Jubilee Editorial

Congenital heart disease: the ductus arteriosus as pathfinder

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When the Cardiac Club was transformed into the British Cardiac Society congenital heart disease was the province of those with a particular interest in morbid anatomy, embryological relations, and the exceptional in clinical practice. Thomas Peacock's volume on *Malformations of the Human Heart* published in London in 1858 remains a joy to read¹; his illustrations are outstanding and some of his observations on natural history remain relevant. But it was a pathologist, Maude Abbott, encouraged in clinical orientation by Sir William Osler, who was the most prolific contributor in the first part of this century. Her atlas based on 1000 cases gathered from her own material and from the world medical literature was a landmark when it was published from Canada in 1936²; her systematic study and classification provided the foundation for future developments.

The early experience

The status of congenital heart disease was to be changed dramatically over the next few years. Although first thoughts on surgical treatment had been raised by Munro's suggestion in 1907 that a persistent ductus should be ligated,³ it was not until the frequency of death from bacterial endocarditis in previously undischarged patients was coupled with Abbott's observation that the original site of the infection was restricted to the narrowed pulmonary arterial end of the ductus that surgical ligation was first attempted to arrest further spread and a fatal outcome. Technical reasons accounted for death of the patient four days after the first ligation on 16 March 1937.⁴ Hubbard in Boston Children's Hospital recognised from his own clinical experience and from that of the medical literature that death with persistence of the ductus in infancy was often associ-

ated with other malformations and that death from bacterial endarteritis was uncommon before the age of ten.⁵ His surgical colleague, Gross, after experimental work on human necropsies and at operation on living mongrel dogs, developed an approach through the left pleural cavity, with collapse of the left lung and identification of the ductus by its relations to the left recurrent laryngeal nerve.⁶ Gross and Hubbard concluded that the optimal age for surgical treatment was six to seven years, although this meant introducing a new operation when disability was slight and life expectancy relatively good. This realistic approach was confirmed by the complete success of their first operation on 26 August 1938⁷ and was re-emphasised by follow up of this patient nearly thirty years later.⁸

The foresight of this calculated risk established the feasibility of the surgical treatment of congenital heart disease at a time when accuracy of diagnosis depended on the correct interpretation of clinical features and the experience of thoracic surgery was limited. This achievement fired the imagination and heralded a new era. The ductus had pointed the way, had emphasised the importance of natural history in timing, and revealed the potential of surgical treatment. The successful cure of bacterial endarteritis by ligation of an infected ductus by Tubbs in London on 5 December 1939 was the next landmark^{9 10} soon to be followed by Touroff in America on 27 January 1940.¹¹ Subsequent developments in the management of the ductus show how advances in congenital heart disease have been based on improved understanding of clinical features, pathophysiology, and natural history and on progress in invasive and non-invasive investigation and treatment.

The outbreak of the second world war in Europe retarded widespread development in this new field. There was much to learn and Gilchrist in Edinburgh was well placed to accept the challenge. The ductus arteriosus had been of particular interest to Edin-

