External cardiac pacemakers date back to the late 1920s and early 1930s, much of the credit going to Australian anaesthetist Mark Lidwell, MD, and American physiologist Albert Hyman, MD. Dr Hyman had an interest in reviving the stopped heart, and he called his first device by the name it has since retained—the artificial pacemaker. Pacemakers were originally mains powered, but in the late 1950s, electrical engineer and TV repairman Earl E. Bakken produced the first battery-operated pacemaker.

It was Dr Rune Elmqvist, however, who made the breakthrough to develop the first fully implantable pacemaker in 1958, after prompting from pioneering cardiac surgeon Åke Senning, MD, of the department of thoracic surgery, Karolinska Hospital, Stockholm, Sweden. Lars Rydén MD, FRCP (pictured left), who currently works at the department of cardiology at the Karolinska University Hospital, sums up the impact of that advance: “To go from an external system with leads through the skin into the heart with all the risks for infection—sometimes serious—to a totally implanted system was a major step forward. Without it, pacing would not have become such a success story. It seems so simple now, but it was not when it was first invented and put into action.”

Born in Lund, southern Sweden, in 1906, Dr Elmqvist gained his MD in 1939, although, interestingly, he never practised medicine. While still a student, he began to develop

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**Figure 1.** A youthful Dr Elmqvist is shown working on an electrocardiograph galvanometer in his workshop circa 1930.

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**Spotlight: Giuseppe Mancia, MD, PhD**
From Olympic sprint hopeful to hypertension expert: Dr Mancia, professor of medicine at the University of Milan-Bicocca, Italy, has been one of the leading European researchers in hypertension for more than 25 years. Page f111

**History of Cardiology: Desmond Julian, MD**
A developing interest in the technique of closed-chest cardiac resuscitation and the problems encountered in its successful application prompted cardiologist Dr Desmond Julian to initiate the introduction of the coronary care unit. Page f113
In 1927, he developed an electron tube potentiometer to measure pH, and in 1931, he came up with a portable multichannel electrocardiograph for recording 3 leads simultaneously.

In 1940, he became head of development at the medical electronics firm Elema–Schonander, a company that later became Siemens–Elema. Siemens–Elema continued to make pacemakers until 1994 when the American company St Jude Medical, of St Paul, Minn, bought the operation. In 1948, Dr Elmqvist introduced the first inkjet recording system—the Mingograph—for direct analog recording of physiological signals. This system saw wide use in the recording of electrocardiograms and electroencephalograms and was also adapted to phonocardiography.

Dr Senning implanted Dr Elmqvist’s first rechargeable implantable cardiac pacemaker into a patient with complete heart block and Stokes–Adams attacks. The patient’s wife, Else-Marie Larsson, had persuaded Drs Senning and Elmqvist to insert the device into her husband, Arne, after she had heard of their experiments (Figure 2).

Dr Senning implanted 2 electrodes into the myocardium via a left-sided thoracotomy, and he placed Dr Elmqvist’s pacemaker in the abdominal wall. It failed after 3 hours, but it was replaced by a second, identical model, which worked for 6 weeks. Dr Senning, who also developed the atrial inversion operation (the Senning repair) for transposition of the great arteries, later moved to Zurich, Switzerland, to become professor of surgery at the University Hospital. There, he and his team performed the first heart transplantation in Switzerland in 1969. He worked at the University Hospital until 1985, and he died on July 21, 2000, aged 85.

Dr Elmqvist’s first implantable pacemaker (Figure 3) had a pulse amplitude of 2v and a pulse width of 1.5ms, at a constant rate of 70 to 80 impulses per minute. It used silicon transistors, which were relatively new at the time and were regarded as more efficient than the older germanium transistors. Two nickel cadmium battery cells powered the device, which was encapsulated in epoxy resin. The unit had a diameter of about 55 mm and was 16 mm thick. The early units had 2 polyethylene-coated twisted stainless suture wires with the ends fixed to the heart to serve as electrodes. However, this stainless steel thread was not durable enough to cope with a heart beating 100 000 times a day and the lead flexing with each beat. A new, longer-lasting, extremely flexible lead rapidly evolved. The batteries in Dr Elmqvist’s pacemaker had only a limited charge, and a radio loop antenna enabled the batteries to be recharged each week by beaming radio energy through the skin to the pacemaker antenna.

