THE EVOLUTION OF ANAESTHESIA

BY

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BLOOD TRANSFUSION

Although the first attempts at blood transfusion and intravenous therapy began in the 17th century, there is one isolated example of the concept of the intravenous administration of remedial drugs dating from the very beginning of the Christian era. This account comes from the Metamorphoses (Bk. 7) of Ovid (43 B.C.—A.D. 17). Jason, seeing his father, Aeson, grow old and feeble, begs his wife, Medea, to exercise her magic powers and restore the old man’s youth. Medea, after suitable prayers, repairs to the home of the gods, where she gathers magic herbs. Aeson is brought to the altars which Medea has erected and where a decoction of the herbs “bubbled and boiled, white-foaming in a brazen vessel” and “wherever the boning broth spat forth its hissing drops, the earth grew bright with soft grass and sweet-smelling flowers”. Medea then “drew her knife across Aeson’s throat and drained out the thin blood, and, in its place, infused that life-giving juice. As his lips and wounded throat imbibed it, his hair and beard shed their silver and shone with the glossy, raven hue of youth; his muscles swelled, the wrinkles filled, the rose, long faded, bloomed in his cheek anew, and every limb was lithe. Wondering Aeson woke to find himself as he had been some forty years before”.

It is not, however, to be thought that such infusions were ever attempted by the ancients: Ovid’s story is merely a flight of fancy, unconnected with medical practice.

However, the doctors of the Scientific Period (585 B.C.—A.D. 200) were well aware of the importance of the blood in maintaining life. The doctrine of the four humours, of which blood was one, had been modified by Erasistratus of Chalcedon (c. 1300 B.C.), who believed that disease was usually caused by a plethora or excess of blood in a particular region. The followers of Erasistratus introduced blood-letting as a form of treatment, and this therapy was used and abused until almost the end of the 19th century.

It was natural that the idea of the circulation of the blood, first promulgated by William Harvey in lectures at the Royal College of Physicians in 1616, should stimulate experiments with blood, but it seems likely that the idea of blood transfusion had already occurred to some. Thus Pegelius of Rostock may have mentioned it as early as 1604, and Andreas Libavius certainly referred to it in 1615. Again, in 1628, the year of the publication of Harvey’s De Motu Cordis, Colle of Padua suggested transfusion as a method of prolonging life.

Developments in England, where Harvey’s doctrine naturally gained greatest currency, were delayed by the political turmoil which preceded and accompanied the Civil War (1642—1649). In the latter year, Francis Potter, a Somersetshire parson, attempted unsuccessfully to transfuse blood into a hen; the idea of curing disease by this method had apparently been in his mind for some ten years.

In 1656, (Sir) Christopher Wren experimented with the intravenous administration of drugs to animals. The first authenticated experiments were carried out by the Royal Society, which had been incorporated in 1662. In May 1665, at a meeting of that body, Thomas Cox related how he had transfused blood from one pigeon to another; in June, Dr. Wilkins reported a similar experiment on dogs; and, in April 1666, Robert Boyle described another attempt. In none of these cases was more than a very small quantity of blood introduced.

Richard Lower, in his Tractatus de Corde (1669) describes in detail how in February 1665
(n.s.) he carried out a series of successful massive transfusions on dogs by the direct artery to vein technique, and this account is confirmed in the *Philosophical Transactions* of the Royal Society. To Lower, therefore, must go the credit of the first successful transfusion.

A year later, Denis of Montpellier carried out similar experiments, not always using animals of the same species and, in June 1667, transfused 3 oz of lamb's blood into the veins of a youth suffering from a chronic fever, apparently a successful form of therapy. Denis continued to use this method of treatment until, in 1668, one of his patients died. A court case ensued, and, by an Act of the Parlement of Paris of 1670, blood transfusion was made illegal in France.

Experiments, however, continued in England, and, in November 1667, Samuel Pepys described how a “poor and debauched man” was transfused with 12 oz of sheep’s blood without ill-effects. The first book on blood transfusion appeared in 1665; it was written in German by J. S. Elsholtz. An enlarged edition of the book reappeared in Latin in 1667, under the title *Clysmatica Nova* and contained a diagramatic representation, the first illustration, of blood transfusion. Other books, dealing in whole or in part with transfusion, and some of them illustrated, were soon published: the anonymous *Relazione dell’Esperienze* (1668), Mercklin’s *De Ortu et Occasu Transfusioin Sanguinis* (1679), Folli’s *Stadera Medica* (1680), Scultetus, *Armamentarium Chirurgicum* (1693), and Purmann’s *Lorbeer Krantz oder Wund Arznei* (1705).

