ApaTech: A biomaterials success story

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Abstract

ApaTech is an excellent example of how innovative technology from a British university can be developed and commercialised on a global scale. Its leading product, Actifuse, competes in the crowded bone graft substitute market. Its competitors include autograft, allograft, recombinant proteins and other synthetic materials based on similar calcium phosphate technology. Discoveries regarding the role of ionic species within normal bone lead to the development of greater insights into the subtle interactions of graft structure, graft chemistry and the biology of bone formation. Financing from 3i and MTI allied to the intellectual property residing in the IRC in Biomedical Materials, Queen Mary University London plus strong commercially oriented management has resulted in ApaTech establishing itself as a major force in the bone graft substitute market. ApaTech has successfully differentiated its products and technology from that of established major orthopaedic company offerings and is capturing significant market share, particularly in the UK and USA where ApaTech has established a direct presence.

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BONE GRAFT MATERIALS

Bone is a living and dynamic biological system, in which new bone is laid down and resorbed in a balanced manner. The growth/resorption rate is influenced by stresses placed upon bone material in its biological and functional situation. The dynamic equilibrium and the remodelling of bone occurs in accordance with Wolff's Law, that is 'form follows function', a point to which we will return later in this paper. Bone grafting, the use of a material to assist the growth and rejuvenation of healthy bone tissue, has been practiced for decades utilising autograft (bone harvested from the patients own skeleton) or allograft (bone donated from another person). This material can exist as fresh frozen material stored in bone banks, often the femoral heads of patients undergoing hip replacements, or as processed tissues, predominantly sourced from the USA. Inevitably, both sources of bone bring with them concerns and issues. Autograft often requires a second operative site to harvest the bone, from say the iliac crest (the outer edge of the pelvic ilium bone), with resultant patient discomfort and post-operative pain as well as infection risk. In contrast, the concerns with allograft tissue surround the quality of the bone material, the risks for disease transmission and the potential for allergenic reactions. More recently, control

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of source material has been raised as a new issue with allograft material following high profile cases of non-consented or diseased tissue entering the supply chain, for example the Alistair Cooke (former BBC radio correspondent) incident widely reported in the press and television in late December 2005.[1]

With this in mind, synthetic bone graft materials have been developed utilising ceramic technologies, and have evolved over time based on a growing understanding of the interaction between graft structure, chemistry and interactions with the host biology.

Bone is predominantly a ceramic material, calcium phosphate in a particular crystalline form, hydroxyapatite (HA), plus a number of trace minerals, notably silicon, magnesium and calcium carbonate. Initial synthetic bone grafts were based on HA derived from bovine or coralline sources (Endobon™, Merck and Pro-Osteon™, Interpore Cross). Subsequently, purely synthetic versions of HA were developed as ceramic processing technology developed through the 1980s and 1990s. During this period, the importance of the internal architecture of the graft material became recognised, as did the concept of controlled porosity, both at a macro (1980s) and at a micro level (late 1990s). Additionally, the importance of surface roughness to encourage bone-forming cells to attach to the surface of the porous ceramic gained recognition.

In chemical terms, the materials available were not phase pure; they contained calcium phosphate in several crystalline forms and contained impurities such as calcium oxide together with tri-calcium phosphate (TCP) and bi-calcium phosphate. Clinically, however, these materials, which promised to remove pain, infection risk, poor quality materials and supply chain constraints that accompany auto and allograft performed poorly. In the clinical setting surgeons were unable to identify if bone was growing in the graft site since the materials were radio opaque on X-ray, they were not resorbed effectively by the body's normal biological processes, and bone growth was not optimal. On occasion when the surgeon re-operated, 'grains of sand' were reported as present in the graft site, with fibrous encapsulation of the material rather than healthy living bone.

