#

27 May 2015

**The next disruptive technologies: new ways to treat old diseases**

Professor Martin Elliott

#### ****"Those who have knowledge, don't predict. Those who predict, don't have knowledge. "****

**Lao Tzu, 6th Century BC Chinese Poet**

I cannot predict the future any more than Lao Tzu could nearly 3000 years ago. Yet I am pretty sure that what we can do now would have been beyond his comprehension. In this lecture, I want to highlight some trends in medicine and surgery that are both relevant to my specialty and at least *likely* have a profound influence on the management of health, illness and the role of physicians and surgeons in society. As someone who has been involved in medical research throughout my working life, I share the view of the Turing prize winning computer scientist Alan Kay who, paraphrasing Abraham Lincoln, said; “*the best way to predict the future is to invent it*.” Much of what I will describe today is about invention and research; but whether we will use these discoveries either appropriately or effectively is truly impossible to predict.

Whilst I was thinking about what to include in this talk from amongst the huge range of innovations, I thought it would be useful to undertake a survey of my fellow cardiac surgeons around the world to see what they viewed as likely to change our world. This survey will be published elsewhere. I will intersperse the slides I show in this talk with some of the findings of that survey, and I am immensely grateful my colleagues who pulled all this together; Dr. Susie Thoms, an anesthetist and proud mum in South Yorkshire, Mr. Edward Green a brilliant young technologist with Block Solutions Ltd., and Professor Jeffrey Jacobs of Johns Hopkins University in the USA who manages the STS congenital database.

There is so much progress in so many areas of medicine that knowing where to start describing them is quite a challenge. I have to be selective, and I am not going to talk about advances in disciplines outside my own such as cancer or gene therapy; there is simply not time to do them justice. However, the pathway I described in my last talk for a child with Tetralogy of Fallot is a good place to start, so lets quickly review again what are the anatomic and physiologic features of that condition and then use that pathway as a guide to the significant developments currently in the pipeline, and their potentially disruptive consequences.

Tetralogy of Fallot comprises a hole between the two ventricles of the heart (ventricular septal defect - VSD), a narrow way out from the right ventricle to the lungs (right ventricular outflow tract muscle bundles and pulmonary stenosis), small pulmonary arteries and cyanosis. Blue blood returning to the heart from the veins finds it easier to pass through the VSD from the right to the left ventricle, thus sending blue blood around the arteries and giving the child a blue, cyanotic, appearance.

Here is the pathway I described in my last lecture, showing how the condition can be diagnosed prenatally, confirmed after birth and managed by surgery, sometimes involving temporary palliation by increasing the flow of blood to the lungs before fixing everything at around 6 months of age. There is lifelong follow up and additional surgery may be needed later.

So much for revision! Let’s get down to what is changing, and start with prenatal diagnosis.

There are three primary reasons why prenatal diagnosis might be of value

1. To give the parents the chance to prepare psychologically, socially, medically and sometimes financially for a baby with a severe problem.
2. To facilitate timely medical and surgical treatment, or plan for appropriate delivery.
3. To give them the choice as to whether to abort the affected fetus.

Knowing what to do with the information obtained by prenatal diagnosis is tricky. There is a dearth of adequate online material1, and parents are dependent on the quality of counseling offered by their carers. You might think that the awareness of a severe congenital heart disease would be a driver for termination. Yet it is worth remembering that, in 2013, there are almost 200,000 abortions each year in the UK, 99% of them for *normal* fetuses. Only 1% of cases was terminated for congenital malformations and of those only 11% for cardiac defects. Eight of those cases were over 24 weeks gestation [<https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/319460/Abortion_Statistics__England_and_Wales_2013.pdf>].

Currently, the theoretical earliest diagnosis of congenital heart defects is around 14 weeks gestation, although in reality it is usually between 20 and 24 weeks, depending on the skill of the sonographer. It is not surprising that there is constant research to bring down the age of fetal diagnosis, to broaden parental choice. But diagnosing structural disease of the heart currently relies on the resolution of the ultrasound machines, and the skill of the operator. Whilst these improving year on year, they remain limiting.

There is currently no maternal or fetal blood test to identify tetralogy of Fallot, or indeed any other congenital heart defect. Whilst the genetics of heart defects are under active scrutiny, so many genes are involved that the ability to make an accurate diagnosis via this route is decades away, and may never be fully achieved. We can identify some of the genes of conditions *associated* with CHD, for example Downs syndrome, but not the heart disease itself. The implication of increased sensitivity or specificity of these tests is yet to become clear; who knows what parents will do with the information? I leave you to consider whether earlier and earlier diagnosis will result in a change in parental behaviour, particularly in relation to termination of pregnancy.

