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Chapter 4

# **ESWL: Efficacy, Safety, and Regulation by the Food and Drug Administration**

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## INTRODUCTION

Extracorporeal shock wave lithotripsy (ESWL) is a novel approach to stone treatment; it has existed only since the beginning of the 1980s and is unlike any of the other alternatives in either cost or character. Currently approved for use only for stones in the kidney and upper ureter, it has the potential to be extended to treatment of lower urinary stones, gallstones, and, possibly, a diverse range of other medical problems. Only one manufacturer, Dornier Medical Systems of West Germany, presently has approval to market an ESWL device in the United States. However, at least three American firms, as well as manufacturers in other countries, are working on their own extracorporeal lithotripters.

This chapter first describes the Dornier lithotripter and its early development in West Germany. It then discusses the investigational period of the device in the United States that culminated in the Food and Drug Administration's (FDA) pre-market approval of the device in December 1984. The next section of this chapter summarizes the current status of ESWL and the evidence on its safety and efficacy. The final section concludes with a brief discussion of other ESWL devices currently under development in the United States and potential future applications of ESWL.

## DESCRIPTION OF THE DORNIER LITHOTRIPTER

In the Dornier lithotripter, shock waves are generated outside of the body and transmitted through water and the outer tissues of the body to the stone in the kidney or upper ureter. Immersion of the patient in a water bath allows the shock wave to pass from the generator (an electrode) to the patient without either damaging tissue or damping the wave, since water and tissue have similar acoustic impedance properties. The water's temperature, gas content, and conductivity are controlled by a treatment system in the lithotripter (187).

The shock waves are generated by an underwater spark from an electrode located at the first geometric focus of a semi-ellipsoidal reflector. The stone is positioned at the second focus of the reflector, which is the point of highest energy density. A two-dimensional radiographic scanning system, using two X-ray units, and a patient-positioning system ensure proper location of the stone. The force generated by the shock wave is

concentrated on a spherical area 2 cm in diameter (the second focus). A large pressure zone is created as the shock wave passes from tissue or urine into the stone. This pressure exceeds the strength of the stone material and causes its destruction. Repeated shock wave applications result in the fragmentation of a stone into small pieces (2 mm or less), which normally are passed spontaneously out of the body in the urine (187).

Each ESWL treatment may use from less than 1,000 to more than 2,500 shocks. The shocks are synchronized with the patient's heart rhythm, as monitored by an electrocardiogram, and are delivered during the contraction of the heart, when it is not responsive to electrical stimuli. This arrangement avoids the complications, experienced in the early clinical trials, of triggering arrhythmias of the heart (22). Appendix C describes the properties of shock waves and the design of the Dornier lithotripter in more detail.



Photo credit: Dornier Medical Systems, Inc., Marietta, GA

In the Dornier lithotripter, shock waves produced by a spark-gap electrode travel through a water bath and the body of the patient to the point of the urinary stone.

## EARLY STUDIES OF ESWL<sup>1</sup>

Shock waves are phenomena closely identified with studies of explosions and of aerospace; the force created by a jet breaking the sound barrier, for example, is a shock wave. Accordingly, a West German aerospace firm (Dornier) was the first to successfully apply extracorporeal shock wave technology to treatment of urinary stones.

The fundamental problem to overcome in early studies of ESWL was focusing the wave on the stone without causing other tissue damage or lessening the power of the wave to the point where

it was not effective (22). Initial *in vitro* studies of stone fragmentation were performed on stones freely suspended in a water-filled plastic bag. Studies in rats showed that shock waves caused destruction of lung tissues, but no trauma to other biological tissues. Studies in larger animals supported the finding that the kidney itself was not harmed by the shock waves, but they also were not successful in every case at fragmenting the stones into pieces that could be spontaneously discharged. The animal trials did result in a rejection of ultrasound in favor of X-rays as a reliable method of imaging the precise location of the stone (22).

The first description of clinical experience with ESWL was published in 1980. In a series of 23 pa-

<sup>1</sup>This section and the one following draw extensively from J.A. Showstack, E.J. Perez-Stable, and E. Sawitz, "Extracorporeal Shock Wave Lithotripsy: Clinical Application and Medicare Physician Payment," paper prepared for the Office of Technology Assessment, Washington, DC, Aug. 1, 1985.