These issues lead to HA being deemed a poor bone growth material in the 1980s and 1990s especially in the USA. Customers demanded a material that would disappear from X-ray at 6 months leaving the site easily visible to assess bone growth and repair. This customer demand led to the development of TCP materials. Based on calcium phosphate chemistry, these materials were often processed at lower sintering temperatures and are chemically less stable crystals than HA products. As a result, they are subject to chemical dissolution and rapidly disappear from X-ray images. Increased understanding of the role of structure also allowed the development of highly interconnected porous materials that facilitated complete bone integration through the graft material. The leading example is Vitoss™ (Orthovita), a 90 per cent porous TCP. The body is, however, a complex biological system and the bone growth process is sensitive to local environmental factors. The design requirement, that is rapid X-ray disappearance, requires TCP to quickly dissolve, releasing supra physiological quantities of calcium and phosphate ions and microparticulate debris into the local environment. This adversely affects osteoblast (bone-forming cells) function and drives the formation of fibrous material at the graft site. In addition, the rapid disintegration of the TCP structure results in microparticulate material causing macrophage infiltration, hence the formation of a foreign body immune response. This in turn leads to further fibrous tissue formation and poor quality bone formation.

The apparently straightforward task of developing a synthetic biomaterial that matched the performance of living bone, with chemistry and structure appropriate to the biological and mechanical requirements, was clearly proving more difficult than the simple chemistry and structural parameters would imply.

BIOLOGICAL DEVELOPMENTS

During the 1990s surgeons in many countries also became more conscious of cost as a product selection criterion. This reinforced

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the status quo regarding the use of autograft that is not paid for, and is deemed free by providers, despite high complication rates, patient discomfort and huge hidden costs. In addition, the creation of local tissue and bone banks and improved tissue processing technologies ensured that allograft remained a viable solution for many surgeons. Perhaps most importantly, the biology revolution hit the orthopaedic market. First, it was recognised that to help bone regrowth much more than an ostoeconductive scaffold was required. Bone growth is dependent on the presence of bone-forming cells and their various precursor cells. Secondly, a complex signalling cascade, triggered by the local environment, controls the bone formation process. The key family of proteins are members of the TGF-β super family, the Bone Morphogenetic Proteins. Towards the end of the 1990s the mantra was that bone formation requires a conductive scaffold, bone-forming cells and control signals. Autograft was deemed the gold standard, supplying all the requirements, albeit with clinical downsides. Allograft also supplied the key ingredients and the industry response, promoting the combination of synthetic materials with bone marrow aspirate or platelet-rich plasma, seemed an overly complex procedure for surgeons more focussed on the surgical procedure.

Parallel to the ceramic technology developments of the 1980s and 1990s were biological developments, namely the isolation, purification and manufacture of recombinant bone morphogenic protein (BMP) molecules. OP1 (BMP 7, Stryker Corp) and InFuse™ (BMP2, Genetics Institute/Wyeth, Medtronic Inc) were developed and marketed as a biological solution for trauma and spine fusion procedures. Their biological action became the new gold standard, the first true alternative to autograft. This is especially true for InFuse, which despite, or perhaps because of, its price ($5,000 per fusion level), has become a $700m product.[2]

ACADEMIC SPIN OUT

With this background in mind, members of the Interdisciplinary Research Council at Queen Mary University London launched a programme to develop a new approach to ceramic bone graft materials. This aimed to more closely mimic the structure and chemistry of bone in an attempt to overcome the disadvantages of existing synthetic materials providing surgeons with a real and cost-effective alternative to auto- or allograft bone.

In the 1970s, Dr Edith Carlisle demonstrated the importance of dietary silicon to healthy bone formation. The level of silicon found in human bone declines post maturity, only returning to about 1 per cent by mass in damaged bone. Once repaired, the silicon declines to negligible levels. Based on these observations, the scientists at Queen Mary embarked on a programme to specifically substitute a number of phosphate groups in the calcium phosphate lattice of HA with silicate groups. Additionally, they set out to optimise the internal architecture and structure of the graft material, providing an ideal scaffold to support bone growth. Finally, based on the observation that phase purity and homogeneity of crystal structure were important contributors to bone growth, a reliable and repeatable manufacturing process was required to consistently produce the ceramic material.

This work, begun under the leadership of Professor William Bonfield at Queen Mary University London in the mid-1990s, resulted in a range of intellectual property that was spun out into an intellectual property (IP) vehicle, Abonetics, in 1999. Further development funding in a Series A round in July 2001, led to the formation of ApaTech.

