owing to the varied natural history of recurrent stone formers and by differences in treatment protocols (see section 5.3) [**110**].

Standard procedures for assessing acute damage immediately after SWL may be insufficiently sensitive to detect all damage. A clinical dose on a pig model caused haemorrhage in aproximately 5 per cent of the functional renal volume [**124**, **125**], a level which would probably not be detected in typical X-ray or computed tomography (CT) scanning, but which could be found through histological examination or, possibly, magnetic resonance imaging (MRI) or positron emission tomography imaging [**126**]. Furthermore, this type of injury is not always accompanied by subcapsular bleeding, and hence the failure to observe a haematoma when a patient is examined through X-ray or CT scanning after SWL (the common methods for assessing patients after SWL) does not mean that injury was avoided [**126**].

Although patients experience significant pain from kidney stones, SWL also induces pain which in some patients is so significant that they cannot tolerate the procedure (in two linked clinical trials, 18 out of 118 patients could not tolerate SWL in the first trial, and three out of 85 in the second trial [**102**]). Sources with larger apertures should reduce pain (section 5.2).

The mechanism for tissue damage in SWL is generally accepted to be inertial cavitation [**104**, **105**]. Cavitation from SWL can be detected by using B-mode imaging [**127**, **128**] and passive monitoring of the 'signature' acoustic emissions from cavitation [**28**, **29**, **75**, **77**, **82**, **89**, **102**, **129–137**] and, with these techniques, cavitation has been detected during SWL *in vitro*, *in vivo*, and during clinical therapy. However, Bailey *et al.* [**138**] conducted experiments to test for the occurrence of cavitation specifically in the kidney parenchyma, where cavitation inception would be expected to be more difficult [**71**, **79**, **102**, **139–143**]. Using a pig model, Bailey *et al.* [**138**] found that, while cavitation occurred almost immediately in the urine, the first unambiguous cavitation signatures observed from tissue do not occur until around 1000 shock waves have been delivered. It has been suggested that bleeding is a necessary precursor to the occurrence of extensive cavitation [**144**]. This line of reasoning would hypothesize a two-step process in the progression of tissue damage in the kidney. A first stage, consisting of the initial rupture of the tissue (with minimal or no cavitation activity present) resulting in pooled blood, is followed by a second stage where the pooled blood provides favourable conditions for extensive and spreading cavitation to produce significant damage to the tissue. It has been proposed that the initial rupture might be caused by expanding cavitation bubbles [**139**, **140**, **145**] or by direct mechanical effects of the shock waves on the tissue [**54**, **100**, **146**]. Neither hypothesis has been demonstrated *in vivo*.

5 CHALLENGES AND OPPORTUNITIES

The present authors are aware that, because the possible opportunities which will be discussed in this section are necessarily at an early stage, many of these are suggestions based on a small number of studies and are flagged as areas for further research rather than innovations which are proven in clinical trials and will appear in the next generation of lithotripters. This illustrates a key conundrum with innovation in an established field, which will now be discussed.

5.1 The gap between innovation and commercial implementation

Exploiting innovation in a mature technology usually requires that industry be placed in a position where the benefits and risks warrant the investment. However, the ability of health services or research laboratories (in academia, government, or industry) to place manufacturers in that position depends on the market and regulatory environments [**15**, **147**]. The particular environment for SWL was described in section 1. Although the market for an established technology can support development, there are aspects of any mature technology which can hinder research and innovation. Citron [**15**] listed regulatory environments, reimbursement policies and practices, product liability, and excessively high expectations as being of particular relevance for innovation with medical devices. Considerations by industry of intellectual property and business models, and the attractiveness of younger technologies to the next generation of researchers and sponsors, can hinder innovation in an established technology.

For such a mature field to foster and exploit innovation, the community must maintain and develop, where necessary, appropriate standards and guidelines and encourage the dissemination of data, where possible, on the performance of specific devices [**148**]. SWL fields are challenging to measure, and the development of new sensors (with bandwidths, linear input–output ranges, frequency and phase calibrations, invasiveness characteristics, ruggedness, etc., which are increasing appropriately to SWL fields) would be expected to proceed hand in hand with the evolution, where appropriate, of current phantoms, standards, and guidelines.