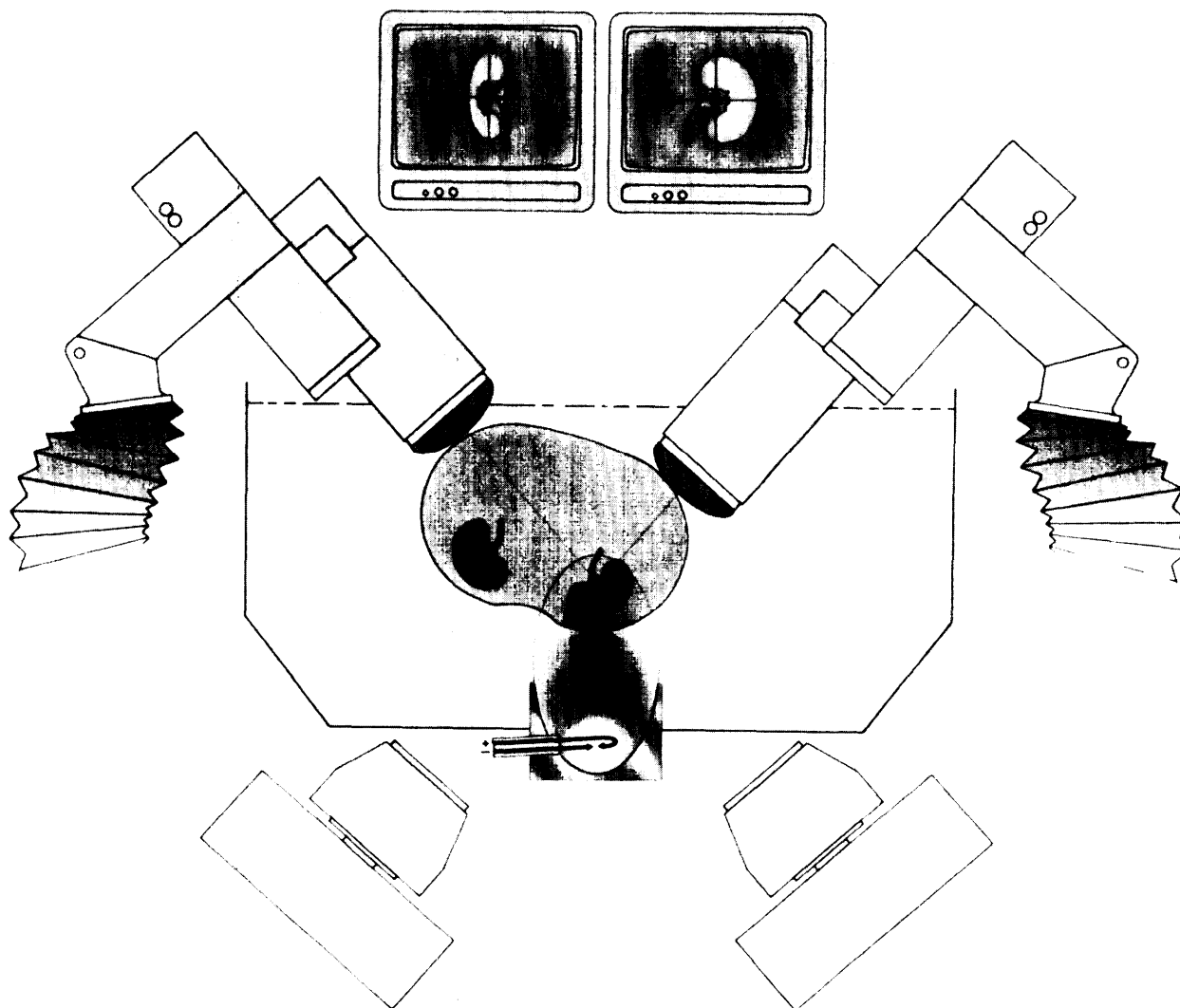


Photo credit Dornier Medical Systems, Inc Marietta, GA

The location of the stone in the Dornier lithotripter is defined in two dimensions by X-ray devices that are attached to the lithotripter.