During the 18th century, comparatively little seems to have been done in the field of blood transfusion. In his *Zoonomia* (1794), Erasmus Darwin advised daily transfusions of human or animal blood to “an old gentleman whose throat was entirely impervious”, but the patient refused. The matter was, however, taken up with enthusiasm by James Blundell (1790–1877), who performed a number of transfusions with human blood and invented some ingenious apparatus for the purpose. He reported a case of postpartum haemorrhage successfully treated in 1829; the patient received 8 oz of blood. Other occasionally successful operators were Blundell’s collaborators, Charles Waller and E. Doubleday. Meanwhile, during the epidemic of Asiatic Cholera in 1831, O’Shaughnessy discovered that the blood of the victims was depleted of both salt and water. This observation was put to practical use by T. A. Latta of Leith in the following year, when he introduced, with great success, the practice of intravenous saline infusion for this disease.

The year 1873 was marked by the discovery of the species specificity of blood by Landois, thus terminating experiments in the transfusion of animal blood to man. In the same year, Aveling described a simple and efficient apparatus for the direct transfusion of blood from donor to patient, so eliminating the problem of clotting. Three years later, Noel described a rotary pump, similar to those in use today, which simplified even more the direct transfusion of blood.

In spite of these improvements, J. B. Murphy, in 1907, described a method of direct anastomosis of the vessels of donor and patient, but this highly technical procedure never became popular.

With the first year of the 20th century, the practice of blood transfusion was placed on a sound basis by the discovery of agglutinins and iso-agglutinins by Landsteiner in Vienna and Shattock in London. The former described three groups; a fourth was added in the following year by von Decastello and Sturli. Further work on the ABO blood groups was done by Jansky of Prague (1907) and Moss (1909), but the numerical notations which they introduced have been supplanted by the international nomenclature. In 1910, von Dugern and Hirschfeld discovered that the inheritance of blood groups was in accordance with the Mendelian theory. By 1911, Ottenberg had drawn attention to the possibility of persons of Group O being used as “universal donors”, and two years later, he and his co-workers described in vitro tests for the cross-matching of blood.

The question of the blood groups was, however, complicated by the discovery of the independent M and N antigens by Landsteiner and Levine (1927). In the following year, the same workers described the agglutinogen P and, since 1945, numerous other agglutinogens have been described (e.g. “Lutheran”, 1945; “Lewis”, 1946; “Kell”, 1946; “Gr”, 1946; and “Jobbins”, 1947). The first of these, P, is widely distributed, but the remainder are only very rarely encountered. The
discovery of "cold" agglutinins, both specific and nonspecific, dates from the same period, as does the introduction of Coombs sensitization test (1945).

The use of intravenous saline in the treatment of burns was begun by Weidenfeld in 1902; by 1912, attention was drawn to fluid loss by other means, such as vomiting, and the study of blood fluids and electrolytes was well advanced.

In 1909, Brewer and Leggett had recognized that the coagulation of blood could be delayed by the use of paraffin-coated glass tubes; this led to the development of the Kimpton-Brown tube (1917), employed successfully by the Harvard Medical Unit in France. Experiments in preventing clotting had begun much earlier; Wright (1891) had tried oxalate; and Leopinasse (1908-9) used hirudin, peptone and sodium citrate, but regarded them all as too toxic. The successful use of citrated blood was first described by Hustin in Belgium (1915), and this work was further advanced by Agote of Buenos Aires. The technique was much improved by Robertson towards the end of World War I. Curiously enough, there was a simultaneous revival of the method of direct transfusion of unmodified blood by Lindemann, who employed a "multiple syringe" technique. The use of heparin as an anticoagulant was advocated by Skold in 1936.

