According to Dr Luigi Biasucci, “Inflammation is one component in a complex pathological process. Its role in the progression and development of atherosclerosis is probably different from its role in acute coronary syndromes, and it is probably more important in some patients than others.”

The inflammatory marker C-reactive protein has been shown to be a good predictor of future coronary events. People with the highest overall risk tend to be those with the higher levels of C-reactive protein. “However, the relative risk attached to high C-reactive protein levels is reduced when risk factors such as obesity, diabetes, and hypertension are taken into account, suggesting that inflammation is probably a reflection of the patient’s overall cardiovascular risk,” explained Dr Biasucci.

“Adipose tissue produces a large number of proinflammatory cytokines, and there is a strong correlation between obesity, metabolic syndrome, diabetes, and inflammation.”

Even people with relatively low levels of C-reactive protein seem to be at greater risk of coronary events. Dr Biasucci believes that these people may have something hyperreactive that can be triggered to induce plaque rupture or thrombus formation. There could be thousands of possible triggers, including viral or bacterial infection, high lipid levels, and stress.

Dr Biasucci said that the process triggered is probably not only inflammatory, but also involves activation of the coagulation system with production of prothrombotic and antithrombotic products. Research efforts need to concentrate on unravelling this activation process so that targeted treatments can be developed. “Statins, angiotensin-converting enzyme inhibitors, or angiotensin-2 inhibitors are the best therapies we have so far. These have strong anti-inflammatory effects, but we don’t know whether the reduction in events is really due to their anti-inflammatory role, or a reduction in cholesterol, or improvement in blood pressure and endothelial function,” he said.

Dr Biasucci’s group has recently shown that tumour necrosis factor-alpha blockers reduce activation of monocytes from patients with acute coronary syndromes in vitro. Other researchers have shown that an antibody for C-reactive protein reduces experimental infarcts in animals. Dr Biasucci pointed out, “We know that C-reactive protein is an important effector of complement and inflammatory cascade after damage. But what I would like to understand is how inflammation causes that damage. This antibody could be useful in infarction if it blocks C-reactive protein,” he continued. “But I do not think it will block the event as it is a cascade, and a large number of other factors such as interleukin-1 beta, interleukin-6, interferon-gamma, and lymphocytes would still be active.”

Pathological studies have shown that the bacterium *Chlamydia pneumoniae* is found in high concentrations in atherosclerotic plaques and the myocardium of patients who died from myocardial infarction (MI). “It is probably not an innocent bystander, as it can produce a number of products, such as heat shock proteins,” Dr Biasucci said. “A number of studies have shown that heat shock proteins are associated with the development of heart disease. There are high levels in almost all patients with MI or unstable angina, and they can cross-react very easily with the human ones, as these proteins are well conserved throughout evolution.”

In ischaemia, human endothelial cells, monocytes (see figure),

**Figure.** Confocal microscopy showing activation of nuclear factor kB p65 (green), a key regulator of inflammatory gene expression, in monocytes. In nonstimulated monocytes (left), p65 was distributed throughout the cytosol. After stimulation with 25 micrograms of C-reactive protein (right), p65 accumulated in the nucleus (blue).
and myocardial cells express a heat shock protein that is 85% similar to those produced by \textit{C. pneumoniae} and \textit{Helicobacter pylori}. Dr Biasucci proposes that these human heat shock proteins might elicit an autoimmune reaction, producing antibodies, interferon-gamma, and natural killer lymphocytes based on the bacterial antigen, and that these could induce damage. “The human heat shock proteins cross-react with the antibodies produced by a process called antigenic mimicry and elicited by a previous contact with the pathogen antigen. This might explain the importance of infective agents but lack of efficacy of antibiotics given after the coronary event.”

Macratials did not support the use of antibiotics as a treatment for coronary heart disease,\textsuperscript{3} but Dr Biasucci believes that they still may have a role. The trials implied that because the antibiotics did not work, infections did not play any role in ischaemic heart disease, but Dr Biasucci does not think that the antibiotics were used in the right way. He said prospective studies are needed to look at the effects of giving antibiotics to patients with high markers of inflammation and high antibody titres against \textit{H. pylori} and/or \textit{C. pneumoniae}, as the data so far have been retrospective.