5.2 The problems with consensus

Consensus establishes a baseline from which to progress, and lack of consensus stimulates enquiry. However, consensus can be misleading, based for example on received wisdom, pedagogy simplified for a specific audience, commercial interests, or impressive presentations by research groups. The audience for consensus in SWL is broad, not only in terms of disciplines (physicists, engineers, materials scientists, clinicians, etc.) but also in terms of skill and experience (e.g. in the clinical field ranging from the students and their lecturers to consultant urologists and medical physicists). In such a community, the tests for repeatability, reproducibility, and counter-explanation are particularly valuable.

Just as the presence of consensus raises issues, so too does its absence. Despite the great amount that has been learnt about SWL and how it works, there is still no consensus as to how shock waves fragment stones, and what the consequences of the adverse effects are. Because of this, there are no metrics by which lithotripter companies can design lithotripters in order to enhance fragmentation while reducing tissue damage. This can be contrasted with an aircraft wing, where the strength of the materials used is well understood and the designers can optimize to reduce the weight while still being able to tolerate the forces generated in flight. Lithotripter designers therefore are probably affected by other pressures. For example, access to the US market requires approval by the US Food and Drug Administration [**149**] and, if ‘substantial equivalence’ to a predicate device can be demonstrated, then ‘premarket approval’ can be obtained with either limited or no clinical trials. The time and cost savings associated with pre-market approval provide a strong incentive to design lithotripters that produce a field similar to pre-existing machines. Without metrics for fragmentation and tissue damage, designers are not in a position to resist such pressures easily.

A specific example can be found in the discussion of the size of the focal zone. The Dornier HM3 is considered by many to be the gold standard for shock wave lithotripters. The HM3 has a relatively large focal zone (12 mm wide and 85 mm long at the −6 dB points) and a moderate peak positive pressure (40 MPa) as measured in water. Second- and third-generation devices tend to be more tightly focused, with higher peak positive pressures and smaller focal zones. For example, the −6 dB contour Stortz Modulith SLX (which has a peak positive pressure of 115 MPa) is 4 mm wide and 35 mm long. However, it is not such a simple thing to say that the focus of the SLX is smaller than that of the HM3, because the temporal peak pressure at the −6 dB points of the SLX is about 58 MPa, which is nearly 50 per cent greater than the value at the centre of the focus of the HM3 (40 MPa). Therefore, if the focal zone were defined in terms of an absolute pressure threshold (say, 35 MPa) then the HM3 would have a smaller focal spot than the SLX. If the effectiveness were better measured by the total acoustic energy delivered to the stone [**150**], then the comparison would require knowledge of the size and shape of the stone. Furthermore, it presupposes that a single dominant mechanism for fragmentation has been identified, when it is possible that a combination of mechanisms could be important for a given stone (e.g. cavitation for opening surface cracks, followed by direct stress to extend these deep into the stone).

With these comments in mind, the perceptions regarding the size of the focal zone can be addressed. At first sight, a smaller focal zone may seem advantageous as it should allow for a greater fraction of the energy generated by the source to be incident on the stone, and for there to be less acoustic impact on the surrounding tissue. A second advantage is that the smaller focal zone is generated because the diameter of the shock wave source is larger. This means that the pressure on the surface of the skin is less, which typically results in less discomfort for the patient. This was the initial motivation that resulted in smaller-focal-zone lithotripters (section 4). Some groups would therefore support the use of a smaller focus [**151**].

Other groups would, however, take the opposite view, citing two potential drawbacks with narrow focal zones. First, the kidney stone is in continuous motion during SWL and this can cause the stone to be placed outside the focal zone [**102**, **152**, **153**]. One *in-vitro* study compared the effect of stone motion on the fragmentation efficiency of the Storz Modulith SLX [**153**]. An artificial kidney stone (a cylinder 6.5 mm in diameter and 7 mm long) was continuously translated laterally to the acoustic beam (as would occur for respiratory motion) in an oscillatory motion. The study showed that motion of 10 mm amplitude resulted in a 50 per cent reduction in stone fragmentation. The adverse effects of movement induced by respiration might be reduced by gating the source to the respiration [**102**] although this is not common practice.