Although there had been some organization of blood donors during World War 1, the first real steps in the formation of a proper service began with the foundation of the London Blood Transfusion Service in 1921. By 1939, more than 5,000 transfusions a year were being provided. The work was further advanced by the British Red Cross Society. At the outbreak of World War II, Regional Transfusion Centres were organized by the Medical Research Council, and these bodies have now become permanent institutions in the National Transfusion Service. The present apparatus for blood transfusion derives from that designed by Marriott and Kekwick in 1935. During all this period, the use of blood and blood substitutes has greatly expanded. Thus, while Weil had recognized that blood was important in the treatment of haemophilia as early as 1906, it was left to Feissly (1928) to show that plasma was equally valuable in this condition. Ward in 1918 had shown also that animals dying of haemorrhage were suffering more from loss of blood volume than from loss of haemoglobin. The value of plasma in the treatment of burns was pointed out by Elkinton in 1939. An interesting development was the dilution of blood with a solution of various salts to ten times its own volume, a device employed by Petrov in 1943; while the great demands for blood also led to the exploitation of that of cadavers by Yudin (1936) and Shamov (1937).

On the other hand, the use of "packed-cells" has been shown to be of great value in the treatment of anaemia without reduction in blood volume. The first to describe the advantages of this method were MacQuaide and Mollison (1940).

Although there have been occasional reports of diseases such as typhoid fever and smallpox being conveyed to the recipient by blood transfusion, by far the commonest disease so spread is virus hepatitis (homologous serum jaundice). This disease and its method of propagation have been recognized since 1885, when there was a severe outbreak following vaccination with human serum in Bremen. The first case after blood transfusion was reported by Janet and Janet in 1938, and the danger of this complication has been underlined by repeated outbreaks. One result has been the introduction of "small group" pooled plasma, which has now entirely replaced the older "large group" pooling.

A dramatic and important step forward in the use of blood transfusion was taken when, in 1940, Landsteiner and Wiener observed that the serum of a rabbit, previously inoculated with the red cells of a rhesus monkey, developed an immune agglutinin, which reacted with the red cells of most, but not all, human subjects. The importance of this "Rh" factor was quickly appreciated, and the connection between it and neonatal haemolytic disease was reported by Levine in 1941. Fisher (1944) introduced his ingenious theory that the various Rh sub-types comprise different combinations of three closely linked elementary genes, inherited by Mendelian laws, one from each of three allelomorphic pairs. Wiener, however, has never accepted the classification of Fisher; but it is fair to say that it forms a convenient working hypothesis.

Blood transfusion has usually been given by
the intravenous route. In 1941, Tocantins and O'Neill introduced the technique of intramedul- lary transfusion; in 1954, intra-arterial trans- fusion became temporarily popular; and, recently, the intraperitoneal administration of blood has been advocated in certain circumstances. A par- ticular aspect of intra-arterial transfusion was the practice of arteriotomy introduced by Gardner in 1946 for the control of blood loss, especially in cerebral surgery. Blood was removed by means of an intra-arterial cannula, and, after addition of heparin, stored until the need for haemostasis had passed; the blood was then re-introduced through the same cannula. The experimental work of Kohlstaedt (1943) on animals had shown that resuscitation was quicker when this route was employed than when the blood was returned intravenously.

A number of so-called “plasma expanders” have been introduced from time to time. Solution of gum acacia, used during World War I, was the first; this was followed by bovine serum treated so as to reduce the risk of an anaphy- lactic response, but none was completely satis- factory. In 1949, Thorsen introduced dextran, a polysaccharide produced by the fermentation of sucrose by the micro-organism, *Leuconostoc mesenteroides*. This has proved a useful blood- substitute, especially since the preparation of large molecule fractions. One difficulty caused by dextran was that it was liable, because it might lead to rouleaux formation *in vitro*, to interfere with the subsequent cross-matching of the patient’s serum with blood. Fortunately, this diffi- culty has been recently overcome.

The history of extracorporeal circulation with the aid of pumps and oxygenators is so recent that what follows must not be considered as the final word on the subject. It has its roots in the crossed-circulation experiments of Starling, so well known to students of physiology, and the impetus for their development lay in the desire of surgeons to perform “open heart” operations. The first practical oxygenator to be described seems to have been the rotating disk oxygenator of Melrose, developed at the Postgraduate Medical School, Hammersmith, in 1949. Bubble- oxygenators were described in the following year by Clark and his co-workers, and were used by Lillehei, while similar oxygenators using a higher flow were also developed at the Mayo clinic. The vertical screen oxygenator of Miller, Gibbon and Gibbon was described in 1951. It was in this year that the first pump-oxygenator seems to have been used in man by Dennis et al. (*Annals of Surgery*, 1951, 134, 709), but cases were compar-atively rarely described before 1954.

