"IT ALL HAPPENED AROUND 1911"

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The years immediately before the First World War saw the culmination of late Victorian enterprise and endeavour. Einstein developed his Theories of Relativity between 1905 and 1915; and in 1913 Niels Bohr (Einstein's collaborator and owner of several 'Cubist' paintings) refined Rutherford's 1911 description of the atomic nucleus. Sherrington defined the neurological synapse in 1910[1]. In May 1911 Gustav Mahler, the great musician of Austria-Hungary's last decades, died; and the 'unsinkable' Titanic was launched. In December 1911 Amundsen reached the South Pole - followed in January by the luckless Captain Scott.

These were politically turbulent times. Overseas, the British Empire was triumphant; but at home there was social inequality and grinding poverty (75% of adult Britons shared 5% of Britain's wealth). Western jingoism was to cause great losses in the 'War to end wars', in human suffering and in delaying economic and welfare developments. More than 8 million were killed, including many promising scientists. The Allied Command expected 30,000 total casualties from the battle of the Somme - actually 60,000 occurred on the first day[2]. (Today's larger hospitals have approximately 1000 beds each for all specialties!). Although the war stimulated medical and surgical practices - including transfusion - these were based on earlier researches. Even had there been no war these advances - and others such as the position of women in society - would have continued. The world was ill-prepared for the 20 million deaths in the 1919 epidemic of "Spanish 'flu".

Until the 1900s pathology was predominantly conducted in mortuaries. No British hospital had a bacteriology department until 1885, although Koch's "postulates" and Pasteur's vaccines had established bacteriology and immunology at pathology's leading edge, and rationalised antiseptics in surgery. But distinctly bacteriological service laboratories - from which developed 'clinical pathology' - were slow to develop in Britain until well after the 1914 - 1918 war. The germ Theory did, however, help Municipal Medical Officers of Health to influence building standards and improve the health of the nation - particularly the inner city dwellers. Observers of the building site at St Thomas's in the 1960s will never forget the amazing sturdiness of the hospital's Victorian sewers.

Landsteiner's discovery of the ABO system[3] in 1900 was an extension of investigations into bacterial agglutinins. In the 1890's Widal had shown that serum from patients recovering from typhoid fever agglutinated typhoid bacilli. This led to the development of typhoid vaccine in 1897 by Almroth Wright, Professor of Pathology at the Army Medical College at Netley by Southampton Water, where he was also investigating blood clotting. In 1902 Wright moved to St Mary's Hospital, London where he attracted many, including Alexander Fleming, to his Institute. This was not a service department but earned income as a semi-independent manufactory of vaccines - often weird and dubious. Production - based on the now-discredited 'opsonic index' - would not have passed today's Medicines Control Agency Inspectors! Wright never forgave George Bernard Shaw for parodying him as 'Sir Colenso Ridgeon' in 'The Doctor's Dilemma' (first produced in 1906). Although a distinguished career lay ahead, Wright's finest contribution was probably the typhoid vaccine; but his antiestablishment attitude hindered its acceptance until the 1914 war. He was not a strong practitioner of 'scientific method', being unduly susceptible to his imagination. There were several other bacteriology 'Institutes' at the time; the 'Lister' - precursor of the IBGRL and BPL - being pre-eminent.

Before the advent of antibiotics, bacteriology was mostly of value in the context of vaccines and 'serum therapy'. But other advances included improved insights into blood clotting when Morawitz described prothrombin (1905), and Thomas Wright in America described the modem method of staining blood films (1910). Also in America, Ottenberg became interested in transfusion while at the German Hospital in New York, where there was good access to Landsteiner's publications. He suggested the Mendelian nature of the ABO system (1908)[4], transfused some cases of haemorrhagic disease of the newborn (1910[5] citing better success by Lambert in 1908), and demonstrated the clinical importance of agglutinins (1911)[6]. At that time these 'agglutinins' (antibodies) were thought to be more significant than the 'agglutinogens' (antigens), even by Landsteiner whose initial 'ABO' version of nomenclature was less clear cut then is often assumed. In 1910 Moss[7] - on a sounder basis - consolidated the emerging 'I-II-III-IV' nomenclature and although Ottenberg's interpretations[6] were better than Moss's, understanding was still uncertain. An alternative and similar-sounding but dangerously different classification proposed by Jansky[8] (see table) plagued transfusion practice until the Division of Hygiene of the League of Nations (the forerunner of the World Health Organisation) ruled in favour of an updated ABO nomenclature in the 1920's.