A second potential drawback with a smaller-focal-zone lithotripter is that, for stones larger than the width of the focal zone, the energy deposited into the stone can be low [**150**]. This would be particularly detrimental to treatment if the shear wave mechanism (described in section 3.1) were to be important for fragmentation under the given conditions, since this mechanism requires that the outer surface of the stone is subject to high-pressure waves to generate large stresses inside the stone [**58**, **59**]. Indeed, an electromagnetic lithotripter employing a wide focal zone was designed based on the ‘squeezing’ principle [**59**], and this has been shown to be effective at fragmenting stones [**154**]. Animal studies have shown that this lithotripter produces very little tissue injury in a pig model [**155**]. However, this lithotripter has yet to be distributed in the USA or Europe.

The barrier to understanding fragmentation and the mechanisms for adverse effects appears to be high. Comprehensive experimentation and modelling are tasks made daunting by the natural variation in numerous parameters. These include, for example, the size of the patient, the different types of tissue present on the propagation path to the stone, the existence of cavitation nuclei and bubble remnants surrounding the stone, and of course the variation seen in the stones themselves (the size, composition, geometry, and location, e.g. within the kidney or in the ureter). The challenge to the research community to understand the mechanisms, even if in a simplified form, still exists.

5.3 Treatment protocols

Treatment protocols vary greatly between centres. This introduces variables in addition to those associated with the physical scenario (such as were listed in the preceding paragraph). Examples of variables include the type of lithotripter and chosen pulse regime (the clinician typically controlling three parameters: number of shock waves, strength, and rate), the assessment and follow-up protocols, the methods for anaesthesia, the method by which stone size is assessed, the imaging used to assess outcomes, and the definition of what constitutes a successful outcome (section 2.2). While these variations can complicate comparisons between studies, and provide too many variables to consider the concept of an 'optimized protocol' to be realistic, it does provide the latitude to test whether simple changes to clinical protocols can reap significant rewards.

Even without the development of new lithotripters, there are a number of strategies by which the performance of current lithotripters can be enhanced through the appropriate protocol by which SWL is delivered, including the possibility of pre-treatment, the schedule for targeting checks, the settings for the strength and rate of delivery of the shock waves and whether (and how) these are adjusted during treatment, and whether the protocols are the same for all patients or are tailored to the individual patient. Some of the protocols of current interest for either improving fragmentation efficiency or reducing tissue injury are discussed below.

5.3.1 Rate of delivery of shock waves

Section 3.2 described how an increased firing rate can shield the stone from the shock waves because of acoustic scattering and absorption by the remnants of cavitation bubbles which persist from one shock burst to the next. *In-vitro* stone fragmentation studies demonstrated that, as the rate at which shock waves were delivered was decreased from 2 Hz to 0.5 Hz, the fragmentation of stones improved [**97**, **156**, **157**]. These results were confirmed *in vivo* using a pig model into which stones were surgically implanted [**73**]. Subsequent prospective clinical trials indicate that the stone breakage rates are better at a 1 Hz firing rate than at a 2 Hz firing rate [**158–160**]. One study found no improvement in stone breakage with reduced firing rate [**161**]. Critical meta-analysis of these various studies concluded that treatment at a 1 Hz firing rate was more effective than treatment at 2 Hz [**162**]. Further studies into tissue damage with dog and pig models have shown that damage is dramatically reduced as the rate of shock wave delivery is lowered [**125**, **163**, **164**]. These data suggest that, by slowing the rate, SWL can be administered more effectively and more safely, albeit at the price of a longer treatment time.

5.3.2 Pre-treatment

The vasoconstrictive reaction of the kidney in response to shock waves has been well documented using a porcine model [**165**]. The data in the pig model indicate that, for a clinical dose of 2000 shock waves at 24 kV with a Dornier HM3, blood flow to the kidney is reduced for up to 4 h after treatment [**166**]. The resulting acute lesion in the pig kidney varied between 1.6 per cent and 7.6 per cent of the functional renal volume, with the higher percentage occurring for smaller kidneys [**167**]. A curious result from these studies was that treating pigs with 100 shock waves, waiting for 3 min, and then treating with 2000 shock waves resulted in a lesion that was 0.3 per cent of renal volume [**168**]. It was hypothesized that the initial 100-shock-wave volley induces a vasoconstrictive response in the kidney that protects the kidney from the damage by the subsequent shock waves. Recent Doppler ultrasound measurements support this hypothesis [**169**]. The vasoconstrictive response has so far only been demonstrated in animals [**126**, **165–170**], but it seems reasonable to expect that it will translate to patients, and the pre-treatment protocol may therefore provide a vehicle by which damage may be substantially reduced. There may be parameters with the pre-treatment (e.g. the number of shock waves and the waiting time) that can further improve the protection protocol. This effect also emphasizes the need for basic *in-vivo* studies; such an effect could not be expected from a phantom or even excised tissue.