The major problems involved in the construc- tion of this sort of apparatus were concerned mainly with the difficulty of building either pumps or oxygenators capable of maintaining an adequate flow or arterial blood. The newest development in this direction has recently been described by Drew and his co-workers. This technique involves the use of a pump-heart-bypass, enabling the blood to be oxygenated in the patient’s own lungs, combined with profound hypothermia which lessens the body’s oxygen requirement.

An important stage in the development of extra- corporal circulation was reached when, in 1952, Delorme described his method of arterio-venous shunt with cooling of the blood, in order to pro- duce hypothermia.

Intravenous infusion and transfusion, extracor- poreal circulation and even the intravenous administration of drugs are all the direct outcome of the work of William Harvey, who may be con- sidered as the Father of Modern Medicine and who has had an especial influence on the science of resuscitation. Yet, after the publication of his great work on the circulation of the blood, his patients, says Aubrey, “did think him crack- brained”. Although we may frequently deplore the sensationalism of the press in medical matters, we may be thankful that we work in a very dif- ferent climate of public opinion, and it is satis-factory to know that encouragement and acclaim have been awarded to those who have furthered the important work in extracorporeal circulation.

**INTRAVENOUS ANAESTHESIA**

The intravenous administration of drugs is closely related to the subject of blood transfusion, which, being derived from the work of William Harvey, dates from the same period: its history is, how- ever, much less coherent than that of transfusion, for the intravenous route seems to have been entirely neglected for more than two hundred years after the first experiments. No doubt this
hiatus is largely due to the lack of a suitable syringe: the invention of the hypodermic syringe by Pravaz, and of the detachable needle by Alexander Wood, both in 1853, provided the tools required by the clinician. Even so, the intravenous use of anaesthetic agents was delayed for a further twenty years.

The earliest experiments of which we have any record were made by (Sir) Christopher Wren in 1656, and were referred to by Oldenburg and Clarck in the Philosophical Transactions of the Royal Society, in 1665. The influence of William Harvey on Wren is to be traced in the fact that, at the time of these researches, Wren was assistant to the celebrated physician, Sir Charles Scarborough, who was a close friend of Harvey. In default of a syringe, Wren made use of a quill attached to a piece of pig's bladder, and, with this crude apparatus he demonstrated the effects of a solution of opium, of crocus metallorum and, according to one authority, of wine and beer when given intravenously to dogs. In 1665, Sigismond Elsholtz confirmed the first of these experiments, bringing about the narcosis of a dog by the intravenous administration of opium.

It was not until twenty-five years after the discovery of anaesthetics that the subject received any further attention. In 1872, Pierre-Cyprien Oté, Professor of Physiology at Bordeaux, described anaesthesia in animals by the intravenous administration of a solution of chloral; two years later, he reported to the French Academy of Sciences the first use of this anaesthetic in man. Chloral, however, is not a satisfactory anaesthetic agent, and the method did not prove popular, in spite of Oté's continued advocacy. The intravenous route was, however, revived in 1898 by E. Dreser of Munich, who employed methyl propyl carbinal urethane (Hedonal); this drug achieved a measure of success, being used, frequently in conjunction with chloroform, by N. F. Krakow of St. Petersburg, until at least 1908.

In 1909, Ludwig Burkhardt used a solution of chloroform as an intravenous anaesthetic and, four years later, Noel and Souttar were using paradehyde by the same route. Soon afterwards, trichloro-iso-propyl alcohol (Isopral) was introduced, and Graefe reported on a series of 359 cases in which anaesthesia had been induced with Isopral and continued with ether.

Meanwhile, the routine use of premedication with morphine and atropine or hyoscine was coming into fashion: the intravenous administration of these drugs was first reported by Elisabeth Bredenfeld of Switzerland in 1916. It was also in this year that Peck and Meltzer advocated the intravenous use of magnesium sulphate as an adjunct to anaesthesia, on the ground that less anaesthetic was then required to achieve suitable operating conditions. It was in 1921 that Nakagawa first recommended ethyl alcohol as an intravenous anaesthetic, but the use of this agent did not become popular until after the work of M. G. Marin of Mexico, in 1929.