tients with upper urinary stones treated with ESWL, 20 patients had stones that were successfully destroyed by ESWL and expelled spontaneously. Only two of these patients were reported as having renal colic after the procedure, but hematuria was present in all (23). The three failures in this series (two patients with ureteral stones and one with a staghorn stone) all required subsequent open surgical procedures (23). Although general anesthesia was used in 65 percent of the patients in this series, eight of the last nine

patients undergoing ESWL were given only epidural (regional) anesthesia.

Updates on clinical experience with ESWL were published in 1982 and 1983, demonstrating very positive results with renal stones but less success with ureteral stones (25,26). Not all patients with renal stones were selected for ESWL. The initial exclusion criteria in selecting patients were: 1) obstruction of the urinary tract, 2) infection of the urinary tract, 3) stones larger than a cherry, 4)

insufficient contrast density for precise localization (the stone could not be seen clearly enough on X-ray to position the patient precisely), and 5) existence of other significant medical problems (22). Thirty-nine percent of the first 206 patients treated with ESWL had previous surgery on the treated kidney for stone disease (25).

A third update in 1983 reported on 498 patients (24). A 3-month post-ESWL evaluation showed 90 percent free of stones, 9 percent with residual stones of small size, and only 1 percent (four patients) requiring open surgical procedures (24). The composition of stones treated with ESWL was reported as 80 percent calcium containing, 15 percent struvite, and 5 percent uric acid or cystine, approximately the same as the distribution of stone types in the population. In mentioning successful subsequent treatment of 30 patients with ureteral stones, the investigators emphasized that all of these stones had moved into the ureter 6 weeks or less before ESWL treatment (24).

In 1984, Chaussy and colleagues summarized the Munich experience with 945 patients undergoing 1,068 ESWL treatments (27). Three months after ESWL, 89.5 percent of patients were free of

stones, 10 percent had detectable stones on radiographic evaluation, and 0.6 percent had undergone open surgery. To achieve this efficacy rate, adjuvant procedures were necessary in 76 patients (8 percent); transureteral manipulations were conducted in 33 (3 percent), and percutaneous nephrostomy was necessary in 43 (5 percent) (27). One ESWL treatment was sufficient in 87 percent, but 11 percent and 2 percent of patients underwent two and three treatments, respectively (27).

Although the high proportion of treated patients with previous surgery on the affected side indicates a patient population of recurrent stone formers with severe symptoms, information is lacking on patient selection and severity of symptoms before ESWL treatment. The early exclusion criteria were eventually discarded, and the only remaining contraindication noted in the 1984 update was "pathologic drainage conditions" below the stone and location inferior to the iliac crest (in the lower part of the ureter, where visualization of the stone is difficult because of the intervening pelvic bone) (27). More than 100 ureteral stones were treated successfully with ESWL when their presence in the ureter did not exceed 6 weeks (27).

## REGULATION BY FDA AND CLINICAL TRIALS IN THE UNITED STATES

FDA regulates the introduction of drugs, medical devices, and biological products onto the market in the United States. Whenever a manufacturer wishes to market a new medical device, or an old device with new features or uses "that could significantly affect the safety or effectiveness of the device" (21 CFR 807), the manufacturer is required by section 510(k) of the 1976 Medical Device Amendments to notify FDA. If the device is found by FDA to be "substantially equivalent" to a prenotification device, it may be marketed. If not, it automatically becomes a class 111<sup>2</sup> device and

requires premarket approval before it can be marketed. To receive premarket approval for a device, the manufacturer must submit an application to FDA showing the results of clinical trials and other safety and efficacy information (179).