THE BONE GRAFT MARKET

Bone graft substitutes are regulated as medical devices, thus requiring an approved quality system to underpin the marketing of the device in Europe. These approvals are provided by Notified Bodies, such as BSI or Lloyds Register, and depending on the class of the device, a range of *in vitro*, manufacturing, *in vivo* and clinical data may be required. In the case of bone graft substitutes, a proven manufacturing process and compelling animal data are usually sufficient to permit initial marketing. In the

USA, the FDA regulates bone graft substitutes through the 510k clearance to market system, which is based on the doctrine of substantial equivalence to a marketed predicate device. For indications for use beyond those of the predicate, clinical data and a Pre Marketing Authorisation (PMA), akin to an NDA for pharmaceuticals, is required.

ApaTech's key commercial challenge was to demonstrate equivalence to a suitable predicate, to reach the market quickly while generating evidence to support the differentiation of its products and demonstrating that the underlying technology had taken synthetic bone graft materials to a new level of performance such that they could become realistic alternatives to auto and allograft solutions. As a small company, ApaTech also faced the problems of resource limitations and credibility with customers.

The bone grafting market is vast. Globally, there are approximately 1.2 million procedures annually covering spine fusion, joint reconstruction, maxillofacial reconstruction and trauma. These mirror patient distributions to major geographies, with the US representing 40 per cent, Europe 35 per cent, Japan 10 per cent and ROW 15 per cent. Spine fusion is the largest indication with approximately 40 per cent of all procedures. Of these, 1.2 million procedures approximately half involve autograft, with the remaining 600–650,000 procedures generating sales of $1.3bn, while InFuse only accounts for about 150,000 procedures, but has sales of $700m. The remaining 500,000 procedures are split between synthetics, allograft and demineralised bone matrix products, with synthetics accounting for 120,000 procedures. With over 50 brands of synthetic product in the USA alone, the market is crowded and commoditised, with little active promotion and differentiation of competing brands. Only Vitoss from Orthovita was aggressively promoted during the early 2000s, generating sales of about $40m. Virtually all other synthetic materials have been seen as 'service items' in the salesperson's portfolio, rather than major sources of revenue that reward their sales effort. In part, this reflects the reality of orthopaedic and spine sales. Whether selling for the giant spine and orthopaedic companies such as Johnson and Johnson, Biomet, Medtronic or Stryker, or one of the multitude of smaller companies, with metal implants and instrumentation often selling at over $10,000 per patient, salespeople, who are remunerated via commission on sales and are set annual sales quotas, naturally focus on the metal implant component of their portfolio. They are usually highly trained to sell the finer points of the biomechanics and engineering of their implant range, finding the biology which underpins the bone graft substitutes a strange diversion from their comfort zone. At $1000 or less per patient, the additional effort to master the subject and to challenge a committed surgeon's choice, for say $100 commission, is a step too far for many sales representatives. This market reality provided ApaTech with both a challenge and an opportunity. In an environment of modest competitive intensity, the potential to differentiate its products and drive sales was clear. The challenge was how to build a simple sales story, and to develop an effective distribution and sales system, particularly in the USA, which accounts for about 70 per cent of all bone graft substitute sales by revenue.

BUILDING THE COMPANY

The Series A fund raising, £3m from 3i, was utilised to develop the manufacturing process and scale it up from lab to small industrial scale, to put ApaPore (Figure 1), a phase pure HA with optimised structure, into animals for the first time and to initiate clinical studies in 2003 following the grant of a CE mark for the ApaPore range. ApaTech received continued support from Queen Mary University and maintained an office and manufacturing clean room in the Biomaterials department. The level of differentiation of the ApaPore range was modest and early laboratory data appeared to indicate a much more fundamental and substantial response to the silicate-substituted material. It was decided in 2004 to focus all efforts on developing this material, later called Actifuse (Figure 1), and to bring it to market as rapidly as possible. Further resource was required to initiate the

