INTRODUCTORY NOTES

The second edition of the text book 'Human Blood Groups and Inheritance' by Dr Sylvia Lawler and L.J. Lawler, was published in 1963 by Heinemann, London – having been originally published in 1951. The first chapter of this book is titled 'Historical Survey and General Principles'.

I have been unsuccessful in my extensive attempts at trying to establish who now owns the copyright for this book and as far as I am aware it is not available to view via the internet. As such, this transcript is presented in this format for personal study only and must not be downloaded, copied, modified or reproduced further – it is provided here as an additional source of information relating to the history of blood transfusion.

Due to the age of this publication it is either rarely encountered by people looking for information on the history of blood transfusion or is ignored because much of the factual material included within later chapters of the book is now out of date. As well as a short overview of the ancient aspects relating to blood 'infusion' the first chapter also includes a basic summary of the causes and effects of an incompatible blood transfusion, which were described by many early investigators following both animal-to-human and human-to-human blood transfusions even though they did not understand the immunological reasons behind them.

HUMAN BLOOD GROUPS AND INHERITANCE

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Chapter 1
HISTORICAL SURVEY AND GENERAL PRINCIPLES

Throughout the ages man has used his blood as a symbol of fellowship or kinship and the mutual letting of blood was a bond of the strongest type. To be "blood-brothers" tied men together inseparably during life as closely as the members of a family. It has always been realised, if only subconsciously, that within a family the blood of the relations has something in common not possessed by those outside. And yet it is only very recently that these beliefs have been shown to have some scientific backing. The blood substance, which looks so similar not only in all races of men but in all the vertebrates, is remarkably varied in its chemical make-up.

It must not be thought that, in the past, no efforts have been made to investigate blood. The ancient Greeks considered that blood was one of the four humours of the body, the balance of which determined the health and constitution of the individual. These four were Black Bile from the spleen, which caused a predominating melancholic temper; Phlegm from the lungs causing a phlegmatic temper; Yellow Bile from the gall bladder causing a choleric temper; and lastly, Blood, supposed to originate in the liver, causing a sanguine personality.

Empedocles, who lived in the fifth century B.C., is thought to have formulated many early biological theories, one of which was that the blood ebbed and flowed in the same blood vessel. He was at least right in the idea that the blood moved, having no doubt deduced this from the observation of bleeding from wounds. The erroneous tidal idea was to last in most men's minds for the next two thousand years.

About 150 years after Empedocles lived, Herophilus is reported as having distinguished between arteries and veins. He noticed that the arteries pulsated during life, but still thought that the blood surged to and fro in the same vessels, alternating like the tide.

One of the greatest of the scholars who learnt at the famous library at Alexandria was Galen, who lived from about A.D. 130 to A.D. 200. Some of his textbooks of anatomy remained the standard for all medical teaching in the West until the early seventeenth century. He believed implicitly in the teaching of the ancients about the blood movements in the body, but he found it very difficult to account for the apparent complete division of the heart by a septum which would block the changing over of blood from one side of the heart to the other. Fourteen centuries were to pass before microscopes were constructed which allowed the minute blood capillaries to be described, and so, to deduce their presence from the gross parts which he could see, was beyond even Galen. Instead of realising that the blood flowed round the double circulation of the body, Galen thought there were very small holes in the septum of the heart which allowed the blood to "seep" through from one side to the other. (Rather like the conditions found in the unborn child when its lungs are by-passed because it is receiving its oxygen from the mother via the placenta.) Nobody found Galen's septum perforations, but this did not deter the vast majority of medical scientists from believing in their presence until the seventeenth century.[1]

The exceptions were men like Cesalpino, who suggested in 1580, purely on theoretical grounds, that the blood circulated, but had not been able to prove it. It remained for William Harvey (1578-1657) to demonstrate clearly this circulation and prove its reality by conclusive experiment. In 1616, he lectured in London on his findings and published his famous book "Exercitatio Anatomica de Motu Cordis et Sanguinis in Animalibus" in 1628.

It is remarkable that, in spite of the opportunities afforded by observation of battle casualties, Harvey's findings had not been more clearly anticipated. It seems strange that the continuous flow from a cut vein and the pumping from a cut artery, which must have been widely observed, did not lead to closer investigation before Harvey's time of the blood's path round the body.

The idea of a one-way flow of blood through the arteries and veins was soon followed by experiments of transfusing blood from one creature to another. In 1658, Dr. Christopher Wren, famous as an architect and an astronomer, was the first of a number of experimenters to introduce foreign substances into the blood streams of animals. Dr. Richard Lower, in 1665 performed the first direct blood transfusion by keeping alive a small dog, almost bled dry from a cut jugular vein, by introducing blood from the carotid arteries of two mastiffs. The connection was made by quills and a piece of a large artery taken from an ox. Another early experimenter was Professor Jean Denys of Montpellier, physician to Louis XIV, who in 1667 introduced lamb's blood into the vein of a feverish boy; later he gave lamb's blood to a man. He described the reactions of a third patient who had been transfused with the blood of a calf. The description included the observation that the patient afterwards passed black urine; this is now known to be caused by the excretion of the broken-down red pigment of the foreign blood.

