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A history of cardiopulmonary bypass

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It is, perhaps, invidious to select from the many who recognized in the 1930s that perfusion techniques used by physiologists to study organ function might be adapted to gain access to the interior of the human heart, but one who put it succinctly was O'Shaughnessy writing in the *Lancet* of 1939. Tragically he was to be killed a year later at the beginning of World War II. In his paper on the 'Future of Cardiac Surgery' he quotes Levine (1937) and writes,

> 'the real key to further advance in the surgical treatment of established cardiac defects will only be provided by the provision of some simple and efficient method of maintaining cerebral circulation while the heart is temporarily out of commission. Naturally there are many other problems of a local nature for solution . . . but so long as the surgeon is faced with the certainty of irreparable cerebral damage if he interrupts the circulation for any appreciable period he has little incentive to devise operative procedures that he cannot carry out'.

As if in answer to this plea Gibbon (1937) had published an account of the first elective cardiopulmonary bypass carried out in the cat. He was able to occlude the pulmonary artery for 25 minutes while shunting the cardiac output through an assembly of pumps and an oxygenator, his aim being to make pulmonary embolectomy possible. It is fitting therefore that Gibbon (1954) was also to report the first successful complete bypass of the heart and lungs in a human, though we must wait until 1953 for that. World War II intervened and though it delayed progress at the time it also acted as a powerful stimulus when it had ended. Many surgeons had successfully dealt with intrathoracic wounds, including those of the heart itself, and the pressure to treat surgically cardiac abnormalities became a real force,

stimulating research in several countries. Crafoord and Andersen in Sweden produced the rotating disc oxygenator which Bjork (1948) described in his thesis. Jongbloed (1949) in Holland, Thomas and Beaudouin (1951) in France and Melrose (1953) in England, joined several American colleagues, Dennis *et al.* (1951), Dodrill *et al.* (1953), Helmsworth *et al.* (1953), Kantrowitz and Kantrowitz (1950), Mustard *et al.* (1954), Clowes (1951) and Miller, Gibbon and Gibbon (1951) in describing equipment used successfully in the experimental laboratory. But whilst the first tentative steps were being taken to apply these machines clinically, Lillehei and Varco (1955) at the University of Minnesota began using cardiopulmonary bypass in infants and young children with a simple pump and a donor adult as an oxygenator. They were able to use their cross circulation technique because they circulated only between 10% and 25% of the normal cardiac output of the patient, accepting the evidence of Andreasen and Watson (1952) that a dog would survive a period of 30 minutes of occlusion of the superior and inferior vena cava provided the azygos vein was patent, thus providing about 10% of the normal venous inflow to the heart. Ethical and other difficulties eventually persuaded them to abandon the use of donors but not before they had carried out elective cardiac surgery for several congenital anomalies. When Kirklin *et al.* (1955) at the Mayo Clinic confirmed their results, using a modified version of Gibbon's machine and a flow rate which was close to the normal cardiac output, modern cardiac surgery really began.

1.1 EQUIPMENT

1.1.1 Pumps

Inevitably, when equipment was scaled up to allow the whole circulation to be carried rather than small proportions of it, it evolved by simple development of the tools of physiology. Virtually all organ perfusion systems included a pump capable of a variable pulsatile output imitating the natural pulse contour. The best known was that of Dale and Schuster (1928). Modifications of this pump or of the principle behind it initiated virtually all of the early whole body perfusion experiments, including those of Gibbon and some of the first human perfusions were carried out with it. Such pulsatile pumps would have continued to dominate the field for pulsatile flow is normal and we must assume that the body is adapted to such a flow. Indeed sophisticated examples of such pumps continued to be used successfully for several years (Melrose, 1955). But, practical as well as theoretical considerations came to govern choice in the absence of any really conclusive evidence of the role of the pulse in the circulation. A very attractive alternative was available in the form of the occlusive roller pump. Henry and Jouvelet (1934) in France and De Bakey (1934) in the USA had given their names to two

examples of this type in the same year and both had devised these pumps to facilitate direct blood transfusion. Enlarged to allow flows in excess of 5 litres a minute they had many advantages at the time. Mention must also be made of the Sigmamotor pump (DeWall, 1956) which substituted compressing fingers for rollers to occlude progressively the tube within it and, though it did not survive as flowrates increased it has an important historical place.