Until the third decade of the 20th century, the advocates of the intravenous route had tried various types of drug and had achieved only moderate success. It was in 1924 that a new chapter opened with the introduction of the first intravenous barbiturate, the forerunner of a large group of drugs of this type which has proved extremely valuable to the anaesthetist. The first barbiturate, barbitone (Veronal) had been synthesized in 1903 by Fischer and von Mering; this drug was later combined with di-allyl barbituric acid (Dial) to form a new compound, Somnifene. Animal experiments were begun with Somnifene by Bardet in 1920, its use in man being first reported by Fredet and Perlis in 1924. It was in this same year that L Bogendörfer of Würzburg used di-allyl barbituric acid alone by the same route. The barbiturates had arrived, and in the following years they have appeared in increasing numbers, and have occupied the centre of the stage. Thus, in 1927, Bumm introduced sodium butyl bromallyl barbiturate (Pernocton), and, in 1929, Weiss tried phenyl ethyl barbituric acid (Luminal); the use of sodium amytal was also described in 1929 by Zerfas and MacCallum. In the following year, Fitch, Waters, and Tatum reported on the use of pentobarbitone sodium (Nembutal), and, in 1933, Döring introduced sodium iso-propyl bromallyl barbiturate (Eunarcon), which latter was favourably received as an intravenous anaesthetic agent.

All these drugs were, however, quickly overshadowed by the first "ultra-short acting" barbiturate, hexobarbitone sodium (Evipan Sodium), which was first employed by Weese and Scharpf in 1932: this agent at once leapt into prominence and favour, so that the introduction of butyl ethyl
barbituric acid (Soneryl) as an anaesthetic by Desplas and Chevillon in 1934 passed almost unnoticed. It was in the latter year that J. S. Lundy of the Mayo Clinic introduced sodium thiopentone (Pentothal Sodium), which was soon to surpass even hexobarbitone in popularity, and which has so far remained the intravenous agent most commonly used, in spite of the debacle of Pearl Harbour and the discovery in recent years of several other barbiturates suitable for intravenous use.

Although the barbiturates have deservedly gained the greatest popularity, there are other drugs which have also been used with considerable success in recent years. Thus, tribromethanol (Avertin), introduced by Butzengeiger in 1926, was employed intravenously by Kirschner in 1929: during the second World War, it found its place as a satisfactory agent for the induction of anaesthesia in patients with "floating tongue", the result of bilateral fracture of the mandible; such patients were notoriously difficult to anaesthetize safely by any other means, but the introduction of the relaxants has rendered this technique obsolete. In recent years, attention has been given to the steroids, which have been shown to have considerable possibilities as anaesthetic agents, but the slowness of onset of unconsciousness and the risk of venous thrombosis have militated against their acceptance by clinicians.

The intravenous use of procaine is in rather a different category. Introduced by Alfred Einhorn in 1904, it was first used intravenously by August Bier in 1908. Bier described a method of regional analgesia in which part of a limb was exsanguinated and isolated between tourniquets, the veins then being filled with a dilute solution of procaine. In the same year, J Goyanes of Madrid used a rather similar technique, employing intra-arterial instead of intravenous injection; this latter method was further modified in 1910 by J. L. Ransohoff, who appreciated the relative lack of toxicity of intra-arterial, as compared with intravenous, procaine, and therefore discarded the tourniquets. The systemic use of intravenous procaine, however, began with the observation of its beneficial action in arteritis obliterans by Leriche and Fontaine in 1935. In 1942, Lundy recommended its use for the relief of the pruritus of jaundice, and Gordon employed it as a general analgesic in the treatment of burns in the following year. Intravenous procaine was first used as a general anaesthetic by Bigelow and Harrison in 1944, and its use in the postoperative control of pain was begun by Burstein in 1947.

The pharmacological importance of the intravenous route for the administration of drugs is that it enables nonvolatile agents to be given in such a way that their effects are rapidly observable, and the administration is thus made safer; from the point of view of the patient, however, their advantage lies in the ease and comfort with which anaesthesia can now be induced. The anaesthetist of today owes a great debt of gratitude to the pioneers of the intravenous route, and those who remember anaesthesia as it was in the days when intravenous injections were by no means a commonplace must often look back with amazement and pleasure on the change which has overtaken our specialty in the last quarter of a century.