5.3.3 Power ramping

A protocol which is related to the pre-treatment discussed in the preceding section is the topic of power ramping. During any SWL treatment, the lithotripter operator has flexibility to alter the shock wave setting during treatment, and lower settings may be used at the start of treatment and after re-targeting. The use of initially lower settings at the start of the treatment is a practice that may have been introduced to give the patient the opportunity to acclimatize to the procedure [**114**, **126**]. *In-vitro* studies have shown that stone fragmentation can be improved by 'power ramping', where the shock strength is increased in stages from lower to higher values during treatment [**171**]. A subsequent clinical trial of 50 patients confirmed greater success for stepwise power ramping compared with conventional protocols [**172**].

5.3.4 Exposure and dose

SWL probably has a greater range of bioeffects (both beneficial and adverse) than any other routine application of ultrasound to the human body and, even within a given bioeffect (say, stone fragmentation), a range of mechanisms probably applies. Because of this, the terms 'exposure' and 'dose' present particular difficulties.

It is simpler to be precise about 'exposure' (compared with 'dose'), since 'exposure' refers to a quantity which can be measured in a standard medium (degassed water for ultrasound, just as dry air is used for X-rays) [**173**]. Perhaps the most constructive concept of the absorbed dose for ultrasonic bioeffects would refer to a useful measure (i.e. one which correlates with the bioeffect) of the active 'ingredient' which crosses some exposure barrier (e.g. the skin) and then is absorbed or taken up by tissue *in situ*. However, across the relevant fields (pharmacology, radiation safety, etc.) there is a plethora of definitions for 'dose', made consistent through qualifications such as 'absorbed dose', 'active dose', or 'biologically effective dose' [**174**]. Some, such as 'equivalent dose', are weighted to reflect the sensitivity (e.g. of a particular organ or tissue) to a relevant risk [**175**]. Key to these is an understanding of the bioeffect and its correlation to the measure of ingredient [**176**, **177**], information which is incomplete with respect to SWL (in common with other ultrasonic uses).

The issue with 'exposure' is choosing exactly which quantity it is appropriate to measure. The most critical of many factors (including ease of measurement) is the extent to which a given parameter reflects the bioeffect of interest. It is unlikely that a single 'exposure' parameter is the best choice for consideration of both, say, hypertension and stone fragmentation, and hence best judgement must be used to find one or more useful compromise exposure parameters. The multiple mechanisms and effects associated with SWL (see above) mean that definition of a single universally relevant 'ultrasonic dose' is unlikely. This is because there is the additional complication that, unlike 'exposure', this 'dose' would encompass a reflection of the extent to which the tissue (which ranges from the stone to kidney parenchyma) 'absorbs' whatever is deemed to be the parameter of interest (which may differ for effects produced by cavitation and shear).

In SWL it is common to find reference to the total energy delivered to the stone or patient, based on the energy or power setting on the lithotripter and the number of shock waves delivered. Such usage probably more appropriately reflects an 'exposure' than a 'dose'. There are many studies that show that tissue damage is sensitive to the amplitude and number of shock waves delivered. Studies in canine and porcine models have shown that damage increases with increasing number of shock waves [**124**, **178**]. In particular, treating with up to 1000 shock waves results in little damage to the kidney [**144**] and this corresponds to the point at which cavitation has been detected in the renal parenchyma [**138**]. It has also been shown in dog and pig models that damage to the kidney increases with increasing power, energy, or voltage setting of the lithotripter [**179**, **180**]. This suggests that the smallest numbers of shock waves should be used at the lowest amplitude necessary to fragment a stone. This motivates the need for accurate targeting during lithotripsy to improve the percentage of shock waves that hits the stone, and reliable end-point detection in order to reduce the over-treatment to make sure that a stone is fragmented. This topic will be explored in the next section.

In conclusion, however, while there are well-established methods for describing exposures in terms of the number and strength of shocks, this does not afford us the same ability to predict the bioeffect for SWL as do the 'doses' used in chemistry or ionizing radiation. Changing the rate of firing would, for example, maintain the above exposure level but could change the bioeffect (as discussed in section 5.3.1).