In England the first transfusion of animal blood into a man was reported by Samuel Pepys. On November 21st, 1667, he wrote in his diary of a man "hired for 20*s* to have some of the blood of a sheep let into his body; and it is to be done on Saturday next. They purpose to let in about twelve ounces; which, they compute, is what will be let in in a minute's time by a watch." Again, on November 30th, 1667, "I was pleased to see the person who had his blood taken out. He speaks well, and did this day give the Society[2] a relation thereof in Latin, saying that he finds himself much better since and as a new man; but he is cracked a little in his head, though he speaks very reasonably and very well."

Soon after these experiments, one of Denys' patients died after receiving a transfusion of animal's blood. The whole procedure fell into disrepute and in France the operation was made illegal. The transfusion of animal blood to man was soon recognised as a very dangerous procedure and, because the reasons for the fatalities were not understood, further transfusions were not carried out until the beginning of the nineteenth century.

To understand what occurs when the blood of one type of animal is put into the blood stream of another type, it must be remembered that the blood of a backboned animal is not a simple red fluid but consists of a number of complex constituents. These may be separated into those which dissolve in water to form the straw-coloured liquid plasma, and those which constitute the living, microscopic, cells or corpuscles. The cells are of two types, the red and the white corpuscles. The red cells, carrying the pigment haemoglobin, which is vitally important as the oxygen-carrier of the body, are more numerous than the white. The white cells are one part of the system which protects the body against infection. One type of white cell, the polymorph, can ingest particles of foreign matter such as bacteria. The pus which comes out of an abscess is largely made up of broken-down white cells and bacteria. The remaining solid particles in the blood are platelets, which form part of the clotting mechanism which protects the body from excess bleeding.

The liquid part of the blood, which is mostly water, contains the plasma proteins. This, in general, maintains the blood volume, and transports, among other things, hormones and enzymes. The plasma proteins are always being broken down and replaced so that they must play some part in nutrition. They are all very complicated molecules which can be separated into three main groups, the fibrinogen, the albumin and globulin fractions. Fibrinogen is essential in the formation of clots, forming the microscopic fibrous network, which holds together the solid particles of the blood, leaving the straw-coloured serum. Serum contains all the components of plasma except those which are used up in the formation of the clot.

It is the globulin fraction which carries the substances which protect us against infection. These substances are called "antibodies." If an animal has had a disease once and has survived the infection then it is especially resistant to another infection of the same disease. The animal is said to have become "immune." If the disease is caused by invasion of bacteria, after the initial infection the serum of the animal is capable of reacting with the bacteria, either by making them clump together or by breaking them down. The invaders are then ingested by the polymorph white cells. The substance in an immune serum capable of reacting with invading bacteria is an antibody, and the foreign substance which causes the formation of antibody is called an "antigen".

It is possible to induce the formation of immune antibodies by giving small doses of the appropriate antigen – for example, disease bacteria which have been rendered harmless. This process is called "immunisation" and is used as a protection against future infection by the same bacteria. Proteins other than those in the bacteria also act as antigens, e.g., egg white, and even the red blood cells themselves carry substances which show antigenic properties under certain conditions.

The antigens of the red cells are controlled by inherited factors, or genes, which the young receive from their parents at the time of conception. These red cell antigens are different in animals which belong to different species, and in certain species there may be differences between individuals so that the species may be divided up into various blood groups.

A child is born with a certain amount of its mother's antibodies due to transfer across the placenta, and, in addition, a breast-fed infant gets some antibody from the mother's milk. This "passive immunisation" does not last very long and so later active immunisation is no less important, e.g., against diphtheria.

In addition to these immune antibodies which are formed as the result of introduced antigenic substances, some antibodies (including certain blood group

antibodies) occur naturally and are inherited. Whether the antibody is immune or naturally occurring, it will react with its antigenic substance in a similar way. If blood containing a blood group antigen is given to someone who has the antibody, the consequences of the reaction between the antigen and the antibody may be violent. When such a reaction occurs, the blood containing the antigen on its red cells is said to be "incompatible" with the blood the serum of which contains the antibody. It is indeed unfortunate that, unlike the protective antibodies which are produced against bacteria, the possession of antibodies corresponding to a blood group antigen exposes the individual to great risk if incompatible blood is given.

It is interesting to note that the reactions of a recipient to a large injection of incompatible blood were well described by those early experimenters who did not understand their cause. Take, for instance, the patient of Denys who died after receiving three transfusions of sheep's blood his reaction to the second was far greater than to the first, and the symptoms were an increased pulse rate, a burning sensation around the point of injection, sweating, pain in the loins and nausea. At the third transfusion, the man died of shock.