Each of the two basic types had merits and demerits. Both shared the useful attribute of allowing the inexpensive disposal of all material with which blood had come in contact and both had eliminated the interference to flow of internal valves. But the roller pump was, undoubtedly, much simpler to set up and use, was easy to drive by hand in the event of power failure, and the low amplitude pulse produced was much more manageable through the relatively small bore peripheral cannulae used at that time. It deservedly won the day.

It is interesting to note that the controversy between continuous and pulsatile flow pumps continues to this day (Taylor, 1984). Much new evidence has, of course, sharpened the debate since Wesolowski (1953) and Melrose (1958) discussed the problem in the 1950s and today there is a considerable and rapidly growing literature on the subject. Two recent reviews indicate that the matter is by no means settled yet (Edmunds, 1982; Philbin *et al.*, 1982).

1.1.2 Oxygenators

When we turn to imitation of the function of the lungs, scaling up primitive oxygenators proved more complex than pumps. Four solutions were initially available and two of these have survived to this day.

Mention has already been made of cross-circulation from a living donor, a technique quickly abandoned, but for many years a variety of homologous or heterologous natural lungs were incorporated into bypass systems and some were even used clinically. Never very successful, the complexity of preparation and unpredictability of performance mitigated against biological oxygenators and in spite of theoretical advantages they are most unlikely ever to be considered again.

The second line of development which is no longer used involved the exposure of blood directly to gas while spread over an arrangement of surfaces. Many and various were the mechanical solutions chosen, the principle involved having a long history from its introduction by von Frey and Gruber in 1885. Two references are useful in following the progress of this line of development: the monograph of Galleti and Brecher (1962) and a review by Hewitt and Creech (1966). Though superseded, the screen and disc oxygenators can rightfully claim pride of place in the 'popularization' of cardiopulmonary bypass. When Dennis *et al.* (1951) performed the first total bypass in man they used rotating screens, and when Gibbon (1954)

performed the first successful total bypass in man he used vertical stationary screens. Developments of the rotating disc oxygenator by Melrose (1953) and by Cross *et al.* (1956) dominated the 1960s as cardiac surgery spread widely around the world.

The problems of the time were best handled by reusable filming oxygenators, complex and difficult to clean though they were, but already the inexorable advance of simple disposable equipment was making itself felt. Most of the tubing was already being discarded after a single use and one by one each durable component was challenged by a disposable alternative. A rather petulant comment at the time reads 'Not only must the actual efficiencies and effectiveness of each of these methods be taken into account, but a study of their practicality will often reject an excellent solution on grounds of complexity, expense, difficulty in maintenance or cleaning. While fully disposable systems have the most appeal they may be prohibitively expensive. It is sometimes better to clean thoroughly a well made item than to risk possible defects in manufacture in a replacable one.' Another comment on this subject was made by Osborn (1958) 'I think disposability is important. When you can get something clean and sterile ready to use and then throw it away afterwards that is important. You have to make a lot of compromises if you want disposability.'

Just as the simple roller pump came to exclude the more elaborate early pulsatile pumps so the third of the alternatives, the disposable bubble oxygenator replaced the filming devices.

The principle of oxygenating blood by the direct injection of gas into its substance in the form of bubbles has, if anything, the longest history of all. Von Schroder is credited with the introduction of the method in 1882 and in several laboratories it became the standard method for organ perfusion. The modern form is derived from the work of Clark *et al.* (1950). They advocated dispersion of oxygen through a sintered-glass filter directly into venous blood and they also introduced the concept of reducing the surface tension of blood after oxygenation by bringing it into contact with siloxane antifoaming agents thus enabling the foam to be more easily debubbled. However it was the disposable helical reservoir bubble oxygenator, originated and described in 1956 by De Wall *et al.* which pointed the way to the future. It was deceptively simple, and though an immediate success in many centres, it proved disappointingly difficult to use in others. New designs followed rapidly, the most widely distributed being that of Rygg and Kyvsgaard (1958), introduced in Denmark and a similar type by Hyman (1956) in the USA. There is no doubt that such devices work much more efficiently on low viscosity blood since it is much easier to defoam, and the ability to select a sterile pack, assemble the machine, and use it without donor blood even in an emergency had obvious merit. But the belief that fresh blood, taken into heparin, was necessary to prevent disastrous bleeding problems waned

