

REUBEN OTTENBERG (1882-1959) – THE ORIGINS OF THE CROSS-MATCH

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I am sure that people reading this article know that it was Karl Landsteiner who discovered the ABO blood group system at the beginning of the last century, but I am unsure how many people know the name Reuben Ottenberg – who was the first person to make practical sense of Landsteiner's discovery by performing the first pre-transfusion serological cross-match.

Karl Landsteiner published his discovery in German in the Austrian journal *The Central European Journal of Medicine* in 1901 (though it was originally briefly mentioned in a paper published in 1900). However, it is a fact that the vast majority of the international scientific and medical community did not take much notice of this publication for more than a decade. In addition, those who did thought that the ABO blood groups were merely genetic differences, relevant only to describing racial differences and possibly disease associations. As such, even though mentioned by Landsteiner, the practical transfusion applications of this discovery were not initially realised.

Prior to the turn of the last century, the vast majority of human blood transfusions were 'indirect' in that they were given by collecting the donor blood from an open vein via a funnel into a syringe and then injecting it into the recipient. Given that anticoagulation of blood by citrate had yet to be discovered, this process had to be performed quickly to avoid the blood clotting and therefore only small amounts (about 4 mL, i.e. a 'syringe-full') could be given at a time. As a result, most transfusions involved only relatively small total volumes of blood being given - an important factor when considering the effects of possible blood group incompatibility on the recipient.

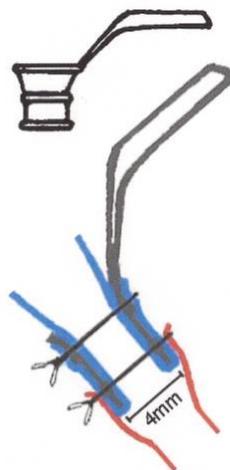


Fig.1: George W Crile's metal cannula for joining the donor's artery (blue) to the patient's vein (red). See: *Annals of Surgery*, 1907; 46: 329-332.

George Crile designed a cannula (Fig.1) for connecting a donor's artery directly to a recipient's vein and in 1907 successfully performed a 'direct' human blood transfusion using this technique. This surgically very difficult but successful technique meant that the blood did not need to be anticoagulated because the

surfaces of the artery and vein were 'seamlessly' joined, but in addition, it also enabled much larger volumes of blood to be transfused. Possibly because of this, more clinicians started to describe 'post-transfusion reactions' occurring in about 30% of their patients, which were characterised by chills, fevers, kidney pain and bloody urine.

Although the blood of the donor and recipient was occasionally quickly mixed prior to a direct transfusion, this was primarily to observe if haemolysis occurred – nobody looked for the red cell 'agglutination' described in Landsteiner's original paper.

It was Reuben Ottenberg (Fig. 2) who was the first person to realise a relationship between incompatible ABO groups and post-transfusion reactions. In 1906 he was senior intern in surgery at the German (now Lenox Hill) Hospital, New York, and had read Landsteiner's papers on ABO group antigens and antibodies ('isoagglutinins' as they were then called).



Fig.2: Reuben Ottenberg (1906)
Photo credit: timetoast.com

In 1908 Ottenberg published his own paper on performing blood transfusion using direct artery-vein anastomosis and mentioned at the end of the paper that he had performed 'compatibility' tests on the donors and patients prior to surgery, even going on the state his belief of the importance of this test. Following his internship, Ottenberg moved to Mount Sinai Hospital, New York, where surgeons such as Charles Elsberg were already using direct blood transfusion techniques. He was convinced that the haemolysis seen in some blood mixtures (which took a long time to develop) was preceded by agglutination (a fact not previously realised) and developed a cross-match red cell agglutination test to determine 'ABO incompatibility'. He later wrote: "I offered to do compatibility tests, but many of the surgeons did not accept the offer – they felt that since Crile had done a large series of transfusions without tests (and with only a few cases of haemolysis and no deaths), they ought to be free from interference by the laboratory men."

To some degree this adverse comment needs to be balanced against what Ottenberg considered a 'pre-transfusion cross-match' at the time – which was essentially 'ABO matching'. His procedure used relatively large amounts (10-15 mL) of clotted blood from the prospective donor and the patient, involved both 'major' (i.e. mixing donor red cells with recipient's serum) and 'minor' (i.e. mixing recipient red cells with donor serum) tests. These tests were performed in large glass tubes that were placed at 37°C for two hours before the agglutination reactions were read. It can therefore be said that this was by no means a 'rapid' procedure and as such considerably delayed the transfusion as far as the surgeon (and donor) was concerned (although many people will remember that routine saline cross-matching serological techniques of the 1970s took a considerable time to perform compared with later LISS techniques – though this did not keep the donor as well as the clinician waiting!).

Ottenberg did however convince some of his surgical colleagues to agree and over a five-year period he collected together 125 cases of transfusion that had been performed after 'pre-transfusion cross-matching'. His paper, published in 1913, concludes by saying "Accidents in transfusion due to the occurrence of haemolysis or agglutination of the donor's blood cells by the patient's serum, or vice versa, can be absolutely excluded by careful preliminary tests." He went on to identify that haemolysis was always preceded by agglutination and that 'minor' cross-matching was less important than 'major' cross-matching.

Although as early as 1920 people were starting to discuss the alternatives of selecting blood for patients using either 'indirect' matching, based only on ABO blood grouping of the donor and patient, compared with 'direct' matching, using compatibility testing of donor's cells and recipient's serum, it was well into the 1920s, after years of "campaigning, experimenting and a few accidents" that 'blood matching' would become a standard pre-transfusion procedure. Other blood group systems had of course yet to be discovered and more sensitive and rapid techniques to detect 'clinically significant' antibodies were yet to be developed, which together with the evolution of pre-transfusion testing would lead eventually to 'electronic matching' and national guidelines on pre-transfusion compatibility procedures. But it was Reuben Ottenberg who was the first person to practically apply Karl Landsteiner's discovery to blood transfusions by performing a 'cross-match' and thereby greatly improve patient safety.

Fittingly, in 1954 Reuben Ottenberg was the first person to be awarded the Karl Landsteiner Award from the American Association of Blood Banks for "distinguished pioneering contributions to blood banking and hemotherapy."