We are becoming aware that there are alterations in the fetal circulation in children with congenital heart disease which can affect brain growth and maturation (for review see Licht2). There has been great concern over the last 30 years that cardiac surgery and the traumas of the heart lung machine were associated with a significant incidence of neurodevelopmental abnormalities in treated children, such as behavioural abnormalities, special educational needs and the need for additional support. It now seems likely that changes to blood distribution in the last trimester of pregnancy may be more important than what we do to fix it after birth. Thus deeper understanding of fetal physiology in CHD may well drive us to intervene earlier, even in fetal life, to optimize the outcome.

There is indeed increasing interest in the potential of intervention of the fetus whilst still in the womb, in the hope of either correcting a defect or modifying the development of the heart and other organs to make post-natal life or treatment better or easier. Attempts at fetal cardiac surgery began in the 1980s, largely in San Francisco, but were abandoned because of the adverse effects of the heart-lung machine on both the fetus and the mother. Since then, the advances in ultrasound technology I described earlier have also made it possible not only to understand more about fetal hemodynamics and how the abnormal heart develops in utero, but also to develop minimally invasive approaches to fetal intervention. It has been said that fetal surgery has the potential for 300% mortality; the fetus, the mother and the next baby (if the uterus is damaged), so it is critical that innovative fetal interventions are subjected to rigorous risk:benefit analysis and the most unbiased informed consent process.

From fetal ultrasonography, we have learnt that outflow tract obstruction of the left or right sides of the heart can result in under-development of the underlying chambers; the ventricles. You will remember I hope that one of the most severe forms of congenital heart defects is hypoplastic left heart syndrome, which requires at least 3 major operations during post-natal life, culminating a circulation supported by only one ventricle. This remains a relatively high mortality and high morbidity course of treatment in most centres, ending in the need for transplantation in many patients in adult life. If the narrowing of the outlet valve, the aortic valve, could be treated in utero, then perhaps the left ventricle beneath it might grow and allow a simpler or less risky set of operations after the baby is born. It might also mean that the larger left ventricle doesn’t have to be written off, leaving two ventricles to support the circulation. This turns out likely to be the case3, although still with a way to go to be widely recommended.

This turns out likely to be the case3, although still with a way to go to be widely recommended. Fetal surgery *is* happening for other conditions in which cardiopulmonary bypass is clearly unnecessary, for example, closure of the open spinal canal in spina bifida, a condition that can otherwise lead to incontinence, weakness or paralysis.

Major change in medicine does not come purely from the lab or from technology, but may also be organisational. For example, where would be the ideal place for a child with tetralogy of Fallot to be delivered? At home, at the nearest nurse-led maternity service, or in a regional unit close to a specialist cardiac centre? And after birth, when should that child be seen by a specialist paediatric cardiologist, and where? How many such centres should there be? Should there be physicians and surgeons who sub-specialise in tetralogy to optimise outcomes? How could you do that in a small centre? These questions have been the subject of intense debate over the last 25 years, and are unresolved (<http://www.gresham.ac.uk/lectures-and-events/the-bristol-scandal-and-its-consequences-politics-rationalisation-and-the-use> ). It is interesting to see the responses of our international group of paediatric cardiac surgeons here. The majority feels that centralization is appropriate and that cost and price reduction are organisational priorities for health systems world wide.

In our putative Fallot pathway, diagnosis is confirmed after birth by echocardiography, a painless and rapid diagnostic tool. It has become the stethoscope of the 21st century. The resolution is improving yearly, the ‘added-value’ tools that add to the precision of diagnosis and description of function (Doppler, strain, 3D) are astonishing, but it remains operator dependent. Let us consider for a moment how that might change.

The echo machine generates digital data and constructs images from standardized views for interpretation either immediately or later at leisure. More experienced physicians can see the images and decisions can be made. But developments in the Internet and data analytics are very likely to change these ……over time. Already, remote interpretation of ECHOs is achieved over the net, with the operator being in one place and the specialist in another. Images and data can be shared and reviewed, and decisions made.

Imagine that the machine is connected to the Internet, and that somewhere in the cloud is a library of ECHO-derived images that accurately reflect the thousands of diagnoses that exist. Imagine that software exists which can search that that library in real time, whilst the operator is doing the scan and feedback to the operator information which guides them to the correct handling of the probe, or matches the current patients image with the thousands of similar images in the library.