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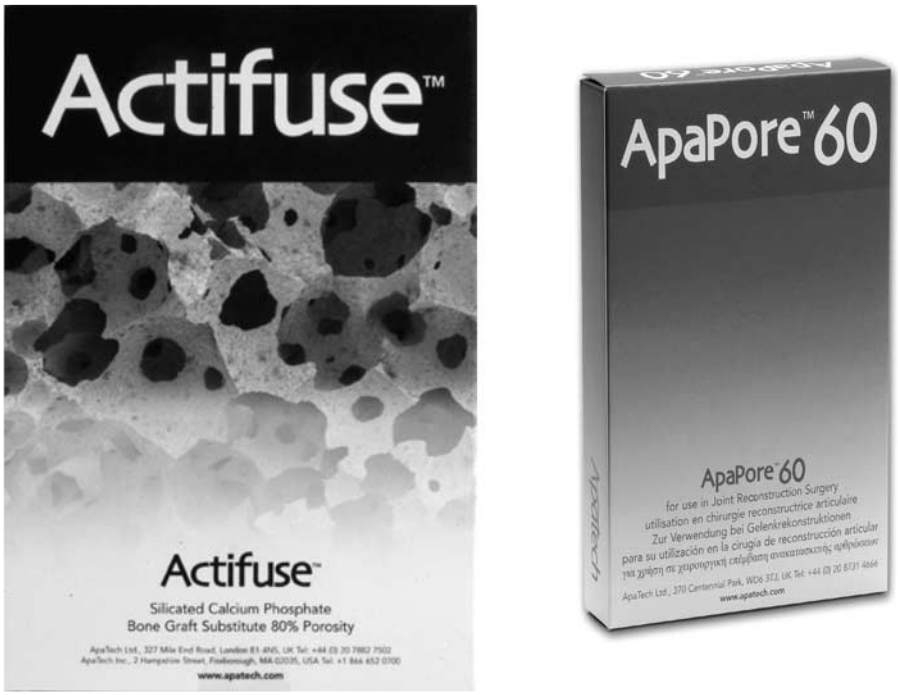

Figure 1: Actifuse and ApaPore 60 packaging

commercialisation of ApaPore, and to scale up both manufacturing and clinical programmes for Actifuse prior to a full commercial launch. This led to a £6.5m Series B round, led by MTI and completed in April 2004. The money raised was primarily used for the conduct of studies to generate the differentiating evidence required to support Actifuse commercialisation, to initiate clinical programmes for Actifuse, to scale up manufacturing sufficiently for global supply and to start commercialisation activities. This principally involved the identification of, and contracting with, stocking distributors in Europe and Old Commonwealth territories plus the incorporation of ApaTech Inc to lead the commercial activities in the USA.

The CE mark was achieved for Actifuse and 510k clearance to market was achieved in the USA in summer 2004. ApaTech Inc was incorporated in October 2004 and its first sale was made in March 2005. Sales developed quickly in the USA through the endeavours of three regional sales VPs appointing, training and managing 31 spine-focussed commission agents, employing 120 sales representatives. With successful initial sales achieved, and interest in Actifuse high, management attention switched to identifying and occupying a new site with sufficient manufacturing capacity to supply global demand for up to five years. A site in Elstree, close to the Royal National Orthopaedic Hospital Trust (RNOH) at Stanmore in Middlesex, UK was identified and a 12-month £2m fit out programme was initiated. To support this activity, a venture loan of £2m was taken with Noble Ventures. The loan was secured against physical assets involved in the building project and with a negative pledge on the underlying IP. US accounts receivable were excluded as an asset class to provide a further asset against which to secure additional loan finance. The Elstree facility (Figure 2) incorporates a state-of-the-art clean room and material flow system, and has sufficient capacity to support sales of circa £40m. It also provides office accommodation for commercial, clinical, R&D and admin functions, in addition to manufacturing and QA activities. Most importantly, the relocation from Queen Mary to Elstree in early 2006 marked a dramatic culture change within the organisation, as discussed below.