slowly and it was not until a more general acceptance of the safety of haemodilution that the bubble oxygenator came into its own. It is perhaps an interesting historical detail that the first completely successful animal perfusions carried out by Melrose *et al.* (1953) were done with a priming solution of 6% dextram saline, rather than with blood which had caused persistent hypotension during the initial experiments. Regrettably when the first patients were operated on clinicians ignored this demonstrably safer technique and, reverting to normal clinical practice, used fresh blood with its attendant difficulties. Now that mass production of efficient and reliable bubble oxygenators is the norm it is proper to pay tribute to the pioneering engineers who brought them to the present state of excellence.

Notwithstanding the present world-wide dominance of bubble oxygenators there remains a persistent suspicion that direct exposure of blood to gas is damaging to blood and that it is better to avoid the additional danger of gas embolism by not creating bubbles in the first place. In the 1950s this suspicion was a great deal stronger and led to the development of membrane oxygenators whereby a semipermeable membrane was interposed between blood and gas. The pioneers in this area were Kolff and Clowes. In 1944, Kolff and Berk had observed arterialization of blood as it passed through the cellophane chambers of the artificial kidney and later Kolff and Balzer (1955) used a coil dialyser as an oxygenator in successful animal experiments. Clowes *et al.* (1956) were most persistent in overcoming the very considerable technical problems of the time and by 1958 were able to report clinical use in adults though the oxygenator required over 25 m^2 of membrane area to support the necessary gas exchange.

Subsequent progress was frustratingly slow. The two fundamental aspects of design: suitable membranes on the one hand, and a suitable structure to support them on the other have both proved to be inherently very complex problems. Nature's ability to grow structures of great complexity and to supply blood to them by the branching of tubes of decreasing size is not capable of imitation. The smallest artificial capillaries we have been able to manufacture of synthetic material are of the order of 20–50 times the diameter of natural ones and as the time needed to oxygenate a film of blood varies as the square of its thickness these relatively large passages are extremely inefficient as diffusion sites. Difficulties attend the even delivery of blood to an array of such tubes, assembled as they must be into manifolds or header chambers. The same strictures apply to designs of sandwich type in which closely opposed pairs of membrane sheets conduct blood between alternating oxygen spaces. Such devices necessarily incorporate some method of establishing a uniform planar flow between the flat membranes and these usually take the form of spaces with grooves of similar surface irregularities designed to encourage even spreading and some mixing on the surface of the membranes. For even were the membrane to impose a truly negligible

resistance to gas diffusion there exists adjacent to the surface a slowly moving boundary layer which impedes convection of the blood to the exchange surface and greatly limits gas transfer. In natural capillaries this boundary layer diffusion resistance is small because their size is small. Blocked by our inability to achieve these dimensions the only solution remains to promote vigorous lateral mixing within the blood passages in artificial membrane lungs and thus to promote increased convection which facilitates diffusion.

Suitable membranes now exist which have excellent gas diffusion properties. The discovery by Kammermeyer (1957) that silicone elastomers could be made with exceptionally high permeability both to oxygen and carbon dioxide whilst being biologically inert provided the impetus to Bramson *et al.* (1965), Kolobow and Bowman (1963), Landé *et al.* (1969) and others to design devices suitable for routine clinical use and commercial production. Improved membranes and better blood distribution reduced the necessary area tenfold from the 25 m^2 of Clowes to 2.5 m^2. Now even this bench mark of efficiency has been exceeded by the substitution of micro-porous teflon or polypropylene membranes for silicone and by active mixing techniques which allow complete adult gas exchange to be achieved in a device whose surface area is only 0.8 m^2 (Melrose and Fleming, 1980).

Essentially the exacting criteria required of an ideal artificial lung can now be met. The membranes available and the configuration in which they are used can be made to produce a closed-circuit device of remarkable efficiency, without sacrifice of safety or simplicity in use, of atraumatic performance over long periods, and of acceptable cost.

Further, the pioneering fluid dynamic analyses of Weissman and Mockros (1968) and of Drinker (1972) and Drinker *et al.* (1969) which led to these increases in efficiency indicate that we are not yet at the end of this development.