He suggested that one way of reducing cardiovascular disease in later life might be to vaccinate the young against \textit{H. pylori} and \textit{C. pneumoniae}, or to treat the infections when they occur. But diagnosis is often difficult. “Another possibility is to test young people and treat those who are positive,” he said. “Treating a 60- to 70-year old man with advanced atherosclerosis with antibiotics is too late. The process has already gone too far, and it cannot be stopped by a 1-month or longer course of antibiotics.”

Dr Biasucci cautioned that while the role of inflammation in plaque rupture is an important area of research, it cannot be the only route followed. “If we were able to understand the mechanism of plaque rupture or the causes, we would be able treat or prevent 50%-60% of myocardial infarctions. However, another 40% are not caused by plaque rupture, but by activation of the endothelium, and 10% of patients who have an MI have normal arteries.

“‘The point is that inflammation is a complex problem. Looking for markers of activation and looking for causes of plaque rupture is extremely useful, but is not all the story.’”

\textit{Ingrid Torjesen is a freelance medical writer.}

\section*{References}


\section*{Pioneers of Cardiology: Francis Fontan, MD}

\textbf{In 1986, 12 men in an airport hotel decided to found the European Association for Cardio-Thoracic Surgery. Dr Fontan reflected upon its beginnings and development with Barry Shurlock, MA, PhD.}

\begin{figure}[h]
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\includegraphics[width=0.3\textwidth]{francis_fontan}
\caption{Francis Fontan, MD}
\end{figure}

\begin{quote}
Unlike so many new ventures that are of uncertain authorship, there can be no doubt who founded the European Association for Cardio-Thoracic Surgery (EACTS). Dr Francis Fontan, honorary professor of cardiac surgery at the University of Bordeaux, France, and president of the Scientific Council of the Centre for Cardiothoracic Surgery, Monaco, was the man responsible. With the help of his colleague, Louis Couraud, MD, of the Hôpital Xavier-Arnozan, Pessac, France, Dr Fontan invited some of the most distinguished cardiac and thoracic surgeons of the day to meet on 1 March 1986 at Schiphol Airport, Amsterdam, The Netherlands. He returned home the same day with a plan for a brand new European association.

Dr Fontan was so confident of the success of the first annual congress, held the following year in Vienna, Austria, that when a financial guarantee was required he and the local organiser, Dr Ernst Wolner, MD, provided it. “I took a chance!” he said.

Dr Fontan, who in 1968 devised the eponymous procedure for redirecting the circulation of congenitally malformed blue babies, had already shown his interest in drawing together Europe’s cardiothoracic surgeons in the unlikely setting of the ski slopes of the Alps. Inspired by similar meetings that took place each year in the mountains of Colorado, he and Dr Lucio Parenzan, MD, from Bergamo, Italy, arranged for 30 or 40 distinguished surgeons to meet informally, first at Cervinia, Italy, in the shadow of the Matterhorn, and then at Courchevel, in the French Alps. Dr Fontan remembers that a morning’s skiing was followed by a late afternoon or evening session of presenting papers. “It was a kind of ‘exercise’ for people before they presented their papers in a more formal setting,” he said.

Recalling the birth of EACTS, Dr Fontan said, “Hans Huysmans, MD, PhD, from the University of Leiden, The Netherlands, helped organise the first meeting at Schiphol. It was held in a room at the Hilton Airport Hotel. I had no specific plans, it was just an idea. Each year at that time I used to go to the meetings of the American Association of Thoracic Surgery (AATS) and other societies in the United States.” He continued, “To establish our work in the scientific community, it was necessary to go to America and have our papers ‘stamped.’ I wanted to help those who could not
\end{quote}
afford to go, for example, to San Francisco or San Diego.” He soon found there was support for his idea.

“At the Schiphol meeting, everyone agreed with me, and then in successive meetings at Frankfurt and Paris (also held in airport hotels), those present laid down the principles on which EACTS was to be founded. We decided on a ‘fair proportion’ of cardiac and thoracic surgeons, with the president being a cardiac surgeon serving for 2 years, followed by a thoracic surgeon for 1 year. The council had 7 cardiac surgeons and 3 thoracic surgeons. The constitution and by-laws were based on those of the AATS, and were largely written by Keyvan Moghissi, MD, from Hull in the United Kingdom.”