Imagine that the operator hears in her ear that what she is seeing matches the diagnosis of some component of tetralogy of Fallot, can simply press a button to ‘code’ that diagnosis into the system, which might then suggest additional views to refine or complete the diagnosis. Now imagine that all the ECHO machines in the world are connected in this way, each adding images to the library, which receives confirmatory data from specialists in due course. Linking all this together could (and I think will) create algorithms that will allow the integrated machines to learn from each other, and from the ultimate outcomes of care, refining and refining the algorithm. We began to collate such a library 10 years ago4, predicting the connectivity and machine learning which is only now becoming reality. The Internet of Things has a clear role in improving diagnosis, and providing decision support at all stages of the pathway. The integration and analysis of such large quantities of data may profoundly affect how we make decisions, who makes them and in what environment.

Let us assume that our baby has severe tetralogy with a very narrow way out of the heart into the lungs and will need to have something done to increase the flow of blood to the lungs to allow growth both of the blood vessels and the baby so that complete reparative surgery is safer. Until recently, such children would have received either a shunt an artery to the body and the artery to the lungs to bypass the obstruction, or a patch to the outflow tract, which whilst done on bypass is a relatively quick operation. Over the last few years, it has become possible to place stents in the outflow tract of the right ventricle5 placed via an artery or vein (2-3mm across) in the groin, avoiding the need for traditional shunt surgery. Later repair is just as safe6. There will be spread of these techniques, and undoubtedly the equipment (less radiation), catheters (smaller, steerable) and stents (new materials, personalized design) will all get better. The less invasive we can make our work the better. And the surgeon can spend more nights asleep, which can only be a good thing.

Babies undergoing invasive procedures get antibiotics to prevent infection being introduced to their circulation by the instruments and devices used. One of the antibiotics used has been gentamicin, which kills a specific group of bacteria called gram-negative organisms. Sadly, some children were found to become deaf after treatment with this drug, used, remember, for their safety. It was discovered that a particular mitochondrial DNA mutation (m.1555A→G) existed in 1 in 520 patients, and that 100% of children with this mutation would become deaf after receiving gentamicin like drugs7. This is a very important discovery. Firstly, it means that if you can screen for and identify the gene, you can prescribe an alternative to gentamicin, and effectively eliminate the risk of deafness, greatly improving quality of life and long term reducing cost. Trials are now taking place. Secondly, it demonstrates the potential of *personalized* treatment, based on a patient’s genetic make up. The more we understand the genome and its mutations, and the more we can associate these with particular responses to treatments, the more we will be able to define therapies which will work well and safely for a *particular* child, rather than for a group of children.

Personalized medicine has become something of a buzz phrase in recent years (19,342 hits on PubMed when I checked 4 days ago; an increase of 17,000 in 2 years8), but it has several interpretations8. Largely it has come to mean the *customization* of medical care with decisions and practices being tailored to the individual patient by the use of genetic or other information. But it includes the ability to classify patients into sub-populations, rather like the gentamicin and deafness story, using genetic or other data to predict their individual response, better to manage their care. Included now is the ability to design, manufacture and implant devices and prostheses specific to an individual. I rather like the all-embracing summary “the right treatment to the right patient at the right time”.

So, our baby is now in ICU or HDU, recovering from either its shunt, patch or stent. She will be attached to multiple medical devices from syringe pumps to ventilators, receiving many different drugs, and being monitored by a series of transducers resulting in a display screen like that of an aircraft. A very highly trained nurse will be by the bedside and physicians will make regular rounds to ensure that all is well. But they rely on their experience and joint expertise to make decisions. It is a complex environment, with multiple potential interactions both within the patient and between staff. Everyone wants to do the best they can, and often have to react quickly to observed changes in blood pressure, pulse, temperature, cardiac output and so on. Under pressure, it is incredibly difficult to make the best decisions, and although experience goes a long way, there may be better evidence out there as to what to do which doesn’t leap to the front of the team’s mind during the event they are treating, especially in an emergency.