1.1.3 Intracardiac suction

Little need be said about other items of equipment used in cardiopulmonary bypass. Gradual improvement in the quality and design of cannulae, tubing and reservoirs has inevitably accompanied the expansion in demand for these products and inevitably they are disposable. But one issue which still causes concern is the handling of blood seeping into the open heart or spilling into the pericardial cavity itself, for there is little doubt that a most destructive element in the extracorporeal circuit is the recovery of this blood.

Too little attention has been paid to this aspect. Osborn *et el.* (1962) pointed out the contribution that careful design of the actual sucker tip can make and Benzing *et al.* (1966) indicated that meticulous control of suction pressure gradient and rate of withdrawal can ensure much gentler handling. But most are content to use a system of roller pumps under relatively crude

control. Recently, an interesting paper by de Jong *et al.* (1980) emphasized that there is little relevance in using a membrane oxygenator instead of the haematologically more destructive bubble oxygenator when all the benefits so gained are counteracted by uncontrolled suction. They further point out that such control can be achieved and a significant improvement in haemostasis gained. Perhaps at last with modern electronics a method simple and reliable enough for everyday use will eliminate the clumsy and traumatic methods which have changed little during the last quarter century.

1.2 HYPOTHERMIA AND MYOCARDIAL PRESERVATION

No history of the development of bypass techniques can be complete without considering the place of hypothermia and of elective cardiac arrest. From the outset there were those who believed that manipulation of the body temperature might of itself be sufficient to provide the necessary operating time. Certainly the hibernating animal has always excited great interest and when Bigelow *et al.* (1949) proved that the period during which an animal would withstand circulatory arrest could be greatly prolonged by reducing the body temperature he reawakened biological interest leading to clinical application. McQuiston (1949) noted the protective effect of mild hypothermia in the operative management of cyanotic heart disease; Lewis and Taufic (1953) and Swan and Zeavin (1954) reported various successful intracardiac operations using direct vision under hypothermia even before Gibbon's important first case. When Andjus and Smith (1955) demonstrated that it was possible to maintain the non-hibernating rat without respiration or heart-beat for more than an hour at a core temperature close to 0°C it seemed that the future was assured.

But it was not to be. Man is not a hibernator and cannot maintain energy-exchange processes during the long periods required to bring about cooling to and rewarming from low temperatures. The nearest we have come to it has been the technique of Drew (1959) who used extracorporeal pumps to maintain the circulation through these periods to provide complete circulatory arrest for an hour at temperatures below 10°C. The technique helped provide evidence of safe time limits but proved too complex to replace conventional bypass procedures and like so many hopeful alternatives it has been abandoned.

However, hypothermia remains inextricably linked with bypass technique. The ability to control tissue temperature and thus influence its metabolism by controlling the temperature of the circulating blood is a fundamental component of all present day cardiac surgery. Fashions change and the ideal body temperature for cardiac surgery has fluctuated to and fro from the normal 37°C down to as low as 20°C. Most are content with modest alterations which are easy to control and which provide well-understood advantages.

The heart itself is a special case. Since it became evident that even a satisfactory perfusion of the whole body did not necessarily provide good surgical access to the heart unceasing attention has been directed to this problem. The goal is a flaccid heart from which all blood flow is excluded and whose metabolism is so reduced that no irreversible damage occurs during surgery. The first attempts to achieve this were proposed in 1955.

Melrose *et al.* (1955) suggested that deliberate manipulation of the ionic environment of the myocardium might provide the answer. Using potassium citrate to exaggerate the effect described by Ringer in 1883, where potassium inhibited and calcium stimulated the heart, they were able to demonstrate in several animal species a reliable method of stopping and starting the heart. Lam *et al.* (1955) described the use of acetylcholine injected into the root of the aorta to achieve a similar but less-dramatic effect. In both techniques simply flushing out the coronary system with blood from the heart–lung machine restored normal function.

The potassium citrate method was widely accepted and by 1957 was in general use. Acetylcholine did not find favour to the same extent and faded from the scene. Sadly, however, the obvious combination of potassium citrate elective arrest and myocardial hypothermia was not exploited at the time though experimental evidence was available to suggest the advantages of this (Baker *et al.*, 1957). Had it been so history would have been different, for potassium arrest at normal temperature only extended the safe period of ischaemia for a relatively short period and as surgical problems increased in complexity and acquired disease brought problems of myocardial inadequacy the technique was found wanting.