In order to conduct a clinical trial (using human subjects) in the United States with a device that has not been approved for marketing and that poses a "significant risk" to users, the manufacturer must obtain an investigational device exemption (IDE) from FDA (85). In principle, the manufacturer must not make a profit by selling the device until the device has premarket approval, although this rule is difficult to enforce. When sufficient data have been collected, the manufacturer submits a premarket approval application

<sup>2</sup>The 1976 legislation established three classes of medical devices; class 111 contains those devices for which general controls are insufficient to ensure safety and efficacy, information does not exist to establish a performance standard, and there is a potential for harm (179).

that includes the evidence of its safety and efficacy and labeling information for the device. Once FDA finds both the evidence and the labeling to be acceptable, it gives the manufacturer approval to market the device (179).

The Dornier company, which had been conducting clinical trials of ESWL in West Germany since 1980, submitted an IDE request to conduct trials in the United States in September 1982 (42). The IDE was granted by FDA in April 1983, and clinical investigations commenced at the Methodist Hospital in Indianapolis, Indiana, in February 1984 (203). The investigations were extended shortly thereafter to five more U.S. hospitals: Massachusetts General Hospital in Boston, Baylor University College of Medicine-Methodist Hospital in Houston, New York Hospital-Cornell Medical Center in New York, University of Virginia Medical Center at Charlottesville, and University of Florida-Shands Teaching Hospital in Gainesville (3). Though FDA did not require that U.S. data be presented in Dornier's premarket approval application, the U.S. trials served the dual purpose of supplementing the German data in the premarket approval application and of allowing the U.S. medical community to become familiar with the device.

The research protocol under the IDE called for each hospital to treat two successive categories of patients. Patients in the first category were required to have the following characteristics:

- a single stone, located in the renal pelvis or calices, that showed up as densely opaque under X-rays and measured less than 2 cm in its longest axis,
- urine that could be sterilized with antimicrobial agents before treatment,
- no obstruction in the urinary tract below the position of the stone,
- normal body structure with no more than 30 percent excess body fat,
- no major coexisting diseases, and
- no significant calcification of the aorta or renal artery.

Once an investigational site had treated 50 such patients, the IDE protocol allowed the treatment of patients with more complicated symptoms, including:

- multiple renal stones,
- stones larger than 2 cm in axial length,
- upper ureteral stones, and
- radiolucent stones (less easily visualized with X-rays) (42,187).

The Gastroenterology -Urology Devices Panel, an advisory panel to FDA, met on May 31, 1984, to consider evidence thus far on the Dornier lithotripter (187). At that time, 317 patients in three U.S. hospitals had been treated with ESWL. Of these, 32 (10 percent) had required two ESWL treatments and 3 (1 percent) had required three treatments. Three patients had experienced minor complications (pancreatitis and urosepsis) associated with the treatment, but all recovered uneventfully in a few days. There were no deaths. The panel, after considering the German data and these corroborative reports, recommended approval of the device subject to minor technical adjustments, labeling requirements, and the submission of followup clinical investigation data and a postmarketing surveillance plan (187).

FDA approved the Dornier lithotripter for marketing in the United States on December 19, 1984 (187). The approved labeling of the lithotripter states that the device should not be used for patients who:

- have lower ureteral stones, bladder stones, or gallstones;
- cannot undergo either general or peridural anesthesia
- should not be exposed to radiation, such as pregnant women;
- have an anatomy that precludes adequate imaging to focus the stone, such as patients with curvature of the spine or excess body fat;
- have a urinary obstruction below the position of the stone;
- have a pacemaker; or
- have renal artery calcification on the side to be treated (187).

This labeling limits Dornier's promotion of its ESWL device to treatment of kidney and upper ureteral stones. FDA regulations prohibit Dornier from labeling the lithotripter for a new use, such as treatment of stones in the lower ureter, without further proof of the device's safety and efficacy when employed for that purpose. However,

FDA cannot prevent physicians from using the Dornier lithotripter for such a use.

The approval of the Dornier lithotripter was announced with great fanfare. The Department of Health and Human Services (DHHS) held a press conference that extolled the virtues of the lithotripter and that was attended by both the Secretary of DHHS and the FDA Commissioner. The device was described by the Secretary as an "authentic modern miracle" that would both lower costs and enhance quality of care (186); it was heralded by the press with headlines such as "Kidney-Stone Crusher Hailed" (143) and "Lithotripsy Smashes Kidney Stones and Health Care Costs" (91).