Figure 2: New ApaTech headquarters, Elstree, Middlesex, UK

COMPETING IN THE ORTHOPAEDICS INDUSTRY – DISTRIBUTION AND DIFFERENTIATION

The orthopaedics and spine industry is very different from pharmaceuticals. There are few large direct sales forces employed by orthopaedic companies in the US, and no contract sales organisations. This reflects the importance of technical excellence of the representatives, and the close relationship they have with their surgeon customers. Representatives will often be present in cases, especially with 'new' surgeons and provide reminders on technique, correct instrument selection etc. As a result, most sales go through commission agents. These are small businesses in their own right, where a principal will contract with various orthopaedic or spine companies to sell their products to the customers with whom they have close relationships. Essentially, these businesses and representatives are selling their relationships to companies who require distribution to those surgeons. As a result, no agent has the same portfolio as another since their independence allows them to build their portfolio independently, even if they have close associations with a major company. As an example, ApaTech has several high performing Stryker Spine agents who have chosen to sell Actifuse, despite the Stryker portfolio including bone graft materials. For their sales endeavour the agent is paid a commission on sales of anything from 20–35 per cent of realised price. Importantly, for a small business like ApaTech, these commissions are not paid until after payment has been received by the company from the hospital or paying institution, thus significantly reducing working capital. From this industry structure, the challenge facing ApaTech, a small unknown UK company selling a relatively minor component of a spine company's portfolio can be readily envisaged.

To address this difficulty, the first US appointment was an individual with significant industry experience and outstanding contacts. Additionally, consultant support was enlisted to identify possible agents across the US. As noted above, three regional sales VPs with exceptional surgeon relationships and industry knowledge were recruited, with all staff incentivised with substantial equity to reward their success and

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endeavour. Given the importance of margin and quantum of commission to the representative/agent, Actifuse was priced at a premium to existing synthetic materials, not just to reflect its superior attributes, but also making the commission meaningful to a representative such that they would not only learn the underlying science of the product but would also deem it valuable to challenge their surgeons current selection of bone graft material. Finally, a group of top name surgeons were identified to participate in helping develop the underlying science story and to participate in early usage, thus lending credibility to ApaTech, Actifuse and the sales story. As a result ApaTech developed an agent network that covered 75 per cent of the surgeon and target demographic population in the US within 6 months. This achievement was greatly helped by a major competitor making significant changes to its distribution system, replacing sales agents with direct representatives in key metropolitan areas, thus putting significant numbers of agents and representatives into the marketplace for a new bone graft material.

Outside the US the route to market is via stocking distributors, who are similar in the way they build the composition of their individual portfolios. In contrast to the agent model in the USA, these distributors, however, take title to the products and sell them on in their own right. Often demanding 40–60 per cent margins on end user prices, these distributors have significantly more control of usage information than the agent model in the US. Importantly for ApaTech, they purchase the product thus minimising working capital requirements, but disappointingly, the realised price per unit in these markets is often only 30–40 per cent of the US, due to lower end user prices, of which ApaTech receives only circa 50 per cent. In contrast to the US, where the agent representative will utilise ApaTech-produced support materials, the stocking distributors often produce their own promotional materials, albeit with ApaTech input. To support this international distribution activity, which has been established in 17 territories – mainly Europe and Commonwealth countries, an International Sales Director has been appointed. He is assisted by a Germany-based International Sales Manager who has specific responsibility for Germanic Europe and Scandinavia (key territories for ApaTech due to product usage, pricing and distributor quality). In the UK, a direct approach to the spine sector has been adopted with two direct representatives and two commission agents in place.

CHALLENGES AND OPPORTUNITIES

Establishing distribution is only part of the battle. The key to ApaTech's sales success has been a fierce determination to effectively differentiate Actifuse from other competitors. Actifuse has been positioned as the first of a new class of synthetic materials. Actifuse is labelled as a silicated calcium phosphate, a technically correct description that avoids association with the perceived problems of HA and aligns it with the perceived benefits of TCP. The science story that has been meticulously developed, however, serves to ensure that Actifuse is seen as the next generation of synthetic material. By taking the sales story beyond the esoteric arguments of graft material structure, and onto the clinical performance that results from the interaction of the material with the host biology, it essentially lends lustre to the material through a biological mode of action and distances it from everything that has gone before. In the emerging age of biology in orthopaedics, the concept of a bioactive biomaterial is one that finds a ready audience. The Actifuse story, however, is not a hollow one. There is a compelling chain of science that links the design criteria for the material through the laboratory *in vitro* science, to its performance *in vivo* and more recently in clinical settings. The timing and roll out of the evidence has been carefully linked to an emerging understanding of the adopter sequence in the spine surgeon community.

Understandably, the strain on the organisation has been huge. First, there has been the establishment of a US organisation of ten people, while also recruiting heavily in production and UK-based sales and marketing. There has been the building of, and transfer

to, the new facility at Elstree. The planning and potential for catastrophe that such a move entails as sales are ramping up has also been a huge responsibility. Perhaps most importantly, there has been an enormous culture change as ApaTech has evolved from being a UK-centric and academically focussed organisation, to a truly global commercial company, where the customer is the most important part of the organisation.