Cross (1957) showed that a very cold heart withstood ischaemia much better than a warm one and then showed that initial arrest with potassium citrate followed by washout with oxygenated blood at close to 0°C further reduced oxygen consumption. But this and several other promising lines of research were cut off as elective arrest was abandoned in favour of a variety of alternatives. Several schools emerged; simple anoxia, individual coronary perfusion at normal temperature or at varying degrees of hypothermia, surface cooling of the heart without perfusion and of course combinations of these. None was so obviously successful as to displace the others and history was to confirm the initial idea, elective cardiac arrest now called cardioplegia returning to complete the full circle in a generation.

It returned because it had been kept alive in Germany. Holscher (1967) had continued to study induced arrest throughout the 1960s but it was the work of Bretschneider (1964) which ushered in the new wave of cold cardioplegia. They substituted sodium-poor, calcium-free, procaine-containing solutions for those previously used. Sondergaard and Senn (1967) took these up clinically in Aarhus with excellent experimental results. Kirsch *et al.* (1972) in Hamburg and Hearse *et al.* (1976) in London devised original solutions after

painstaking analysis of the effect of individual components in the light of much greater knowledge of the metabolism of the heart. They also produced excellent clinical results. Roe *et al.* (1977), Tyers *et al.* (1974) and Buckberg (1979) in the United States all made powerful contributions and today it is unusual for cardiac surgery to proceed without cardioplegia. However, only time will tell whether this time the biochemists, physiologists and surgeons have got it right.

The history of the safe entry into the cavities of the living human heart to allow surgical repair is a short one but one full of fascination. For it spans also the entry into medicine of the enormous power of technology. My own experience in this field commenced when the only aids to clinical acumen were the X-ray machine, the microscope, the test-tube, the electrocardiogram and the cardiac catheter. The art of medicine was not yet accompanied by the science of medicine. Perhaps the present is best exemplified by the many national and international societies of artificial organs. These associations have brought together experts from all the appropriate disciplines.

Countless people live without natural kidneys, a man has lived without a natural heart for several months, every organ is under scrutiny for replacement. While advance in cardiopulmonary bypass will be less spectacular than in the heady 1960s it will be relentless and based more securely on a wealth of confirmed fact. The prospect is wonderful.

REFERENCES

Andjus, R. K. and Smith, A. N. (1955) Reanimation of adult rats from body temperatures between 0 and +2°C. *J. Physiol.*, **128**, 446.

Andreasen, A. T. and Watson, F. (1952) Experimental cardiovascular surgery. *Br. J. Surg.*, **39**, 548–51.

Baker, J. B. E. *et al.* (1957) Arrest of isolated heart with potassium citrate. *Lancet*, **ii**, 555–9.

Benzing, G. 3rd, De Forest, D. and Kaplan, S. (1966) Multiple line single-reservoir automatic cardiotomy return system. *J. Thorac. Cardiovasc. Surg.*, **51**, 238.

Bigelow, W. B. *et al.* (1949) Hypothermia; its possible role in cardiac surgery investigation of factors governing survival in dogs at low body temperatures. *Anaesthesiology*, **10**, 590.

Bjork, V. O. (1948) Brain perfusions in dogs with artificially oxygenated blood. *Acta Chir. Scand.*, **96** (Suppl. 137), 1–122.

Bramson, M. L., Osborn, J. J., Main, F. B. *et al.* (1965) A new disposable membrane oxygenator with integral heat exchanger. *J. Thorac. Cardiovasc. Surg.*, **50**, 391.

Bretschneider, H. J. (1964) Uberlebanzeit under Wiederbelebungszeit des Herzen bei Normo- und Hypothermia. *Verh. Dtsch. Ges. Kreislanfforsch*, **30**, 11.

Buckberg, G. D. (1979) A proposed 'solution' to the cardioplegia controversy. *J. Thorac. Cardiovasc. Surg.*, **77**, 803.

Clark, L. C. *et al.* (1950) The oxygenation of blood by gas dispersion. *Science*, **III**, 85.