It is incredibly difficult to keep up to date with the developments in modern medicine. We practice in an information jungle. New medical articles are published at a rate of at least 1 every 26 seconds, and if a physician were to read every article she would need to read >5000 articles a day9. How is it possible to sort the wheat from the chaff? And there is a lot of chaff. We need help to sort this out, and certainly access to the literature close to the bedside. The whole field of Knowledge Management has grown around such proliferation of sources, helping us to find ways to store, catalogue, interrogate and interpret this mass of data. We have astonishing search engines like PubMed and of course Google, but you need to be very precise about what you ask to get close the right answer, and whilst you can narrow down your search, you still have to do a lot of reading to get insight from the information you find.

Alternative search strategies have evolved, and a number of them have real significance for medicine. The one in the lead at the moment is IBM’s Watson, although there are several open-source options being developed and Microsoft has entered the game with Azure. Here is a short clip (from IBMs advertising) describing clearly how it works. Watson has already beaten humans at the game Jeopardy and is now said to have acquired the same amount of medical knowledge as a second year resident. These developments represent the rise of ‘the digital doctor’, and whilst we cannot fully envisage where it is going, it is clear that where the evidence is complex, massive but reasonably robust, it works. This is most likely to appear first in oncology, since most patients are in clinical trials anyway and the data are well managed. But as more data is fed into the systems and more experts join in to help teach it what they intuit, the more important these methods of decision support will become. We will have to find ways to monitor the effectiveness and safety of these decision support trees, but I think it will improve the discipline of data collection, help us realise the importance of data quality and help modify pathways like the one I show you.

The information displayed on the child’s monitor screen is a continuous display of aspects of its physiology. In other fields, engineers have used such continuous waveform monitoring to develop models that predict when something is about to go wrong, and provide warnings or even suggestions as to what to do to prevent it. These models are also based on integrating large amounts of data and employing predictive analytics. These techniques are now being applied in the intensive care unit in several centres including Toronto, Boston and Birmingham in the UK. Here is my friend Peter Laussen talking about it. When he made this film he was in Boston, but he now leads the paediatric unit at Toronto Sick Kids. T3 is beginning to work, and as more units develop similar tools (Birmingham Children’s are working with McLaren Electronics), and the machines network and learn then, with predictive ability combined with the knowledge base searchable by Watson, our chances of doing the right thing at the right time must be greatly enhanced.

I am going to jump now to the time that our baby is going to need her ‘big’ reparative operation. What is going to change there? As we stand here today, it is difficult to believe that we won’t still have to operate by open-heart surgery in the decade to come. But iterative improvement in all aspects of the process are likely to continue apace, with better materials, smaller bypass machines and the better monitoring and in procedure decision making we have just discussed. But there are already major changes occurring in how we decide exactly what we are going to do, make it just right for *that* patient, how we might minimize the trauma involved and how we quality control the entire process.

There is no getting away from the fact that surgery is a practical 3-dimensional procedure in which the operator changes the relationships of parts of the heart, and alters the flow of blood around the organ. Traditionally, planning for an operation in cardiac surgery has required the surgeon to integrate anatomical and pathological information from their training with 2 dimensional information from echocardiography, CT or MR imaging. Recently, we have become able to reconstruct images in 3D from these modalities, and with echo do so in real time at the bedside. These visual advances have been staggering, and daily I find it amazing to discover exactly how much information and detail can be both demonstrated and shared. Lets look at a few examples.

Whilst this allows much better preparation and discussion of one’s plans, you still can’t ‘feel’ what you have to do or really get to grips with scale and access. In the last few of years though, there has been a radical shift in how we can prepare for surgery, and that has come through the medium of **3D printing**. Now it is possible to print the heart of the baby that you are planning to operate on and rehearse exactly what you are going to do, as you can see in this clip prepared by Phoenix Children’s Hospital The hearts can be printed in different colours, different materials and in different sizes, including exact scale. Routes of access, avoiding at risk structures, and even pre-measured patches can be worked out, and with the whole team helping deal with complex communication issues in the operating theatre and the specific problem of small children that most people in the room cannot see what the surgeon is actually doing. As imaging and 3D printing become faster, cheaper and more precise, it is a matter of time before this approach is not just routine, but mandated. Those of us who have been using this technique have all found it valuable, but it has the additional advantage of allowing safe creativity. You can design an operation around the needs of the specific patient; personalized surgery, even designing and printing specific prostheses for the specific child, as has recently been demonstrated in Ann Arbor, Michigan where they have printed a bio-absorbable external stent for the airway.