At a time when many French specialists found it difficult to accept that English had become the international language of science and medicine, Dr Fontan suggested that EACTS should operate in English. He prepared for his own forays into the English-speaking world at a Berlitz language school.

There seems to have been no dissent among the 12 people Dr Fontan invited to participate in the founding of EACTS: They insisted that he be the first president, with Dr Moghissi, a fluent French speaker, as vice-president, Marko Turina, MD (Zurich, Switzerland), as secretary general, and Ingolf Vogt-Moykopf, MD (Heidelberg, Federal Republic of Germany), as treasurer. Hans Borst, MD (Hannover, Federal Republic of Germany), became the editor of the European Journal of Cardio-Thoracic Surgery (EJCTS), which from the beginning was a key part of the plan. The only member of the 12 who was not on the council, Dr Wolner, was given the task of organising the first congress in 1987, to be held in his native city of Vienna. He later sat on the council and became a president of the association.

Happily, Dr Fontan recalled, the first meeting was a great success. “Almost 1000 people attended, of whom 500 were delegates, and we were strongly supported by industry. Surgeons throughout Europe had the chance to meet in the same place; there were also many people from non-European countries present. It was not a great financial success, but at least we didn’t lose money.”

The next meeting took place in the following year in Dr Fontan’s home town of Bordeaux, France, and attracted twice as many delegates. Since then, the meeting has grown year by year, so that the 19th meeting held last year in Barcelona, Spain, attracted more than 3000 attendees, making it the world’s largest assembly of cardiothoracic surgeons. In the beginning, membership of EACTS was only open to surgeons with a senior academic appointment, but in recent years the membership has been broadened to include a wider spread of people, including trainees. The publication of EJCTS was for some years plagued with financial problems, but after a change of publisher in 1997, it now “brings some money into the association,” said Dr Fontan. Academically it has also improved, and in 2004 commanded an impact factor of 1.616 (Journal Citation Reports 2004, published by Thomson Scientific), approaching that of major US journals.

EACTS funds 7 awards. The largest is the Francis Fontan Prize of €30 000, which is presented to a young cardiothoracic surgeon to allow him or her to spend a year at a European centre. “It was suggested by a former president. These things are usually posthumous, but I could hardly object,” commented Dr Fontan, who chairs the jury that makes the award. Recipients have included physicians from Europe and elsewhere, including a US citizen and others from China and India.

EACTS has today become a major force in Europe and the world in general. Constituents now come from 70 countries around the globe, and membership automatically ensures entry to its US “cousin,” the Society of Thoracic Surgeons. Among its recent achievements are the online journals Multimedia Manual of Cardiovascular Surgery (http://mmcts.ctsnetjournals.org/) and Interactive Cardiovascular and Thoracic Surgery (http://icvts.ctsnetjournals.org/). When asked what the key factor was that made EACTS successful, Dr Fontan had no doubts: “It was the members of the first council and their successors, who were all devoted to the cause, and the activities of the nominating committee that proposed new members.”

Barry Shurlock is a freelance medical writer.

Surgeons at 4 centres in Europe are conducting trials to carry out successful beating human heart transplants using a new system designed to maintain human organs in a functioning state outside the body. The first such procedure in the United Kingdom was performed at Papworth Hospital near Cambridge on 22 May 2006 by a team of surgeons led by Dr Rosengard, a professor of cardiology who trained at Johns Hopkins University, Baltimore, Md, and who is the principal investigator for the trial in the United Kingdom.

The heart was removed from the donor at Addenbrooke’s Hospital in Cambridge and placed in a specially designed

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**Beating Heart Transplantation**

**Following the first transplant in the United Kingdom using a beating heart, Bruce Rosengard, MD, FRCS, discussed the procedure with Mark Nicholls.**
device, (see figure), the TransMedics Organ Care System (TransMedics, Inc, Andover, Mass). The new system has significant benefits over conventional transplant technology, which keeps organs waiting to be transplanted in a cold state with no blood circulation and sees them deteriorate after 4 to 6 hours.