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burgh physicians since the turn of the century.¹² Gilchrist, who had been resident medical officer in the Princess Elizabeth Hospital for Children in East London, had developed lasting admiration for American enterprise in medicine when he was an assistant physician at the Rockefeller Hospital, New York, and he had established a cardiac clinic for schoolchildren in the Royal Infirmary in 1928. His colleague, Sir John Fraser, had been surgeon to the Royal Hospital for Sick Children before his appointment to the chair of surgery; he was no stranger to thoracic surgery, performed lobectomies for lung cancer, and was an early advocate of surgical attempts to increase myocardial blood flow in angina by cardio-omentoplexy. "Ligate a ductus? Why not?" was his immediate response when Gilchrist first put the suggestion to him in 1939 (AR Gilchrist, 1979, personal communications). What is now a straightforward exocardiic procedure was then a major event. Andrew Wilkinson, Sir John's assistant at the time and later the first professor of surgery at Great Ormond Street, describes how the ductus was exposed, how its posterior surface was cleared with cholecystectomy forceps, and how it was firmly ligated with catgut at both ends with a clear gap between the sutures. Sir John, deep in the British surgical practice of the time, would not contemplate using silk but it was clear that surgery had come to stay. Expressing his gratitude for the opportunity to perform the first successful ligation of an uninfected ductus in Britain in October 1940, Fraser, sensing that he was on the threshold of new beginnings, wrote "You have given me the greatest surgical experience in my life" (AR Gilchrist, 1979, personal communications). Early experience needed that enthusiasm and the confidence that "in no other branch of cardiology are the results likely to be so perfect".¹³ Everyone was aware that ductal surgery broke new ground. Gilchrist's house physician, Lowe, who twenty four years later described the diagnostic value of its abbreviated form in infancy,¹⁴ demonstrated the continuous murmur to his clinical clerk, Marquis, with all the anticipatory excitement of an explorer in new territory. The physician attended the operation and with a sterilised stethoscope confirmed the abolition of the murmur before the chest was closed. Great emphasis was placed on the method of ligation and the tightness of the knot. It was important to obliterate the shunt without fracturing the media. Recanalisation could occur within a few days when catgut was used or the knot was not tight enough and a few weeks later if the media were fractured; recanalisation was then through a false channel with or without aneurysm formation. The continuous murmur had been reduced but not obliterated in two of Gross's first four patients. Nor was

the postoperative course always smooth. It was not customary to leave a drain in the pleura, pleural effusions and residual pulmonary atelectasis were common, bed rest was sometimes prolonged, and so correction of flat feet was an inherent part of post-operative physiotherapy.

Not everyone was prepared to accept the need for operation in children who appeared so well. Jones's review of his twenty five years' experience¹⁵ of the risks and complications of those early years makes daunting reading today. Benn asserted that for some of those treated surgically the immediate risk of operation was greater than the ultimate risk of bacterial infection and premature death.¹⁶ His view that "fewer cases should be operated upon" must have struck a cord with the anguish still felt by those responsible for patients who died at operation in those early years—an anguish shared by many as each surgical advance has been initiated. Their successors and their subsequent patients have good reason to be grateful for the faith which established the first steps in the elective closure of the ductus arteriosus. Initial setbacks were counterbalanced by the high risk of bacterial endarteritis, once estimated at 53% in those over three years of age.¹⁷ Its incidence bears no relation to ductal size or disability and may escape recognition until necropsy.¹⁸ In contrast, the risks of surgery during infection remained high in the pre-antibiotic era although blood cultures became negative within minutes of occluding the ductus.¹⁹ The torch had been lit and Campbell in requesting a reprint of an early Edinburgh paper explained his resolve to interest Brock in cardiac surgery (AR Gilchrist, 1979, personal communications).

Further developments

Helen Taussig's concept that the surgical creation of an artificial ductus could relieve the pulmonary ischaemia in the tetralogy of Fallot and the publication of her book on congenital heart disease²⁰ opened up the new field. Meanwhile the postwar development of the subject and its surgical treatment in Britain followed an irregular pattern. In Liverpool John D Hay, son of a much loved founder member of the Cardiac Club, took the lead in the Children's Hospital, together with Ronnie Edwards who was brought into the hospital to perform the surgery.²¹ In London Guy's Hospital became the Mecca for the diagnosis and treatment of cyanotic congenital heart disease. Campbell had played a major part in arranging Blalock's sabbatical leave in Guy's Medical School and congenital heart disease became the dominant interest of the rest of his professional life. In Edinburgh, where two cots in the

centre of the wards had been a tradition, the ductus had established the Royal Infirmary as the centre for cardiac surgery. It was many years before infants and children ceased to be referred from the Children's Hospital to the cardiac clinic; this was the converse of events in Boston where adults were treated in the Children's Hospital in the early years. In retrospect initial progress appears inordinately slow. Gilchrist's authoritative report on the ductus¹³ was based on a total of twenty eight patients, fourteen of whom were a control group observed at the time without surgery. For many the continuous murmur^{22 23} remained the key to surgery. Infants and younger children were followed until the murmur became continuous, and thereafter for possible spontaneous closure, until six or seven years of age. As complications of surgery became rare the clinical diagnosis became increasingly accepted as an indication for surgical occlusion in childhood and early adult life.