The FDA regulatory process probably did little to hinder the introduction of ESWL in the United States. Dornier received approval to conduct clin-

ical trials into the United States in April 1983 (203), but the company did not begin them until early 1984 simply because it had no machines to deliver (125). The Dornier lithotripter's brief investigational period in the United States was probably as important to introducing the device to U.S. medicine and potential purchasers as it was to providing additional data to FDA. It is ironic that this technology, which had a relatively smooth passage through the FDA regulatory process, should be later cited as an example of FDA bureaucracy and overregulation. One commentator has called FDA to task for the fact that the Dornier lithotripter "had already been used for two and a half years in West Germany before the FDA bureaucracy began to evaluate it" (61), despite the fact that FDA had no jurisdiction over ESWL until the manufacturer decided to take steps toward marketing the device in the United States.

## SAFETY AND EFFICACY OF ESWL: CURRENT STATUS

ESWL has already emerged as the preferred treatment among many urologists for most upper urinary stones (54,133). This enthusiasm is based on data showing up to 95 percent effectiveness in eliminating stones in patients for whom ESWL is selected, when ESWL is used either as a single modality or in conjunction with other techniques (22,57,90,137). The complete avoidance of a surgical incision and the short period of convalescence adds to ESWL's attractiveness and have been featured in well-publicized reports of patients who have undergone the procedure (28).

During 1984, more than 7,000 ESWL treatments were performed around the world, including about 2,400 procedures at six centers in the United States (11). By October 1985, over 50,000 treatments at over 90 ESWL centers worldwide had been performed (81), and the number has continued to climb. As mentioned above, the available data on the world experience to date indicate that up to 95 percent of patients are free of stones 3 months after ESWL. An adjunct procedure is necessary in 10 to 25 percent of patients to achieve this degree of success, and 10 to 15 percent require more than one ESWL session. Recur-

rence rates with ESWL of new symptomatic stones have not been reported. Also, the role of medical management and preventive measures after ESWL has not been addressed in the literature.

The U.S. experience reported in the literature appears to corroborate the German reports used as the basis for Dornier's application to FDA. At Methodist Hospital in Indianapolis, 500 patients had undergone ESWL treatments for stones in the kidney and ureter by July 1985; only 14 percent were completely stone-free at discharge from the hospital, but at 3 months 75 percent had no radiographic evidence of stones (90). The proportion requiring secondary stone manipulations was 7.5 percent, but only five patients required a percutaneous approach. Repeat ESWL was necessary in 9 percent. Open surgery for stone removal was necessary in one patient (90).

Researchers in the New York Hospital-Cornell University ESWL unit have reported that, in 467 patients undergoing 518 treatments, 92 percent of disintegrated stones passed spontaneously after ESWL (138). Twenty-three percent of treatments required prior cystoscopic procedures, with FDA category B stones more likely to need these pro-

cedures (137). (These stones include those that are greater than 2 cm, are located in the ureter, are partial or complete staghorns, and are accompanied by infection). Seventy-five percent of patients were stone-free after 3 months. Complications included colic, vomiting, infection, and one symptomatic perirenal hematoma requiring blood transfusion (137).

A West German group has recently reported on 750 patients receiving ESWL treatments; stone disintegration was achieved in 99.1 percent, while 0.6 percent underwent percutaneous nephrolithotomy alone and 0.3 percent open surgery (57). Immediate secondary measures were necessary in 16 percent, including repeat ESWL treatments. X-ray evaluations 3 months after ESWL showed that 85 percent of patients were stone-free; a second ESWL session was required in 3 percent of cases (57).

Open surgery for stone disease will likely be used for relatively few patients in the future. Percutaneous nephrostomy with ultrasonic lithotripsy, the most likely alternative to ESWL for upper urinary stones, is effective in 95 percent of upper urinary stone cases but carries a risk of serious complications greater than that for ESWL. Bleeding from trauma to vascular structures occurs in 1 percent of percutaneous nephrostomy cases (120) compared to an approximately 0.6 percent incidence of similar complications (usually perirenal hematomas) from ESWL (27). On the other hand, concomitant procedures are more likely to be necessary with ESWL than with percutaneous nephrolithotomy. ESWL is rapidly becoming the preferred treatment for many stones in the renal pelvis or calices that cannot be adequately treated with drugs, but percutaneous nephrolithotomy is also being widely adopted. The precise clinical indications for one treatment rather than the other, when only a single treatment modality is necessary, are still unclear.