During his lifetime, that first patient, Arne Larsson, had almost 30 pacemakers fitted. He later used himself as an example to those who doubted the success of pacemakers, and he became chairman of a patient advocacy organisation that successfully influenced pacemaker manufacturers to improve their products. His heart and its pacemaker worked well until his death on December 28, 2001, in Stockholm, Sweden, at the age of 86. Even then, neither his heart nor his pacemaker had failed him—he died from an unrelated condition.

Dr Rydén emphasises that the pacemaker was not Dr Elmqvist’s only contribution to modern medicine. “He was an ingenious engineer, and the Mingograph system was another very important innovation he contributed,” he says, pointing out that although Elema–Schonander was not the only company developing such systems, “to be a pioneer encourages and stimulates the activity of many others, and this is important enough in this perspective. He and Senning are 2 of only a few, if any, Swedes who are written about internationally in the history of cardiac pacing.”

Dr Rune Elmqvist’s son, Hakan Elmqvist, PhD, professor of medical technology at the Karolinska Institute, says his father made
several important contributions, but his electrocardiographic
developments and the first implantable pacemaker are the
most notable. “I think there must be around 5 million people
today with cardiac pacemakers fitted, and it has become a
major industry,” he says. “Death from Stokes–Adams attacks
has nearly disappeared, and most patients with a cardiac
pacemaker have the life of a normal healthy person.” He
adds, “Before cardiac pacemakers, patients had perhaps a 50%
chance of survival at 1 year, so they have been an enormous
advantage to the patient and have made a great deal of dif-
ference the world over.”

Dr Hakan Elmqvist also recalls the impact that news of
the invention had in the family home. “When news of the
invention spread,” he says, “I remember the telephone at our
house started ringing at all hours of the day and night with
people who wanted to get their hands on the device.” He also
explodes a myth. “It is often said that the first pacemaker
was constructed by my father on his kitchen table, but that
was not actually true.” But, he says, “It is true, however, that
the first pacemakers were moulded in Kiwi shoe-polish
tins!”

In 1976, Dr Rune Elmqvist received the Gold Medal of
the Royal Academy of Technological Science of Sweden. He
lived to celebrate his 90th birthday with family and friends
on December 1, 1996, and he died soon afterwards on
December 15, 1996.

Mark Nicholls is a freelance medical writer.

Spotlight: Giuseppe Mancia, MD, PhD

The Story of a Man Who Went From Olympic Sprint Hopeful
to Illustrious Hypertension Expert

Dr Giuseppe Mancia, professor of medicine and chair of the Department of Clinical
Medicine, Prevention and Applied Biotechnologies at the University of Milan-
Bicocca, Italy, has been one of the leading European researchers in hypertension for
more than 25 years. He talks to Emma Baines, MSc.

Dr Giuseppe Mancia was born in Carrara in northern
Tuscany in 1940. Although destined for an illustrious
career in medicine, as a young man he seriously considered
a very different career path. In 1957, while finishing his
secondary school education, he ran the 100 metres in 10.7
seconds and became a probable Olympic runner for the
Olympic Games, which were to take place in Rome in 1960.
He faced a difficult choice between going to Padua
to train as an athlete and going to study medicine at Siena.
“I would have done it if I was sure of participating in the
Olympic Games, because that would have been an experience
that you would never think of giving up. But in the end, I accepted my family’s suggestion that I could still
continue to run if I went to study medicine.” He recalls,
“There was a good team at Siena, but I did not improve
enough, and in the end I missed the games.”

He graduated from the Medical School of Siena in 1964.
There, he had first become interested in hypertension
thanks to the influence of Cesare Bartorelli, MD, a founding
father of European hypertension research and, at that
point, professor of internal medicine at the University of
Siena. For several years, Dr Mancia worked under him,
looking into the mechanisms governing the neural control
of circulation in animal models.