Advances in the surgical management of more complex malformations preceded the availability of investigative facilities in many centres. Early investigators were often self taught. Cine-angiocardiology and left heart catheterisation were at an early stage and available to few. In 1957 Paul Wood highlighted the unknown in a provocative symposium to celebrate the centenary of the National Heart Hospital; the report of the proceedings²⁴ does not reveal the feelings of inadequacy that many of the opening speakers must have felt. The evening before the conference James Brown, whose book on congenital heart disease had become a classic,²⁵ was much relieved to learn that he was not alone in not knowing the answers to questions which Wood had chosen for the speakers. Pulmonary hypertension with and without shunt reversal was discussed at length. The surgical view was that as long as there was some left to right shunt through a ductus success could be expected. This was challenged and the difficulties of accurate assessment of pulmonary vascular resistance emphasised.

Subsequent follow up studies have shown that even when the pulmonary arterial pressure is 75% or less than the aortic pressure, elevation of the pulmonary vascular resistance sometimes progresses relentlessly after occlusion of the ductus in childhood²⁶ and sometimes resolves completely in adults²⁷ and that the ultimate outcome could not always be predicted from an initial decrease measured in early postoperative catheter studies.²⁸ Unrelieved pulmonary vascular disease with progression of the pulmonary hypertension is well recognised after surgical closure of a defect of the ventricular septum but although the same

phenomenon may follow ductal closure it still tends to be underplayed when surgical treatment is considered.²⁹

The Centenary Symposium gave pride of place to congenital heart disease in older children and adults. This was an accurate reflection of British experience in 1957 although knowledge of all age groups had been increasing rapidly. The Scandinavian book on diagnosis demonstrated the high quality of angiocardiology that could already be obtained.³⁰ In the United States and Canada paediatric cardiology had become established as a specialty in its own right.^{31 32} In order to widen understanding of congenital heart disease in the very young Bonham-Carter early in 1957 was asked to report the findings from the Children's Hospital in Great Ormond Street. Members of the British Cardiac Society present on that occasion may recollect his opening explanation that his primary interest was in the newborn, that the hospital now felt overwhelmed by the sudden influx of cardiac problems in infancy, that he regarded medical and surgical management of congenital heart disease as a unified problem, and that greater mortality without surgery justified a high mortality from surgical endeavour. David Waterston had been appointed as cardiothoracic surgeon in 1952 and it was his figures that he was going to report. Ninety of the 217 admissions with acute cardiac illness during 1947-1953 had been under one year of age and 73% of them had died. From 1953 to 1956 surgical treatment, mostly exocardiac, had reduced this initial mortality among the 141 admissions for acute cardiac illness in those aged less than one to 57%. Forty six per cent of the 141 cases had been judged to be operable and their operative mortality had been 46%.³³

These figures provide a telling demonstration of the debt those with congenital heart disease owe to the foresight of the Boston decision to accept prevailing limitations and to initiate surgical treatment at the optimal phase in the natural history of the ductus. A decision which also exemplifies the courage of a famous Scottish revolutionary:

"He either fears his fate too much
Or his deserts are small
That puts it not unto the touch
To win or lose it all."

These early figures from Great Ormond Street also provide a striking contrast with Bonham-Carter's 1966 Mannheim Lecture in Helsinki in which he reported the impressive results of the hospital's management of transposition of the great arteries.³⁴ Those who were privileged to be present will recollect the tribute he paid to Ian Carr's detailed investigations of the disorder. They were the preface to Tynan's original contributions to the

investigation of infants and presaged the British Heart Foundation chair of paediatric cardiology in 1975. In that chair, Macartney, who had trained with Olive Scott in Leeds, before and after secondment to the Mayo Clinic, brought a fresh analytical approach to the problems of congenital heart disease which orchestrated a remarkable quartet of complementary minds and interests—Tynan, Anderson, Shinebourne—and established London in the forefront of paediatric cardiology.