Stones located in the ureter are more difficult to manage than stones in the kidney, and only those in the upper portion of the ureter are common candidates for ESWL. Some stones found initially to be in the lower ureter (below the iliac crest) can be moved, through transurethral manipulation, to the upper ureter or renal pelvis where ESWL is effective (105). Direct application

of ESWL to lower ureteral stones is currently being tried on an experimental basis (82). Ureteral stones lodged in the same place for more than a few weeks are not removed effectively by ESWL (24,47). A combination of transurethral or percutaneous procedures and ESWL may be expected in a greater proportion of ureteral than renal stones (137).

ESWL, alone or in combination with secondary procedures, can remove over 85 percent of ureteral stones (137), but many of the advantages of the noninvasive procedure (ESWL) are lost when a second, invasive procedure (such as percutaneous ultrasonic lithotripsy) is required (155). Still, ESWL in combination with percutaneous stone removal is probably less traumatic than open surgery (89) and is likely to replace open surgery for many ureteral stones.

The U.S. experience with ESWL offers one encouraging fact: many of the adjunct manipulations have been transurethral and not percutaneous. This fact may be due in part to the use of prior transurethral manipulation of ureteral stones to make them amenable to ESWL treatment. Nevertheless, emphasizing transurethral rather than percutaneous approaches can limit the risks involved with adjunct procedures performed before or after ESWL, since transurethral manipulations are considerably safer than are percutaneous procedures (155).

The safety of ESWL in the short run has been well established, and morbidity from the procedure compares favorably with open surgery and percutaneous techniques (88). Some patients have pain when passing the fragments, which may be treated with oral or intramuscular medication, and some morbidity from anesthesia is expected (155); one patient in the United States has died from anesthesia complications (203). Radiation from the X-ray system is a concern, but it is less per treatment than with percutaneous lithotripsy (58). Furthermore, it is comparable to the radiation required to visualize a stone before and during open surgery<sup>3</sup> if ultrasound rather than X-rays are used for post-ESWL imaging (58).

<sup>3</sup>Radiography is sometimes used to identify the location of a stone during surgery. Intraoperative ultrasonography is also occasionally used (98).



The long-term effects of ESWL, including the effects on the kidney of repeated ESWL treatments, are still in need of study (155). One major concern regarding long-term effects is that between 10 and 25 percent of patients treated with ESWL still have residual stones (visible on plain X-rays) at 3 months (27,57,90,137). These fragments ("stone dust") may act as a nidus for new stone formation and lead to higher recurrence rates than would otherwise have occurred. Recurrence rates of 40 to 60 percent have been reported after open surgical procedures (100), implying that combining medical management and preventive measures with any surgical or ESWL treatment of stone disease is very important (130).

The majority of stones to be treated by ESWL will be calcium containing. Besides being the most frequent type of stone encountered, calcium stones are radiographically dense and often fairly small, making ESWL a likely first choice for therapy. ESWL may also be important in treating certain struvite stones, which can grow to enormous size. A combination of ESWL, and percutaneous lithotripsy has been proposed as the optimal therapeutic approach for many of these stones (89,137). Cystine stones are more difficult to treat with ESWL, because they are not as brittle as other stones and do not fragment as easily. Two groups have reported using chemolysis in combination with ESWL to disintegrate cystine and struvite stones (47,149).