In 1966, Dr Bartorelli moved to the Medical School of
Milan, Italy, and Dr Mancia left Siena to accompany him.
There, he completed his PhD in physiology in 1970. He has
worked in Milan ever since, with the exception of 3 years
in the United States. Dr Mancia first spent 2 years as a
research assistant at the Mayo Clinic, Rochester, Minn,
from 1972 to 1974. “They were very exciting times,” he
says. “I was very lucky when I went to the United States,
because at the Mayo Clinic I worked with 2 of the best
scientists in the world, John Shepherd, MD, and David
Donald, MD. They taught me a great deal and made my experience there unforgettable and extremely productive.”
He published several important papers during his time
there, including the first demonstration that the release of
renin from the kidney is governed by reflexes in the heart.

When he left the Mayo Clinic, he spent a further year in
the United States as a postgraduate fellow at the
Postgraduate Cardiology School of the Junior
Commonwealth University in Richmond, Va, learning to
do cardiac catheterisation. “I wanted to learn this technique
to transfer some of the concepts developed in animals into
humans,” he says.

On his return to Milan, he started applying the tech-
niques he had learnt in Virginia to clinical studies of the
autonomic control of circulation in people with cardiovascular
diseases. He developed a new technique for measuring
the number of bursts of activity of the sympathetic
nervous system in people by inserting microelectrodes into
the perineal nerve. “This allowed us to look at sympathetic
involvement in a number of conditions, not only hyperten-
sion but obesity, heart failure, and coronary disease,” he
recalls. “In a number of instances, this allowed the first
demonstration that the sympathetic nervous system was involved in these conditions at all.”

Dr Mancia also was one of the first doctors to use ambulatory blood pressure monitoring to measure the variations in blood pressure throughout the day in hypertensive and normotensive patients. His team was the first to demonstrate the “white coat effect.” In a landmark study published in 1983,1 they showed, using intra-arterial blood pressure measurements, that patients’ blood pressure usually went up when a doctor was in the room. “We couldn’t believe our eyes,” says Dr Mancia. “There were people in whom blood pressure increased by nearly 18 mm Hg during the 10 minutes of the doctor’s visit.”

In 1992, he left the central hospital in Milan and moved to the San Gerardo Hospital in Monza, Milan (see Figure), where he set up an observational study recording the ambulatory blood pressure of a random sample of 3000 people from the population of Monza—the Pressione Arteriose Monitorate E Loro Associazioni (PAMELA) study.2,3 Dr Mancia says, “PAMELA has been a lot of fun in its way. We’ve been able, by studying a large sample of the population of Monza, to amass a lot of data from each subject.”

The study has identified blood pressure variability as one of the key factors affecting outcomes for hypertensive patients. “Our fate depends not only on the level of our blood pressure, but also on how variable it is,” Dr Mancia explains. “The greater the variability, the worse for the patient’s outcome.” Dr Mancia points out that PAMELA is still running and is continuing to provide new insight into the factors that predict morbidity and mortality in subgroups of patients with hypertension.

One of Dr Mancia’s goals for the future is to finally identify the cause of essential hypertension. “This problem has completely eluded investigators so far,” he says. “We have the frame, we have the factors, but it is impossible to know in any particular patient why his or her blood pressure is elevated.”

Throughout his career, Dr Mancia has accumulated many awards for his work, including the Heymans Lecture and Award of the International Society of Pharmacology, the Folkow Award of the European Society of Hypertension, and the Life Achievement award of the Italian Society of Hypertension.

He also received the prestigious Franz Volhard Award from the International Society of Hypertension at its meeting in October last year, in recognition of his outstanding work on the role of the autonomic nervous system on blood pressure control in cardiovascular events.

In addition to his awards, he has been president or chairman of half a dozen specialist societies, including the International Society of Hypertension (1988–1990), the European Society of Clinical Investigation (1980–1982), and the European Society of Hypertension (1999–2001). Dr Mancia will chair the 17th European Meeting on Hypertension in Milan from June 15 to 17, 2007, where the European Society of Hypertension and European Society of Cardiology will announce new joint guidelines for the management of hypertension.