The frequency of associated lesions was not always the only factor in the high mortality of the ductus in infancy. Ziegler emphasised the danger of the isolated lesion and the success of its occlusion in infancy.³⁵ Results from the Liverpool Children's Hospital confirmed his conclusions.³⁶ It is often possible to recognise clinically a large ductus during infancy but it is seldom wise to progress to surgery during the first year of life without further investigation. The unwary can be misled by deceptive similarity of the clinical features in such disparate lesions as pulmonary atresia with major aortopulmonary collateral arteries.³⁷ Fortunately cross sectional and Doppler echocardiography have replaced the invasive techniques^{38 39} that previously were necessary in the investigation of these critically ill infants. Increasing experience had led to recognition of the advantages of early elective closure of the ductus; this has been increasingly adopted during the past thirty years. The success with the ductus was not mirrored in the initial stage of surgical closure of simple defects of the ventricular septum. Few will now deny that many were closed unnecessarily at an unacceptably high risk. The tendency for large defects to get smaller or close spontaneously had been underestimated as had the risks of cardiac bypass and damage to the conducting pathways during the learning phase of intracardiac surgery. The optimal timing for surgical closure of defects of the atrial septum has not yet been agreed. Defects of the atrial septum had not been diagnosed clinically until 1941⁴⁰; those early patients were for the most part middle aged, and diagnosis was a sequel to Parkinson's development of radiology in cardiac assessment. Now that cross sectional and Doppler echocardiography can establish the diagnosis and precise size of the defect⁴¹ I believe that the ostium secundum will follow the lead of the ductus and should be closed electively during the first few years of life.

Prematurity and the ductus

The greatly improved survival in recent years of premature infants of low birth weight has been associated with increased understanding of the normal

ductus.⁴² Unfortunately lack of precision in nomenclature has confused many into thinking of delayed closure of the normal ductus as similar to persistence of the congenitally abnormal ductus.⁴³ Specific inquiry in early experience of the congenital lesion did not reveal prematurity as an aetiological factor⁴⁴; the histology of the normal ductus in prematurity is different⁴⁵ and unlike the congenital lesion the ductus in premature infants responds to prostaglandins and their inhibitors in the same way that the normal ductus does in experimental studies.⁴⁶ Spontaneous closure with or without the aid of prostaglandin inhibitors is almost invariable in the premature but rare in the congenital lesion. Moreover, even when surgical closure is advisable⁴⁷ in the premature it is usually needed before what would be normal gestation in a full term infant.

The major risk in these sick infants is prematurity itself. Hospital mortality varies between 10 and 30% and only half the hospital survivors remain alive and well one to five years later⁴⁸; what a contrast with the normal life conferred by surgical occlusion of the congenital lesion. It is therefore mistaken to confuse statistics by linking two different forms of ductus just because infants with both these conditions may be ill and require urgent surgical occlusion.

Even in its premature form the ductus has had a beneficial, albeit secondary, effect on the management of congenital heart disease. When survival depends on maintenance of ductal blood flow, postponed closure by prostaglandins has changed such lesions from surgical emergencies into carefully investigated and planned procedures. Olley's work in Toronto⁴⁹ is also a manifestation of John Keith's enormous contributions to cardiology, well-demonstrated in Britain. Olley remained in Canada after training in Leeds but, like many who now hold senior appointments in paediatric cardiology in Britain, he had been a research fellow under Keith's warm and welcoming guidance.

Contemporary surgical practice

The operative risk of elective surgical closure of the uncomplicated ductus has been near zero for the best part of forty years. Most authorities will agree with Kirklin and Barrett-Boyes²⁹ that the presence of a persistent ductus is an indication for its closure, that the optimal age for operation is beyond the first month but within the first year of life, and that the method should be division and suture except in the newborn and in some infants. The Edinburgh practice reflects the progressive reduction in age at operation. From 1940–49 90% of patients were over five years old, from 1977–86 80% were less than five years old and most were less than two years old.

Premature infants have not been included in these percentages.

Assessing success

With nearly fifty years' experience it should be possible to assess to what extent aims originally envisaged by the pioneers have been attained in practice. Hubbard had warned that years of observation after ligation would be required before the prevention of bacterial endarteritis could be confirmed.⁵ Keith predicted that operation within the first year of life would eliminate the problems of the pulmonary hypertensive ductus in the future.⁵⁰ Benn argued that thirty years' observation of symptomless patients with a small ductus would be necessary to estimate the risk of elective surgical treatment in youth.¹⁶ The numbers from any one centre are too small to resolve these doubts or predictions but the Edinburgh figures come from a loyal and relatively stable population and are encouraging.