The distribution of treatment modes used for urinary stones is still changing rapidly as more experience with both ESWL and percutaneous stone removal on a wider variety of patients (and with a wider variety of urologists performing these procedures) accumulates. For example, early ESWL treatments employed around 500 to 1,000 shocks per patient (26). An average of about 1,300 shocks per patient in the United States was reported in mid-1985 (11), and an average of 1,600 shocks per patient in 16 surveyed hospitals was reported in April 1986 (40), indicating that increasingly more difficult stones are being successfully treated with ESWL. The average may continue to climb as more centers regularly perform ESWL on difficult stones; or, it could stabilize or even decline if patients with simple stones who would not have been recommended for surgery

in the past nevertheless are recommended for the less traumatic ESWL. A likely scenario is that both percutaneous and extracorporeal lithotripsy will be employed as an alternative to open surgery for many patients with very large or difficult stones.

The role that ESWL may play in the management of urinary tract stones is illustrated by the experience of the Stuttgart, West Germany Stone Clinic. During the first 11 months after the introduction of an ESWL unit, 1,302 patients were treated and 762 (58.5 percent) received ESWL (105). Kidney stones were found in 877 patients, and 77.5 percent of these were treated with ESWL alone. An additional 19 percent of kidney stone patients were managed with a combination of ESWL and percutaneous nephrolithotomy. ESWL treatment of ureteral stones was limited to those located above the iliac crest, and thus ESWL was applied in only 19.3 percent of ureteral stones. A total of 80 patients (6.1 percent) required open surgery. The referral nature of the Stuttgart patients limits the applicability of this experience to the general population of patients with upper urinary stones. The Stuttgart report, however, does bear out the central role of ESWL in the management of stone disease.

The Stuttgart experience can be contrasted with the experience of an American hospital with ESWL during the investigational phase of the Dornier lithotripter in the United States. Researchers from this hospital reported the following distribution of alternative treatments among 304 patients: 37 percent received simple one-treatment ESWL, 35 percent required a second ESWL treatment or a supplementary transurethral manipulation, 13 percent received simple percutaneous nephrolithotomy, 10 percent received percutaneous nephrolithotomy with or without adjunct ESWL to treat staghorn stones, and 4 percent required open surgery for stones (109). Thus, approximately three-quarters of upper urinary stone patients at this hospital were treated with ESWL during its introductory phase, either alone or in conjunction with other treatment modes.

These experiences suggest that open surgical procedures for upper urinary tract stones may well be reserved in the future for less than 10 percent of all patients requiring more than conserv-

ative medical management. What is not yet clear is the mix of ESWL and endoscopic procedures that will be used to treat the remaining 90 percent or more, and the extent to which the availability of these procedures will encourage more aggressive management of stones. No randomized clinical trials comparing ESWL to other treatments for upper urinary stones have been performed;

such investigations could greatly assist medical decisions regarding the appropriate applications for the various alternatives.<sup>4</sup>

<sup>4</sup>In a randomized clinical trial, patients with a common condition (e. g., a kidney stone of particular size and type) are randomly assigned into two or more treatment groups. Statistical tests can then be performed on the aggregate results of the treatments to determine which is more effective (177).

## OTHER EXTRACORPOREAL SHOCK WAVE LITHOTRIPTERS

At least three U.S. manufacturers are developing ESWL devices, with quite a bit of diversity in components. As of December 1985, only one manufacturer (Medstone) had begun clinical trials (103). The devices, summarized in table 4, are expected to be cheaper and more versatile than the Dornier lithotripter, but whether they prove to be as effective remains to be seen. All of the devices under development use shock wave energy to fragment the stones, but they produce the energy in different ways. They differ in two other important ways as well: in the acoustic interface (whether the patient is actually in a water bath or whether some other means is used to convey the shock wave) and in the imaging equipment used. Since precise imaging is a vital component of ESWL, advances in imaging can have a substantial effect on the technology. An important factor to demonstrate in the clinical trials of ESWL devices under development is the ability of less

costly equipment to produce a rapid and accurate image of a stone's position.

The impacts on these new devices of FDA premarket requirements are twofold. First, they ensure that future ESWL devices on the U.S. market will meet some standard of safety and efficacy. Second, they force developers to consider the time necessary to conduct scientifically valid clinical trials when anticipating the speed with which the developers can introduce their devices on the open market. All new ESWL devices must undergo extensive clinical testing before FDA approval. With the possible exception of Medstone's device, which could conceivably be awarded premarket approval in late 1986, none of the U.S. lithotripters is likely to be available for general marketing before 1987. Even Dornier, which submitted its premarket approval application largely on the basis of 4 years of West German data, had its device in clinical trials in the United States for 10 months before the lithotripter received formal premarket approval.