Emma Baines is a freelance medical writer.

References
The Concept of the Coronary Care Unit Was First Suggested by a Cardiologist From Scotland

A developing interest in the technique of closed-chest cardiac resuscitation and the problems encountered in its successful application prompted a cardiologist from Edinburgh, Scotland, Dr Desmond Julian (pictured right), to initiate the setting up of what would become known as the coronary care unit. Diana Berry relates the story.

William B. Kouwenhoven, MD, and colleagues pioneered the idea in the United States that closed-chest massage could produce adequate arterial blood pressure; in 1961, Peter Nixon, MD, a lecturer in medicine at Leeds University, demonstrated this technique for the first time in the United Kingdom. In an article in The Lancet,1 he reported the successful management of asystolic cardiac arrest in a patient with gross mitral disease, and he detailed the changes to the arterial pulse throughout recovery.

Dr Nixon also set out the case report of a 43-year-old woman with a past history of pulmonary oedema and congestive heart failure who was suffering from mitral valve disease and atrial fibrillation. The patient’s heart was enlarged, with a cardiothoracic ratio of 77%, and Dr Nixon performed left-heart catheterisation. Although the patient seemed comfortable and the monitoring ECG showed no change from the previous week, within 15 minutes of the procedure the patient became unconscious.

Dr Nixon then performed closed-chest massage; as he knelt on the table beside the patient, “pressing on the sternum with outstretched arms, it was not difficult to produce arterial pressure pulses reaching more than 100 mm Hg.” Massage at a demanding rate of 80 to 90 strokes per minute continued, with occasional slowing to allow for insufflation of the lungs. After 10 minutes, all involved agreed that “in this case the circulation was as well maintained by closed-chest massage as it could be by direct massage.” In his article,2 Dr Nixon listed the possible injuries that closed-chest massage might cause, such as fractured ribs, haemothorax, haemopericardium, and laceration of the liver. He pointed out that the frequency of such injuries diminishes with proper staff training and familiarity with the technique.

Dr Desmond Julian wrote an article on the treatment of cardiac arrest when he was a senior medical registrar at Edinburgh Royal Infirmary, Scotland. His article stated that “cardiac arrest due to ventricular fibrillation or asystole is a common mode of death in acute myocardial ischaemia and infarction and is responsible for several thousand deaths each year.” Interestingly, cardiac massage was infrequently attempted because it was assumed to be useless for patients with severe heart disease, but Dr Julian noted that in many cases, pathological studies revealed only slight myocardial damage.

Importantly, Dr Julian added that when myocardial damage is not severe, “the major cause of failure is delay in starting effective cardiac massage, for a delay of more than 4 minutes means a very high mortality and morbidity.”

In attempting to deal with this problem, physicians entered the realm of special intensive care facilities that later became known as coronary care units. In these units, all the medical, nursing, and auxiliary staff would receive training in the necessary techniques. In Dr Julian’s opinion, the necessary apparatus, if dedicated specifically to such units, would not prove prohibitively expensive. His opinions were in accord with Dr Nixon’s; he stated that “closed-chest cardiac massage has been an outstanding advance and in our opinion it is always capable of producing good femoral artery pulsations even in patients dying of shock.”

Some 5 years later, cardiologists moved on to assessing the relative benefits of home or hospital care for patients suffering from myocardial infarction. In an article entitled “Problems in Evaluating Coronary Care Units,” Dr Julian, together with Michael Oliver, MD, FRCPed, and Kenneth Donald, FRCPed, both of Edinburgh Royal Infirmary, outlined the comparisons that had been made, and detailed the problems (or, perhaps, virtual impossibility) of conducting valid controlled trials.