Eleven patients with bacterial endarteritis were seen in the first ten years of surgical experience 1940–49, five in the second ten years 1950–59, and only four in the twenty seven years 1960–86; the most recent occurred in a child under two years of age in 1974. Penicillin has been important in management and probably in prevention of infection since the second world war, but in the Children's Medical Centre, Boston, the incidence of bacterial endocarditis has increased despite the use of penicillin in cyanotic congenital heart disease (this has been in association with palliative cardiac surgery and prolonged survival) whereas no incident of an infected ductus was seen in the last ten years of the forty year review 1933–72.¹⁸ Moreover, two of the four incidents in Edinburgh during the past twenty seven years were in patients specifically instructed in the prophylactic measures they should take to protect themselves from infection; the first because an early decision against surgery had been made on the grounds of lack of symptoms in middle life, the second because elective surgical treatment had been firmly declined by her parents. No patient with a persistent ductus in Edinburgh has been known to die from bacterial infection since 1949, but this decreased frequency in no way diminishes the importance of its early recognition.⁵¹

The frequency of pulmonary vascular disease in association with persistence of the ductus arteriosus has also decreased progressively. The reverse ductus with right to left shunt probably escaped diagnosis in the early years. Even so, thirty three such patients have had their diagnosis confirmed in Edinburgh since 1939. Fifteen of them were born before surgical treatment became available: thirteen were born

in the twenty years 1940–59, five in the twenty years 1960–79. No patient recognised in Edinburgh as having a reversed ductus had been born since 1974.

The policy of elective closure of the ductus irrespective of symptoms has prevented accumulation of the evidence demanded by Benn.¹⁶ A recent review of older patients (over 50) seen in Edinburgh and followed with and without subsequent surgery, however, found no evidence to discourage and much to support the policy of early elective surgical closure.⁵²

The success of surgical treatment has long since ceased to be in doubt; but a complete cure is not invariable. Ligation of an uncomplicated ductus, as opposed to division, may leave a small diverticulum at the aortic end and there has been one report which suggests strongly that this later became the site of bacterial endarteritis.⁵³ Whether the ductus is detected in infancy or later the outcome will also depend on the behaviour of the pulmonary vascular bed. In some patients there is evidence of shunt reversal since birth.⁵⁴ Like persistence of the ductus arteriosus itself, primary pulmonary hypertension may run in families.⁵⁵ There is histological support for the contention that in some patients with persistence of the fetal circulation the primary fault is persistence of a large cylindrical ductus of congenital origin.⁴⁵ The pulmonary vascular resistance may also become high early in infancy and has increased after successful ligation at four months of age.⁵⁶ A little reported sequel of successful occlusion of a large ductus is the development and progression of discrete subaortic stenosis.⁵⁷ This is probably the result of an independent but previously undetected abnormality of the endocardium of the outflow tract of the left ventricle. Discrete subaortic stenosis may coexist with persistence of the ductus^{58 59} and is known to evolve from a previously unobstructed left ventricular outflow tract independent of other congenital valve malformations.⁶⁰ Five patients are known to have developed subaortic stenosis after ductal occlusion in Edinburgh and its development was not prevented by operation in infancy. A large ductus was occluded by division and suture in two siblings at two and six months of age; neither had had left ventricular obstruction on preoperative investigation, but both required surgical resection of severe discrete subaortic stenosis within nine years of ductal occlusion.

The Boston enterprise of 1938 has been increasingly endorsed over the first fifty years of the British Cardiac Society. Increasingly complex investigative methods became justified. Accuracy of diagnosis, and anatomical and haemodynamic variations during life have revealed new therapeutic possibilities. The ductus, coarctation, and simple

defects of the atrial and ventricular septa, which account for most cases of congenital heart disease, are now curable. The lives of those with less common and more complex lesions have been revolutionised by surgical procedures that are almost curative although improving fetal echocardiography may diminish the call for palliative surgery in the future.⁶¹ But the last decade of the Jubilee Years has also witnessed a new and exciting challenge. The ductus arteriosus has once more been in the forefront. The role of surgery is likely to diminish in the future as the cosmetic, emotional, and economic advantages of transcatheter closure gather force as experience advances.