By using the TransMedics device, surgeons have the opportunity to evaluate the organ immediately prior to transplant and to test it more extensively for existing diseases. More comprehensive tissue matching may also be possible in the future, which could reduce the risk of organ rejection, and the Organ Care System may also allow hearts to be transported to more distant locations, broadening the number of usable organs as well as the number of potential recipients.

In the TransMedics Organ Care System, the heart is perfused with warm oxygenated blood from the donor in a sealed chamber.

In this case, the heart was transferred in the organ care system to Papworth Hospital where it was transplanted into the recipient. The patient was a 58-year-old man from Norfolk with terminal heart failure. Dr Rosengard said that after the transplant the patient was doing “extremely well,” and went on to say, “We are excited by the possibilities that the Transmedics Organ Care System offers. Papworth is one of only 4 hospitals in Europe currently taking part in this trial, and if the system continues to prove successful, it could significantly increase the number of donor hearts available.”

The first beating heart transplant operation was carried out on 16 January 2006 at the Bad Oeynhausen Clinic for Thoracic and Cardiovascular Surgery in North Rhine-Westphalia, Germany, by a team led by Reiner Körfer, MD, professor and medical director of the Heart and Diabetes Centre. The recipient was a 55-year-old female patient.

Dr Rosengard said, “The next step after this is to retrieve hearts from a group of donors where death is not by cessation of brain function but by cessation of heart function. We believe we can take hearts from these patients and resuscitate them on the device.” He referred to the scenario of the early heart transplants, where organs were taken from nonheartbeating donors and the organ was resuscitated once introduced into the recipient. He said, “The implications are manifold. More research and development needs to be done, but what this will mean is that we can double, possibly triple, or potentially quadruple the total number of transplants we can do in a year.”

This is much needed, as at present, the number of heart transplants is progressively falling. During the period April 2005 to March 2006, a total of 146 people received a heart or heart and lung transplant, down from 170 during 2004–05.

Dr Rosengard explained that the recent operation took around 4 hours and was no different from any other transplant from the recipient’s point of view. “What was different here is that when we stopped the heart and removed it from the donor, we immediately linked it up to the device,” he said. “The heart only stops beating for about 20 minutes before it is perfused with warm oxygenated blood taken from the donor. Once the heart starts beating again rather than remaining in a state of suspended animation, it can be transported with a normal blood supply. Not only is it not deteriorating, it is actually getting better.” The heartbeat is then stopped for about an hour while it is placed in the recipient.

“In the UK, there is considerable travel time for donor organs, because that is mainly done by ground transport,” Dr Rosengard pointed out. “As a result, most organs that are transplanted have between 3 and 5 hours without a blood supply. But what this is going to mean is that organs will only have one to one-and-a-half hours of ischaemia, which is a considerable saving. For good hearts, this will mean they are in a better state of preservation. Hearts with a shorter period of cessation of beating do extremely well — we know this from experience.”

Dr Rosengard referred to evidence gleaned from domino heart operations where heart and lungs are donated to one patient and that patient’s heart to a second recipient. “The heart that goes to that second recipient does much better,” he said.

The ongoing trial using the TransMedics Organ Care System is being carried out at 4 European centres. These are Papworth and Harefield hospitals in the United Kingdom, and Berlin and Bad Oeynhausen hospitals in Germany. The Pitié-Salpêtrière Hospital in Paris, France is joining the project this month. A further trial planned for North America has yet to start. Transplants on a total of 20 patients in the 4 original centres are planned.

“The device has worked very well thus far — in our case, it has been spectacular,” said Dr Rosengard. He puts much of that down to the team effort at Papworth. For the May 27 transplant, Dr Rosengard recovered the organ with Cliff Choong, FRACS, of the Department of Cardiothoracic Surgery at Papworth, while David Jenkins, MS, FRCS, of the Papworth Hospital Department of Cardiac Surgery, started the recipient operation. Dr Rosengard also praised the recipient: “He did have the opportunity to have a routine transplant but decided it was important to help make these advances happen.”

Mark Nicholls is a freelance medical journalist.
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