They stressed that in the 5 years after the establishment in 1962 of the earliest coronary care units providing continuous cardiographic monitoring, “a remarkable uniformity of opinion concerning the design, equipment and staffing of coronary care units” had developed, although “by contrast there [were] striking differences in admission and discharge policies, and considerable controversy on the real value of coronary care units as opposed to conventional methods of treatment.”

On the basis of experiences in the coronary care unit set up in Edinburgh Royal Infirmary, the authors of the article examined factors that included unit design, staffing, differences in clinical management policies, age and sex of patients, admission and discharge policies, and difficulties in evaluation. In summarising the results of the study, they stressed the difficulties in assessing the full extent of achievement of intensive coronary care. In their opinion, this was partly because “striking differences in policy among coronary care units, particularly with regard to admission and discharge of patients, and partly because the lack of comparability between patients in coronary care units and those in general..."
After Dr Julian’s original article, the idea of resuscitating patients in specially designed facilities quickly caught on in the United States (see Figure), but Europe was slow to follow. Despite such misgivings, trials of home versus hospital treatment were later undertaken in various centres in south-west England and in Nottingham. The study group comprised men <70 years of age who had suffered an acute myocardial infarction within the previous 48 hours. “Four hundred fifty patients were randomly allocated to receive care either at home by their family doctor or in hospital initially in an intensive care unit.” The groups were similar in terms of age and disease history. In follow-up studies during the year after onset, “the mortality rate at 28 days was 12% for the random home group and 14% for the random hospital group; corresponding figures at 330 days were 20% and 27%.” Discussion of the trial revealed that of all factors considered, mortality was related “most strongly to age, a history of angina or a previous infarction and initial hypotension, and comparisons of treatment on subgroups of cases distinguished by these factors are important.” The trial results confirmed and, in fact, extended preliminary findings supporting home care as an acceptable form of treatment for many patients experiencing acute myocardial infarction, particularly those aged >60 years and those with uncomplicated attacks seen by general practitioners.

A further trial of home versus hospital management of suspected myocardial infarction was undertaken in 1978. The authors of this trial considered that “for the majority of patients to whom a general practitioner is called because of suspected infarction, hospital admission confers no clear advantage.” The article suggested that, despite the considerable investment of financial and human resources in the provision of hospital units and prehospital coronary care, community mortality had not changed in the past few years. The same article also pointed out that a joint working party of the Royal College of Physicians and the British Cardiac Society had dismissed the results of the Mather study on the basis of design defects, and many patients had seen doctors late after symptom onset.

Yet, this same working party unanimously advocated for “some form of specialised accommodation for the care of patients after cardiac infarction” and recommended that the United Kingdom’s Department of Health should actively develop mobile coronary care units such as those pioneered in 1966 by Frank Pantridge, FRCP, MD, CBE, of the Royal Victoria Hospital, Belfast, Northern Ireland. These units were soon reporting successful resuscitation outside hospital. Sadly, this revolutionary initiative was not immediately followed up in the United Kingdom because of doubts about cost-effectiveness, and suitably trained paramedics would not conduct good-quality resuscitation in well-equipped ambulances carrying defibrillators until the 1990s.

After Dr Julian’s original article, coronary care units such as the one shown here quickly caught on in the United States, but Europe was slow to follow. Medical wards [made] it impossible to contrast the benefits of intensive with conventional care.”

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After Dr Julian’s original article, the idea of resuscitating patients in specially designed facilities quickly caught on in the United States (see Figure), but Europe was slow to follow. However, the realisation that doctors could avoid sudden death in many cases if appropriate facilities were at hand gradually led to an expansion of the practice of continuous cardiac monitoring and an organised system of cardio-pulmonary resuscitation employing defibrillators and drugs. This also required appropriate equipment and specially trained staff. In other words, the concept of the coronary care unit, as proposed by Dr Julian back in 1961, eventually became recognised as standard practice.

As Dr Julian himself said recently when interviewed for this article, “The coronary care unit has come a long way in the 40 years of its existence. Although at one time it was anticipated that it would be gradually phased out, it seems probable that it will continue to provide a critically important component in the management of heart attacks.”

Diana Berry is a medical historian and a freelance medical writer.

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