Transcatheter closure

When Watson introduced Bill Rashkind and atrial septostomy to the Cardiac Society in 1966⁶² few of those present can have realised the breadth of the therapeutic benefits that the originality of the Rashkind mind, with his gloriously infectious joy of living, was introducing to cardiology and vascular disease. Plug closure of the ductus had first been successful in 1966⁶³ and the use of an Ivalon (polyvinyl alcohol) plug to occlude the ductus in children of over three years of age has been widely practised in Germany and Japan.⁶⁴⁻⁶⁶ The double umbrella system of Rashkind has undergone a large number of modifications since its first successful application in 1977.⁶⁷ It has become relatively safe and reliable in patients as young as three months of age but one hundred and forty six patients have now been treated in three American centres⁶⁸ so the results can be compared with those of the early years of surgical treatment. Shapiro and Keys in 1943⁶⁹ reviewed 107 patients in whom an uninfected ductus had been treated surgically in the largest American centres—more than half of them operated on by Gross of Boston and Jones of Los Angeles, whose mortality was half that of the other surgeons. Surgery was completely successful in 76% compared with 66% with the umbrella closure, but the non-surgical success rate is improving progressively; it had increased to 76% in the last 82 patients, and to 84% in one of the three centres, since January 1984. Residual continuous murmurs were present in 13% of the surgical compared with 10% of the umbrella series. The rates for major complications (rupture, infection, diagnostic, or surgical error in the surgical series, embolisation of the prosthesis requiring subsequent surgery in the umbrella series) were the same (13%) in the two treatment groups but the embolisation rate was reduced to 10% from January 1984 in the umbrella group. There were nine deaths in the surgical series

and none in the umbrella series. The greatest complication in the umbrella series was the requirement for subsequent surgical occlusion.

These figures highlight the ductus arteriosus for the second time as a pathfinder. Transcatheter treatment can now close ostium secundum defects of the atrial septum, correct anomalous drainage of the left superior vena cava into the left atrium and pulmonary arteriovenous malformations, and can relieve stenosis of the aortic and pulmonary valves and coarctation of the aorta as well as break down the atrial septum in transposition of the great arteries.³⁹ Once more American enterprise has shown the way. The torch has been handed to the paediatric cardiologists who will have to show the extent to which transcatheter techniques can now replace contemporary surgical achievements.

The future

We would, however, be mistaken to think that success has removed all the problems of the persistent ductus any more than it has those of other forms of congenital heart disease. During the ten years, 1977-86, in Edinburgh five of those with a persistent ductus had escaped detection until adult life. One had only recently become slightly disabled at 67 years of age. Her ductus was small and she required no more than simply medical measures. The remaining four were in their late teens or early twenties. None was disabled, indeed one was an athlete competing in the Commonwealth Games. The clinical evidence of the ductus was unequivocal and would in the past have led to elective surgical treatment without special investigation. Such a decision is now less easy for cardiologists who treat adults and who may not have had personal experience of younger patients with persistence of the ductus. In the future it is likely that investigations will be part of the routine for closure with a transcatheter device—presumably by the paediatric cardiologists. Close liaison will be essential as it will be the adult cardiologist who will also have to cope with the problems of postoperative congenital heart disease. Jane Somerville has emphasised the importance of experience of paediatric cardiology in the training of adult cardiologists and has highlighted many of the difficulties and problems that are likely to arise in the years ahead.^{70 71} The prevention and treatment of complications in those whose surgical treatment, unlike that of the ductus, has not been curative will assume increasing importance as their ages advance. Important as these new demands on cardiologists are bound to be, the revolution in knowledge, understanding, and treatment of congenital heart disease, witnessed during the fifty years of the

British Cardiac Society, is one to which no leading article can pay adequate tribute.

I am deeply grateful to past colleagues and successors who allowed free access to their records so that Edinburgh figures could extend beyond my own retirement to the end of 1986.

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