As an aside, 3D printing and other modern forms of printing will also have an important impact on the way we manufacture and dispense drugs. Different shapes of tablet are absorbed at different rates, and we will be able to vary release for the needs of the individual. Ink-jet printing of drug dosages has even more potential for personalization and also for other routes of drug delivery for example on stents, via micro-needles, or slow release micro-polymer capsules. I can imagine that we will be implanting such systems of drug delivery at the time of surgery in the future, delivering drugs directly to where they are needed rather than having them distributed by blood or absorbed via the gut.

Most of us would not want to have a conventional operation. The anxiety, the pain, the scars etc are all to be avoided. In cardiac practice there has been increasing use of catheter-based techniques to close holes in the heart, or to stretch valves and arteries with balloons or stents. Even complex holes in the heart can be closed this way, as two papers presented from China last year demonstrated. Both closed holes with devices, but one used a mix of surgery allowing the device to be inserted under ECHO control, with no X-radiation. When I heard this paper, I thought I should buy a set of golf clubs! Who will need over-skilled cardiac surgeons!

Many other types of surgery, for example abdominal and orthopaedic make use of minimally invasive techniques using telescopes, and in some cases robots. These robots are amazing and have proven dexterity. But they are slower at the moment than humans. Because of the need to stop the heart in most circumstances, there are time limits on cardiac surgery which do not apply in other specialities, and currently the manufacturers of the robots do not foresee that they will be in use in congenital heart disease for decades. However, a mix of smaller incisions and help from the specialised instruments that have been developed will evolve quickly and will result in smaller incision, and shorter stays in hospital. Imaging supported surgical navigation to remote and specific areas of internal organs will certainly happen, and indeed is already part of core brain of the patient is superimposed on the 3D image obtained by MR preoperatively allowing instruments to be guided through to deeper layers without damage to the intervening structures. This Augments Reality, providing more valuable information to the surgical team... It remains to be seen whether health systems will pay for this transition.

I have little doubt that, if machine dexterity improves, and machine learning increases the available scenarios they can understand then such devices will form part of our armamentarium. These devices are currently controlled manually, but I was fascinated to read of developments of the developments in thought or mind control of devices.

Non-invasive imaging techniques have also contributed to ensuring that surgery is done well. Echocardiography probes can be placed in the oesophagus so that the repair of the heart can be visualized in the operating room and checked. This is done routinely in the best centres, but will, perhaps even must, be done everywhere. Having to revise operations later is much worse for the patient, and also much more expensive, than correcting any imperfections at the end of the first operation.

After surgery, recovery will continue to be managed as I described earlier, with improved monitoring and decision support. I shall assume our patient goes well and returns home well and happy, with all the data associated with their stay in hospital being stored in an electronic patient record. That however is a big assumption in the UK. Very few hospitals have an adequate Electronic Patient Record, but to take advantage of the advances in genetics, big data analytics and decision support, we need them badly. We are already well behind many other western countries, despite the fact that the NHS has more opportunities to contribute important public health knowledge because it is a single, theoretically integrated system. In the early 2000’s, the NHS started a program called Connecting for Health, which was supposed to provide such integration, but turned out to be a costly failure, estimated by the media at £20 billion pounds. We have a lot of catching up to do, and individual hospitals are facing multi-million pound bills to get in the race.

Primary care is much more computerized, but getting data from patients into those systems still requires the staff at the health centre to enter it. The patient is source of crucial information about how well they are, and how the treatment they have received has worked. Getting hold of this information, integrating it with the EPR in the hospital and the GPs data is a holy grail now close to being grasped.

I am sure you will have heard much of the publicity surrounding the launch of the Apple Watch. Some of you may be wearing a FitBit or other kind of activity monitor. Many of you will have an App on you phone that can track your whereabouts and record the work you do, the distance you travel and the heights you climb. Here is Road Bike Pro, which I have on my phone to map via GPS my cycling routes and times. There are similar Apps for running and skiing.

With the advent of nanotechnology, sensors are able to measure more variables and are becoming smaller, more sensitive, more specific, implantable, and able to communicate via WiFi or Bluetooth. From biochemical values like blood sugar to pulse rate and temperature, and from voice changes and activity related to mood these devices have huge potential to help individuals control not only their fitness, but also monitor their health and change medication. Google has produced a contact lens capable of measuring sugar concentrations which will have obvious advantages for diabetics, and tiny self powered devices are being developed to measure a huge range other things. Already these are having an impact on aspects of care. For example by fitting a GPS devise into an asthma inhaler and superimposing use data on urban maps, areas of significant stimulation like busy roads and so on can be highlighted, providing hard evidence for town planners and legislators to reduce pollution.