Some of the reasons for these symptoms can now be described. The first transfusion of incompatible blood may or may not cause visible reactions according to the presence or absence of naturally occurring antibodies, the amount of blood introduced, and the individual concerned. Usually the second transfusion has a much greater effect than the first as the recipient is immunised, or sensitised, by the first transfusion. It is not known precisely what occurs during immunisation and the antibody formed as a result of the first dose of the antigen is not necessarily detectable in the circulation. If the individual is subsequently given additional doses of the same antigen, there will be antigen-antibody reactions. These antigen-antibody reactions take several forms, the most important of which being haemolysis, or breakdown of the introduced red cells, actual damage to the tissues of the body, and agglutination, or the clumping together, of the introduced red cells. The haemolysed remains of the transfused cells are excreted rapidly and cause the urine to go black. The agglutinated cells may stop the circulation in the finer blood vessels, which may be one of the factors giving rise to the symptoms which Denys described. The upsetting of the circulation has repercussions which manifest themselves as fever, sweating, increased pulse-rate, shivering and nausea. These shock reactions may be severe enough to cause death, as they were when Denys transfused his patient for the third time.

In the early part of the nineteenth century the transfusion of blood from one human to another was tried. This was sometimes successful although the great difficulties caused by the clotting of the blood were not easily or quickly overcome. James Blundell (1790-1877) gave the first demonstration of such a transfusion although many people, including Erasmus Darwin, had been talking about experimenting before. Blundell's patients were often near death when he tried, but four successful transfusions were performed. The search for a method of preventing clotting during transfusion was a long one and it was not until 1913 that the use of vessels lined with a smooth layer of paraffin wax was discovered. This method works because the lack of a rough surface retards the breakdown of the platelets in the blood, which is an important part of the clotting mechanism. The next year there followed the simultaneous discovery by a number of workers that sodium citrate was an anticoagulant which was harmless in the quantities required for a transfusion. This discovery enabled blood to be stored over several weeks. Many other substances, both harmless and poisonous, are now known to be equally efficient anticoagulants, *e.g.*, heparin, which can be administered to patients with safety, and sodium oxalate, which is a poisonous substance sometimes used to prevent blood samples, taken for laboratory examination, from clotting.

The successful transfusion of blood between creatures of the same species had been demonstrated with dogs and horses. It was soon found, however, that the

blood of one human being could not always be given to another human being with safety. The reasons for this incompatibility were finally explained by Dr. Landsteiner in 1900.

If a sample of whole blood is allowed to stand, it separates into a clot of cells which sinks to the bottom, leaving a clear straw-coloured fluid, the serum. Dr. Landsteiner and his coworkers demonstrated that mixing the red cells of one person with the serum taken from another sometimes resulted in agglutination, that is, a clumping together of the red cells. In other words, they discovered that human blood contained naturally occurring antibodies which reacted with the antigens of other humans. Naming these antigens A and B, Dr. Landsteiner formulated the classical ABO blood group system.

Hence, each human being possesses naturally occurring species antibodies which agglutinate the red cells of animals of other species, and, in addition, they may have naturally occurring antibodies corresponding to the A or B antigens. Infrequently, naturally occurring antibodies corresponding to other more recently discovered antigens are found. In addition, a recipient may become immunised against some antigen in transfused blood, in which case new immune antibodies appear in the serum. Occasionally immune antibodies may be formed in a mother's blood when the baby's blood contains antigens inherited from its father, which she herself lacks. This is summarised in Table I.

In 1927, following experiments in which animals were immunised by having human blood injected into them, it was shown that there were two more human blood group systems called MN and P.

In 1940, the Rhesus blood group system was discovered following experiments in which an antibody formed by a rabbit, immunised by the blood of a Rhesus-monkey, was shown to be the same as an immune antibody found in the serum of a mother. Five other blood group systems have since been discovered[3]; the Lutheran (1945), Lewis (1946), Kell (1946), Duffy (1950) and Kidd (1951) systems. Since the discovery of the Kidd system no new major blood group has been described. Thus at the present time there are nine well-defined human blood group systems.

TABLE 1: BLOOD GROUP ANTIBODIES

Blood Group ANTIGEN on Red cells	*reacts with*	corresponding ANTIBODY in serum which may be
NATURALLY OCCURRING by inheritance	*or*	IMMUNE i.e. made in response to a foreign antigen introduced by
TRANSFUSION (immunisation due to incompatible red cells in circulation)	or	PREGNANCY (immunisation of mother by incompatible foetal red cells which have crossed the placenta)

[1] In the foetal circulation the lungs are by-passed by the blood passing directly from the right to the left atrium via the foramen ovale, and also by the ductus arteriosus (between the pulmonary arteries and the aorta) both of which normally close at birth.

[2] The newly-formed Royal Society.

[3] At the time of the reprinting in 1963 this list had been extended by the discovery of the following systems: Diego, 1956**;** I, 1956; Sutter, 1958**;** Auberger, 1961; Xg, 1962. (The gene determining the antigen of the Xg system is carried on the X chromosome and studies of this system which are at present in progress will undoubtedly lead to mapping of the sex chromosome in man).