5.4 Targeting and end points

Although the lack of standardized treatment protocols or measures of success discussed in the previous section complicate the issue, it is commonly acknowledged that currently around 30 per cent to 50 per cent of patients need re-treatment with SWL [**37**, **38**], with some of these patients undergoing more than three treatments for the same stone [**26**, **39**]. One study [**102**] found that only 19 out of 79 treatments were successful but noted a possible contributor to this. The in-theatre clinician during the trial was only able to identify correctly seven of the 19 successful treatments (36.8 per cent sensitivity): four treatments, which at follow-up 3 weeks later proved to be unsuccessful, were considered by the in-theatre clinician to be successful, and 12 treatments, which at follow-up proved to be successful, were in theatre thought to be unsuccessful [**102**]. This suggests that the current imaging systems are largely inadequate for indicating when stone fragmentation is complete [**102**, **181**]. Improving the ongoing diagnostic capabilities of the operator during the treatment could have very considerable benefits. The operator has a significant role in minimizing the ionizing radiation exposure by restricting the fluoroscopy exposure time within the constraint of achieving accurate shock wave targeting of the stone [**182**]. The operator also selects the shock wave strength setting, typically using the highest setting compatible with the level of pain tolerated by the patient [**26**]. Ideally the operator would also have a role in limiting the morbidity associated with shock wave exposure, e.g. by terminating the treatment when the stone has fully fragmented or in the case where a stone appears resistant to SWL.

Developments to ameliorate this include an in-clinic active targeting [**183–185**] and passive acoustic monitoring system [**78**, **82**, **102**, **136**, **137**] to provide more information on treatment progress and targeting during clinical SWL, and therefore may allow the operator to exercise greater control over many of the factors that influence re-treatment rate and morbidity. This automated passive acoustic sensor achieved a greater sensitivity than the in-theatre clinician did [**102**, **136**, **137**]. Clinical trials are yet to be completed to determine the extent to which these promising results translate into a reduction in retreatment rates. Maintenance of accurate targeting throughout the treatment can be expected strongly to influence treatment effectiveness [**186**], as can improved ability to assess the end point; this will be explained in the following section.

5.5 The patient pathway

Since its introduction into health care in 1985 [**187**], the concept of 'clinical pathways' has gained ground in many countries [**188**, **189**]. The 'patient pathway' has become a significant issue in the UK, reflecting the demands of its 'free on the point of delivery' mode of health-care provision. The extent to which this is perceived to be an important issue in other health provision systems will reflect the relevant factors that hinder local operation and improvements [**2**]. The patient pathway describes the route taken by the patient through the health-care services. It encompasses all the personnel, testing, treatment, waiting, etc. that a patient must negotiate in progressing from one part of the health-care system to another and, in particular, the route from first symptom to final discharge. The UK philosophy [**190**] is that, in general, savings and improvements for the patient, staff, and health-care system follow if the path is condensed, e.g. by reducing the number of times that the patient needs to visit the hospital to see different people. Reduction in inaccurate diagnoses, ineffective treatments, and waiting times are all ways of condensing the patient pathway. If condensing the patient pathway becomes a priority, then the environment may stimulate and support engineering innovations (in addition to the administrative and medical options) which can achieve this objective.

Although inaccurate initial diagnosis of kidney stones is not usually a problem, selecting the appropriate treatment modality is more challenging. It has long been recognized that certain stones do not respond well to shock waves [**191**]. X-ray or CT scanning can be employed to assess the structure of kidney stones, and has the potential to predict their response to SWL [**192–194**]. In addition, patient factors, such as skin-to-stone distance, have also been shown to impact on SWL [**195**]. Use of SWL on stones that are resistant to shock waves results in the patient pathway containing wastage, particularly in terms of multiple treatments and inability to recognize stones that will break from those that will not.

Real-time monitoring of the effectiveness of SWL could greatly benefit the patient pathway, if it is accurate [**196**]. Real-time diagnostics include passive acoustic monitoring (which, in addition to the techniques of section 5.4, include alternative approaches [**13**, **82**, **132–135**]), improved active ultrasonic diagnostics [**197**], and imaging. An obvious example of this would be to allow the clinician to adjust the targeting in real time to ensure effective stone fragmentation using some sensor [**102**, **183–185**]. A more revolutionary adjustment would be to use such a sensor as a diagnostic tool while undertaking a testing period of only a few hundred firings in order to diagnose (perhaps before the onset of any adverse effects [**144**]) whether a stone is likely to be fragmented by SWL [**196**]. If this diagnostic session determines that the stone will not be susceptible to SWL, the patient could be sent directly for surgery (so bypassing repeat hospital visits for unsuccessful SWL and reducing the possibility of adverse effects) [**196**]. Given that multiple SWL treatments can increase the possibility of adverse effects (section 4), then elimination of ineffective SWL sessions can mitigate against the possibility of adverse reactions, which not only harm the patient but also consume further health service resources. This is one example of how the patient pathway for kidney stone treatment might be reduced.