Already sensors exist for children, which reduce the need to disturb them to monitor basic pulse, temperature, ECG and respiration etc. This makes for more accurate monitoring, frees up nurse time and allows information systems to activate protocoled escalation policies when things don’t go right.

There is massive investment from the technology industries in this field of wearable or implantable sensors. With a proven track record in sport and this scale of investment, it seems highly likely that this will have a major impact on medicine. Let’s have a look at how it might work.

The patient will effectively be beaming back data in real time to a computer at the base hospital where data can be integrated from other patients and related to results of treatment. The physicians, with the help of complex analytics, will be able to define what are acceptable parameters for the particular thing they are measuring and which may be important to the patient, say blood sugar, oxygen or activity levels. If values were normal, the computer would leave both patient and physician alone. Above a certain threshold then we would be alerted and a phone or video call with advice could take place. But if an alarm threshold were to be reached, then we would make arrangements to either see the patient, or initiate treatment locally. Such systems would greatly reduce the need to see patients in outpatients, but demand a whole new way to relate to patients and other healthcare providers. There is the potential for wearable or implantable devices to be the source of anxiety for the worried well, a security risk, or a driver for increased cost. There is already a ‘Measured Man’, Larry Smarr and you might find it interesting to read about him. Star Trek fans will undoubtedly remember the Tricorder**,** which was capable of astounding feats of medical monitoring and diagnosis. Well Qualcomm have offered a $10,000,000 dollar prize for the first team to make one; they are down to 10 finalists, including two groups from the UK.

So our patient is at home, sending data in real time to our intelligent information system, and we are just seeing her when she needs to be seen, and ensuring that she is on the right pathway of care. Sadly, we know now that a significant number of patients with tetralogy of Fallot will need another operation in teenage to replace the pulmonary valve between the right ventricle and the lungs. For most of my working life this has needed an open operation and the implantation of a valve obtained from a human donor or an animal valve or one manufactured from animal tissue. Times are changing. Early in this century, one of my former colleagues at Great Ormond Street, Philipp Bonhoeffer developed a valve using a bovine jugular vein valve, which could be mounted on a stent and inserted into the correct place via a catheter. This worked well and has been commercialized as the Melody valve by Medtronic, Inc. Thousands have been inserted. Others worked on the aortic valve and over 100,000 of various types have been inserted in the last few years, freeing thousands from the pain of surgery.

Advances in imaging and rapid prototyping have meant that 3D modeling and MRI functional assessment have a huge role in this are, allowing the design and use of a device built to the exact needs of the patient. Wouldn’t it be good though, if we did not have to use an animal valve in this setting and could either build one from materials onto which the patients own cells will grow after insertion, or even better build one from the patient’s own stem cells. Several groups, including one at UCL led by Professor Alex Sefailian, have designed valves based on spun or extruded polymers derived from nano-technological science. These polymers can be used for almost anything, and have the advantage that the surface is designed to be suitable for human cells to attach themselves. New nano-based materials emerge constantly, and exploiting this ability to sustain human cells creates a new concept in medicine of tissue engineering.

There is real and active interest in the field of tissue engineering, sometimes called regenerative medicine. This field really began in the 1930’s when Alexis Carrel, the father of transplantation, received funding and engineering support from Charles Lindbergh, the first man to fly across the Atlantic. They saw a future that is now with us. This science is based on the observation that the body has cells within it that have the potential to become different cell types. All humans grow from the merger of two cells and during differentiation and growth develop different cell types which themselves organize into organs. Harnessing this power of growth and differentiation would give us the opportunity to repair or replace damaged cells or to build tissues and organs for replacement. Salamanders can replace their tails and zebra fish their hearts. Humans can repair their skin quite well but don’t do so well for complex organs.

I am honoured to say that I work with some of the pioneers in this field, and have been involved in its early clinical application. It is a massive field, but to give you some insight into what might be possible in years to come, and how it might change medicine, I will show you some examples, which demonstrate where this field might lead.

This is the story of Ciaran who has always been one of the first 10 of every treatment he has received. When Ciaran was born, he couldn’t breathe because his trachea was only 1mm across. He was placed on ECMO to keep him alive and I repaired his trachea with a patch. Later he needed a stent to keep his trachea open, which worked well, until 3 years later when his stent eroded into his aorta. I repaired that with another patch, but 8 years later his stent eroded into his aorta gain and the patches we used were no longer available. A group of scientists around Europe led by Prof Martin Birchall and Paolo Macchiarini had been developing techniques to use recipient’s stem cells to repopulate skeletons of the trachea prepared from human donors by stripping the donor cells from them and leaving just a collagen framework. This repopulation took place in an in vitro bioreactor. Because Ciaran did not have time to wait for this to be done, we decided to adapt the technique and let him be the bio-reactor10. This short animation shows how we did it.