There are qualifications to both of these impacts. Although FDA standards require a certain level of safety and efficacy, they do not affect other aspects of a device related to quality, and the future spectrum of ESWL devices may demonstrate a range of differences in attributes such as imaging clarity and average time required per procedure. The potential cost vs. quality trade-offs of alternative ESWL devices cannot be evaluated in advance. Also, the necessity of conducting thorough clinical trials for FDA purposes will not slow the development of alternative devices whose manufacturers would have conducted trials for marketing purposes in any case. FDA regula-

**Table 4.—Extracorporeal Shock Wave Lithotripters Under Development in the United States, December 1985**

	Developer		
	Medstone International	Northgate Research	International Biomedics
Shock wave generator	Spark gap	Spark gap	Laser
Imaging system	X ray	Ultrasound	X-ray
Acoustic interface	Fluid-filled bag	Fluid-filled bag	Water-filled chest waders
State of development	Clinical trials	Animal studies	Animal studies

SOURCES: American Urologic Association, *Report to the American Urological Association Ad Hoc Committee To Study the Safety and Clinical Efficacy of the Current Technology of Percutaneous Lithotripsy, and Non-Invasive Lithotripsy* (Baltimore, M.D. AUA May 16, 1985); G. Clisham/Medstone International Inc. San Diego, CA, personal communication, October 1985; W. Shene Monaghan Medical, Plattsburgh NY personal communication November 1985.

tions do not prevent manufacturers from distributing some ESWL devices before premarket approval, because they permit the distribution of devices necessary to conduct the clinical investigations. Still, the FDA premarket approval process acts to ensure that Dornier is the only unrestricted seller until the next ESWL device obtains approval. Thus, Federal policies that regulate the marketing of medical devices could ultimately have some effect on the overall distribution of the Dornier lithotripter relative to other ESWL devices. The primary determinant of distribution, however, will probably remain Dornier's advantage of being the initial manufacturer of the device.

U.S. manufacturers are not alone in developing new ESWL devices; other manufacturers around the world are also developing products for the ESWL market. For example, Yachiyoda Industry in Japan is working on a water bath ESWL unit (1). The use of microexplosive pellets for endoscopic lithotripsy, described briefly in chapter 3, is a Japanese innovation with potential application to ESWL.

A French company, EDAP, is developing a unit that uses ultrasound imaging equipment and a water-filled pouch instead of a bath to transmit the shock waves (2). The shock waves in the French device are produced by a series of piezoelectric transducers, s which need not be frequently

replaced. If this method of wave generation proves to be effective, it may be less expensive than the spark-gap generator used by most other manufacturers to produce the wave energy.' EDAP is currently conducting clinical trials in France and expects marketing approval in that country to be imminent; it anticipates beginning clinical trials in the United States in 1986 (2). A second French company has recently announced the development of its own ESWL device (110). Given the anticipated market for ESWL in the world, it is likely that other manufacturers are investigating ESWL as well.

Research on extended applications of ESWL is rapidly expanding. The current model of the Dornier lithotripter is in clinical trials in the United States for use on lower urinary stones (82), and a new model to be applied to gallstones is undergoing clinical trials in West Germany (93,147). In addition, U.S. researchers have discovered that shock waves can destroy cancer cells *in vitro* and delay tumor growth in animals, a finding with potentially significant medical implications (144). Applications such as the use of shock waves to treat arteriosclerotic plaque are other promising areas of research (173).

<sup>5</sup>When voltage is applied to a piezoelectric transducer, it causes a crystal in the transducer to expand. Shock waves can be created by the repeated expansions and contractions of this crystal.

<sup>6</sup>The spark-gap electrode in the Dornier lithotripter usually must be replaced at least once during each procedure; Medstone's electrode is predicted to need replacement for each new procedure (11,31).