5.6 Competing technologies

Although SWL has dominated as the preferred modality for treating kidney stones since the 1980s, there have always been competing technologies. Early examples included alternative ways of generating shock waves, such as liquid drop impact, and the use of small explosives, lasers, and ultrasonically activated invasive probes [**198–202**]. The principal competition today is ureteroscopy, a procedure in which an endoscope is inserted through the urethra, across the bladder, and up the ureter to the kidney. The endoscope provides the surgeon with direct visual imaging of the interior of these structures. Ureteroscopy can be used as a diagnostic tool and also as a vehicle to delivery therapy. Here the term ureteroscopy is used to describe the treatment of kidney stones which is accomplished by inserting implements through a channel in the endoscope; these implements include optical fibres for delivering intense laser beams for ablating stones, and baskets for grabbing and retrieving fragments [**203**, **204**]. Ureteroscopy is minimally invasive, as the endoscope enters the body through a natural orifice. Ureteroscopy offers success rates between 81 per cent and 94 per cent; the most recent AUA–EAU guidelines on the management of ureteral calculi [**44**] commented that, compared with SWL, ureteroscopy 'has developed into a safer and more efficacious modality for treatment of stones in all locations of the ureter'. The invasive nature of ureteroscopy demands more training by the surgeon and more support facilities than SWL and for this reason tends to dominate at large hospitals [**9**]. After two decades or so as the favoured technique, SWL appears now to be in decline. Unless there is a significant advance in SWL, it appears that ureteroscopy will soon become, if it is not already, the preferred modality for treating smaller kidney stones.

For large stones, greater than 10–20 mm in diameter, the amount of debris produced by fragmentation, either by SWL or ureteroscopy, is too much to be passed effectively through the ureter. For large stones, a percutaneous approach is used, in which a small tube is inserted through the flank of the patient into the kidney [**44**]. Because the tube does not need to pass through the small lumen of the ureter, its bore can be much greater than those used in ureteroscopy, and it therefore allows for the efficient removal of large volumes of fragmented material which is not easily passed through the ureter.

6 CONCLUSIONS

Following its introduction in 1980, SWL rapidly evolved into the preferred modality for the treatment of kidney stones. There has been a surprising lack of advance in SWL since the introduction of Dornier HM3. There are multiple factors that may have led to this: first, the initial design appears to have been excellent and so there were few easy paths for improvement; second, there has been no consensus on the basic mechanisms by which shock waves fragment stones, which is arguably necessary in order to improve current designs; third, the high acceptance of SWL meant there was little incentive to innovate. Today industry faces fewer sales opportunities for new products, and clinicians and researchers see greater training, funding, and breakthrough opportunities in alternative modalities. There are still innovative ideas, some of which could offer dramatic improvements to patients and the health-care services (section 5). However, the time when industry would fund such innovation, or government sponsors support it in preference to younger fields, will pass unless an overwhelming case can be made. Such cases require that the innovators encompass the gamut of research and study techniques, to bridge the gap to those who would exploit and commercialize the ideas. In addition to the emerging ideas described in section 5, shock wave therapy may find application in new arenas for urolithiasis in the developing nations or further afield [**205**], and may provide effective therapies for musculoskeletal indications, such as plantar fascitis, heel spurs, epicondylitis, and non-union of fractured bones [**26**, **206–209**]. There are also currently experimental bactericidal, cancer, and cardiac treatments [**206**, **210–215**].

The use of SWL on humans has produced a wealth of benefits beyond the millions of patients who have been successfully treated. It has allowed the scientific community to study high-amplitude shock waves, and the effects that these generate, in the human body. This not only has helped to foster the active research community but also has provided basic information (e.g. on cavitation nucleation in humans *in vivo*). Without this, the current developing biomedical ultrasound technologies would have been built on a smaller and less informed scientific community.

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