He is now 5 years after his surgery, 25kg heavier and with a good quality of life. He is on NO anti-rejection drugs (his annual treatment costs very little now), and still plays the drums in show bands.

The success of this treatment (and similar ones around the world) accelerated developments and increased research funding, allowing Paolo di Coppi and his team to apply the methods to other tissues. They have engineered diaphragm used to treat congenitally missing muscle; oesophagus for oesophageal atresia; small bowel11 and bladder. We have also been able to strip cells from both liver and lung, opening the door on more complex organ transplantation without rejection. Oesophageal replacement will be next in clinical practice.

We really don’t want to be relying on human donors to provide scaffolds for organ replacement. Jonathan Fishman, working with Paolo at UCL, has demonstrated12 that rabbit muscle can be stripped of its cells, replaced by recipient rat stem cells and implanted into the rat, without being rejected, offering the potential of other species tissue being used for transplantation.

Wouldn’t it be even better if we did not have to use any animals to build organs? The combination of nanotechnology, electro-spinning, and conventional 3D printing opens up the potential for the printing of organs. This has been done with some success for the trachea**,** is developing for the ear, but can even be considered for complex organs like small bowel as shown in this slide.Atala in Wake Forest has even ‘ink-jet’ printed skin cells on to burn sites, and heart cells derived from stem cells to create a contractile heart chamber.

It seems highly likely that our young patient with tetralogy will, if she needs a pulmonary valve in later live, receive a tissue-engineered valve built from her own stem cells onto a 3D printed matrix mounted in a personalized stent and inserted via a vein in her groin, rather than requiring complex open-heart surgery. Some of these printed matrices are already being constructed of bio-degradable material and thus she may be left with a valve of her own cells, in the correct position with little or nothing remaining of what was used to get it there.

Hopefully she can now live a full and happy life, monitored from home and feeding back data continuously to our intelligent systems to inform the decisions we make with the next baby that comes in with tetralogy of Fallot.

I have outlined many changes, most relying on the rapid progress in technology with which we have become familiar. But not everyone is convinced that this is either appropriate or ethical. As Bjorn Norten Hofman put it in an analysis in the BMJ earlier this year13, we run the risk of becoming technological Titans and ethical Lilliputians. He pointed out that technology is the biggest driver of expenditure in health care, far outweighing the effects of an aging population, increased public demand, raising prices or falling efficiency. Most of the increased expenditure comes form high priced items, over-diagnosis and over treatment, and thus is particularly important in the role of screening, when all it may do is increase anxiety, reduce value and undermine trust. He is absolutely right in his view that technological advances should be subjected to the same rigorous objective review as drugs or procedures.

Robert Wachter14 is even more cynical. He argues in his book ‘The Digital Doctor’ that the disruptive change of computing in medicine is “just plain disruptive to the doctor-patient relationship”, and that medicine is being “dehumanized”. I think he goes too far. My specialty would simply not have the results it has without computers; indeed much of what we do now would simply not be possible. We have much to learn about how to use the strengths of computers and guard against their weaknesses, but we have only had about 40 years to learn to use them at all compared to hundreds of years of building the medical model we have used until now. It is my view that our learning is about to accelerate in ways we have not so far been able to imagine.

The expansion of electronic medical records across health systems, whilst replete with advantages of public health, decision-making and individual patients, also poses considerable risk, not least from data loss or hacking. Workers in California recently published [JAMA 2015:313;14] a review of data breaches in the USA, each affecting more than 500 individuals, over a 3-year period. The results were alarming. There were over 949 breaches affecting 29.1 million records, mostly associated with criminal activity, largely theft of computer equipment, but with 57 episodes of hacking. Even children’s hospitals have been subjected to denial-of-service attacks and there is significant anxiety that medical equipment and even Wi-Fi or Bluetooth enabled implantable devices are vulnerable. This may be to do with the fact that Dick Cheney has a programmable pacemaker!

It is clear that cyber security in medicine must improve if we are to take full advantage of these advances. The risks **must** be mitigated, but the genie is out of the bottle. Implantable medical devices are forecast to grow by 7.7% this year and form a $52 billion dollar business.