Looking forward, the key challenges facing ApaTech are to continue to grow sales from the early adopter and innovator surgeons who are believers in the underlying science in the short term. For the medium term, the Company is vigorously pursuing the completion of clinical studies in a range of applications that demonstrate conclusively the effectiveness of Actifuse, and in particular its equivalence to autograft and Infuse, the two benchmarks. This clinical data will be pivotal in addressing the unspoken disbelief of many surgeons that Actifuse, a ceramic synthetic material, can have a positive effect on the rate of bone re-growth and that it is capable of producing not just more bone in less time than conventional synthetics, but that it can deliver results equivalent to those produced by biological solutions. This proof will be the key to unlocking the majority of surgeons who require clinical data, particularly in the US, given its drive for conformance with best practice, the societal and litigation pressures on surgeons, plus the need for health economic data to support reimbursement and pricing. In the case of Infuse, which is growing exceptionally fast, its manufacturers clearly do not wish to see its scientific pre-eminence undermined by a significantly more cost-effective solution, which delivers equivalent or even superior results. And yet it is the cost and growth of Infuse that is causing payers to look for other alternatives. In response to this ApaTech has established APPRAISE, a direct comparison of Actifuse and Infuse in posterior lumbar fusion, and is in the process of establishing a comparison in interbody fusion. The pilot studies and anecdotal case reports are supportive of ApaTech's contention that Actifuse may be a viable alternative to these products.

PORTFOLIO EXPANSION

A further challenge is portfolio development. ApaTech is currently a one trick pony and surgeons value ease of use features. As a result, the Company has a number of line extensions in development including a putty formulation, a paste for interbody procedures and fractures, trauma applications, etc, composite synthetic polymer devices for weight bearing applications and a specific formulation for a rapidly growing segment of the spine market, vertebral compression fractures. These product developments will assist not only in driving the top line sales growth but also to diversify the revenue stream, reducing risk and making the establishment of a direct sales force in territories other than the UK a viable proposition.

The profile of ApaTech in mid-2007 will be profitable, cash generative, with a broadened portfolio, selling in 18–20 international markets. Such a business will inevitably attract the attention of trade buyers and makes ApaTech a candidate for an initial public offering (IPO). As a consequence, a major challenge for the organisation is planning the long-term development strategy for the business to meet investors' requirements.

SUMMARY

In summary, ApaTech is an emerging success story for the British orthopaedic biomaterials industry. From a classic beginning as a university spin out, a truly international sales story has developed based on a differentiated product in a sector that had for sometime been over looked by competitors. With modest investment from committed backers allied to a truly commercial vision, a strong management team has been assembled to drive the commercialisation of its leading product on a global scale, with a particular emphasis on the US market. While resources have been tight so far, by focussing on the major opportunities and rigorously prioritising and planning the key steps, a strong scientific and clinical story has emerged, underpinning the product differentiation claims. By being bold and going for the high ground, surgeon interest

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has been captured and the competitors have started to take this small British start up seriously.

As for lessons to be taken from ApaTech's success, the principle ones are the funding of commercially viable projects at university level, access to private equity to take the resulting IP to the product stage, recruitment of experienced commercially oriented management to take the product to market and a fierce determination to not let legacy issues impede the commercial needs of the business. Changing management and the Board at an appropriate time is a key feature of virtually all successful small businesses, and the development and retention of a pool of entrepreneurial and experienced British-based management is a key requirement if the medical device and biotech industry is to flourish in the UK. ApaTech has shown clearly what can be achieved when these factors come together behind a marketable product proposition.

Notes

1. See for example http://www.telegraph.co.uk/news/main.jhtml?xml=/news/2005/12/23/ncooke23.xml&sSheet=/portal/2005/12/23/ixportal.html, http://www.abc.net.au/news/newsitems/200602/s1577193.htm, and http://news.bbc.co.uk/1/hi/world/americas/4552742.stm.
2. See www.medtronic.com/corporate/investor_relations/Q2-FY07-Commentary-for-Post.pdf.