Clowes, J. H. A. Jr (1951) Experimental procedures for entry into the left heart to expose mitral valve. *Ann. Surg.*, **134**, 957–68.

Clowes, G. H. A. Jr *et al.* (1956) An artificial lung dependent upon diffusion of oxygen and carbon dioxide through plastic membranes. *J. Thorac. Surg.* **32**, 630.

Cross, F. S. (1958) Discussion on cardiac arrest in *Extracorporeal Circulation* (ed. J. G. Allen), Charles C. Thomas, Springfield Ill., p. 491.

Cross, F. S. *et al.* (1956) Evaluation of a rotating disc type reservoir oxygenator. *Proc. Soc. Exp. Biol. Med.*, **93**, 210–14.

Dale, H. H. and Schuster, E. H. J. (1928) A double perfusion pump. *J. Physiol.*, **64**, 356–64.

De Bakey, M. E. (1934) Simple continuous-flow blood transfusion instrument. *New Orleans Med. S. J.*, **87**, 386–9.

de Jong, J. C. F. *et al.* (1980) Hematologic aspects of cardiotomy suction in cardiac operations. *J. Thorac. Cardiovasc. Surg.*, **79**, 227.

Dennis, C. *et al.* (1951) Development of a pump-oxygenator to replace the heart and lungs: an apparatus applicable to human patients and application in one case. *Ann. Surg.*, **134**, 709–21.

DeWall, R. A. *et al.* (1956) A simple, expendable artificial oxygenator for open heart surgery. *Surg. Clin. N. Am.*, **36**, 1025–34.

Dodrill, F. D. *et al.* (1953) Pulmonary valvuloplasty under direct vision using the mechanical heart for a complete bypass of the right heart in a patient with congenital pulmonary stenosis. *J. Thorac. Surg.*, **26**, 584–97.

Drew, C. E. (1959) Profound hypothermia. *Lancet*, **i**, 745.

Drinker, P. A. (1972) Progress in membrane oxygenator design. *Anaesthesiology*, **37**, 242.

Drinker, P. A., Bartlett R. H., Bialer R. M. *et al.* (1969) Augmentation of membrane gas transfer by induced secondary flows. *Surgery*, **66**, 775.

Edmunds, L. H. Jr (1982) Pulseless cardio-pulmonary bypass. *J. Thorac. Cardiovasc. Surg.*, **84**, 800–4.

Galetti, P. M. and Brecher, G. A. (1962) *Heart–Lung Bypass*, Grune and Stratton, New York.

Gibbon, J. H. Jr (1937) Artificial maintenance of circulation during experimental occlusion of pulmonary artery. *Arch. Surg.*, **34**, 1105–31.

Gibbon, J. H. Jr (1954) Application of a mechanical heart and lung apparatus to cardiac surgery. *Minnesota Med.*, **37**, 171–85.

Hearse, D. J., Stewart, D. A., Braimbridge, M. V. *et al.* (1976) Cellular protection during myocardial ischaemia: The development and characterization of a procedure for the induction of reversible ischaemic arrest. *Circulation*, **54**, 193.

Helmsworth, J. A. *et al.* (1953) An oxygenator-pump for use in total bypass of heart and lungs. *J. Thorac. Surg.*, **26**, 617.

Henry, H. and Jouvelet, P. (1934) Appareil à transfusion du sang. *Bull. Acad. de Med. Paris*, **111**, 312–19.

Hewitt, R. L. and Creech, O. Jr (1966) History of the pump oxygenator. *Arch. Surg.*, **93**, 680–96.

Holscher, B. (1967) Studies by electron microscopy on the effects of magnesium chloride–procainamide or potassium citrate on the myocardium in induced cardiac arrest. *J. Cardiovasc. Surg. (Torino)*, **8**, 136.

Hyman, E. S. (1956) Simple, disposable, autoclavable plastic unit to substitute for heart and lungs. *Trans. Am. Soc. Art. Int. Organs*, **2**, 1.

Jongbloed, J. (1949) The mechanical heart lung system. *Surg. Gynec. Obstet.*, **89**, 684–91.

Kammermeyer, K. (1957) Silicone rubber as a selective barrier. *Ind. Eng. Chem.*, **49**, 1685.