Medicine is rapidly changing, and we will have to learn to work differently and interact with each other in new ways. The old specialisms will wane, and new teams form. In my world, these are forming as heart teams, or airway teams; much less worried about whether you are a physician or surgeon, and more concerned with the right skills at the right time to the patient by working together. Because of technology, the patient will become more a part of that team; contributing to and owning their own records. This is reflected in the survey results about centralization and the role of IT. Most of my international colleagues are of the same opinion.

I believe many of the things I have shown you tonight will indeed be disruptive. I am optimistic that the majority of it will be advantageous. Medical life is certainly changing around me, but if we want to get benefit from all this investment and progress we need to maintain our focus on what value it has for the patient, and not for the surgeon, physician or hospital. The rest of us are here t make their lives better.

 © Professor Martin Elliott, May 2015

Special Thanks are due to the following people

**Dr Susannah Thoms**

**Mr Edward Green**

**Professor Jeff Jacobs**

Professor Andrew Taylor

Professor Paolo di Coppi

Mr Parker Moss

Mr David Barron

Mr Michael Bone

Dr Sara Pasquale

Dr Michael Burch

Dr Silvia Schievano

Professor Neil Sebire

Professor Andrew Copp

Professor Martin Birchall

Professor David Goldblatt

Professor William J Gaynor

Professor Francesco Muntoni

Members of the American Society of Thoracic Surgeons

European Congenital Heart Surgeons Foundation

Catherine Mohr, Da Vinci, Inc.

Anne Berner MP (Finland)

Afshad Mistri, Apple

**Selected References**

1. Carlsson T, Bergman G, Karlsson A-M, et al. Content and Quality of Information Websites about Congenital Heart Defects Following Prenatal Diagnosis. Interact J Med Res 2015;**4**(1):e4.

2. Licht DJ. ThePath Forward is to Look Backward in Time. Fetal Physiology: the new frontier in managing infants with congenital heart defects. Circulation 2015;**131**:1307-09.

3. Freud LR, McElhinney DB, Marshall AC, et al. Fetal Aortic Valvoplasty for Evolving Hypoplastic Left Heart Syndrome. Post natal outcomes in the first 100 patients. Circulation 2014;**130**:638-45.

4. Giroud JM, Jacobs JP, Spicer D, et al. Report form the International Society for Nomenclature of Paediatric and Congenital Heart Disease. Creation of a visual encyclopaedia illustrating the terms and definitions of the international paediatric and congenital cardiac code. World Journal for Pediatric and Congenital Heart Surgery 2010;**1**(3):300-13.

5. Stumper O, Ramchandani B, Noonan P, et al. Stenting of the right ventricular outflow tract. Heart 2013;**99**(21):1603-8.

6. Barron DJ, Ramchandani B, Murala J, et al. Surgery following primary right ventricular outflow tract stenting for Fallot's tetralogy and variants: rehabilitation of small pulmonary arteries. Eur J Cardiothorac Surg 2013;**44**(4):656-62.

7. Bitner-Glindzicz M, Pembrey M, Duncan A, et al. Prevalence of Mitochondrial 1555A→G Mutation in European Children. NEJM 2009;**360**:6.

8. Redekop WK, Mladsi D. The Faces of Personalized Medicine: A Framework for Understanding Its Meaning and Scope. Value in Health 2013;**16**:S4-S9.

9. Garba S, Ahmed A, Mai A, et al. Proliferations of Scientific Medical Journals: a burden or a blessing. Oman Med J 2010;**25**(4):311-14.

10. Elliott MJ, De Coppi P, Speggiorin S, et al. Stem-cell-based, tissue engineered tracheal replacement in a child: a 2-year follow-up study. Lancet 2012;**380**(9846):994-1000.

11. Totonelli G, Maghsoudlou P, Garriboli M, et al. A rat decellularized small bowel scaffold that preserves villus-crypt architecture for intestinal regeneration. Biomaterials 2012;**33**(12):3401-10.

12. Fishman JM, Lowdell MW, Urbani L, et al. Immunomodulatory effect of a decellularized skeletal muscle scaffold in a discordant xenotransplantation model. Proc Natl Acad Sci U S A 2013;**110**(35):14360-5.

13. Hofmann BM. Too Much Technology. BMJ 2015;**350**:h705.

14. Wachter R. *The Digital Doctor*. New York: McGraw Hill, 2015.