TABLE I
Moss and Jansky nomenclatures of the ABO system

ABO	Moss	Jansky
A	II	II
B	III	III
AB	I	IV
O	IV	I

In 1910, Duke described the earlobe "bleeding time", and demonstrated the role of platelets. His most successful case was an Armenian tailor in New York who developed severe thrombocytopenia[9]. The bleeding time was very prolonged. A large 'direct' transfusion was administered (technique not given, but probably artery-to-vein, or possibly vein-to-vein; the donor became tachycardic). The donor was an Armenian friend (the only criterion for selection) and the platelet count increased to 123,000 per mm^3. The bleeding time shortened but got longer over the next 6 days as the platelets fell. Then the platelet count rose spontaneously, and the bleeding time (and the patient) recovered. The figures are from Duke's original photographs, and a more modern example prepared by the author.

In 1911 Cohen[10] reviewed the curious variety of clotting time techniques - including one of Almroth Wright's - and how different tissue extracts affected clotting. These studies were seriously compromised by using capillary blood from fingers or earlobes. Intravenous sampling was novel then. (Wright never used oxalated venous blood even though he showed oxalate to retard clotting and argued that haemophilia was caused by calcium deficiency). Although Cohen mentioned Duke, he made no reference to platelets. Cohen was soon out of date; in 1913 Lee and White reported their experience of the "whole blood clotting time" of unanticoagulated venous blood[11] taken directly into the test tube, describing 37 conditions including haemophilia and jaundice (prolonged times) and 'aortic disease' (shortened). They cited the use of venous blood by Pratt in 1903 who, nevertheless, did not consider this 'feasible' as a routine.

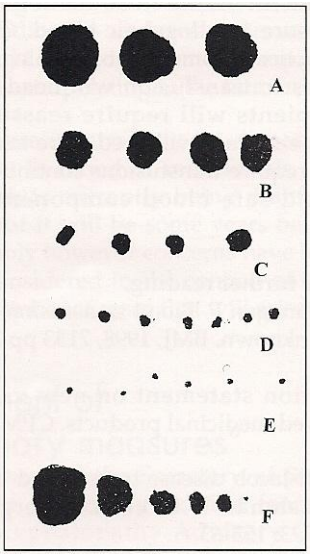

Figure 1 - Blots of blood token from an incision into on earlobe. Each row represents 30 second intervals. Rows A - E before transfusion; Row F after transfusion. The bleeding time pre-transfusion was 90 minutes; post-transfusion, when the platelet count was 123,000, it was 3 minutes. From the case described in the text (Duke, 1910)

By 1910, Thomas Addis in the laboratories of the Royal College of Physicians of Edinburgh - who featured in Cohen's review - had already switched to venous blood samples collected into oxalate. He culminated this phase of his work by showing that normal plasma corrected the defect in haemophilic plasma[12], his impeccable analyses indicating a fault within the "prothrombin component". His approach was, however, too intricate for pre-war hospital diagnostic services. Had his investigations been applied clinically, haemophilia treatment would have developed more quickly; but the necessary infra-structures - i.e. clinical pathology services - just weren't there. It was 20 years before his correct findings gained even some acceptance, and another 20 before therapeutic application. In 1912 Addis settled in California, got married, became eminent in renal medicine, and described the "Addis count" of white cells in infected urine.

A scholarly monograph in 1911 by the 'Ambridge' sounding authorship of Bulloch and Fildes[13] assembled the family trees of all the then published cases of haemophilia - more than 500 families. This clearly showed the "sex linkage" pattern of inheritance, although apparent father-to-son transmission among earlier generations of some families indicated faults in their mythology. Particularly notable was "pedigree 493", earlier described by Treves in 1886[14], which included a homozygous female - her parents were cousins. In the early 1970s I met a younger sister of Treves' propositus - also reported in references 15 and 16 as "case V8". She had 5% of factor VIII as did her four sons, thereby finally establishing her as a true homozygote - admittedly of a moderate form of the disease. Sir Frederick Treves, of the London Hospital, was the surgeon who rescued John Merrick, the "Elephant Man", from the undignified exploitation of fairground showmen. He operated on Edward VII's appendicitis the day his coronation was due in 1901. (The coronation was deferred.)

The close links between these early 'haematological' examples and bacteriology within clinical pathology are illustrated by the fact that Bulloch and Fildes were recognised bacteriologists. Fildes (from 'The Middlesex') was the co-inventor of the MacIntosh and Fildes jar - a device which neatly allowed bacteria to be cultured

anaerobically; and Bulloch was Lecturer in Bacterial Pathology at the London Hospital Medical College - where he crossed swords with the Director of the Clinical Pathology Laboratory in the London Hospital, the rather better established Noel Panton. Panton, who deserves credit for establishing clinical pathology in the Emergency Medical Services of 1939 to 1945, and Bulloch worked at the London from about 1910 to 1940. The subject of most dispute between them was the treatment of syphilis[17].

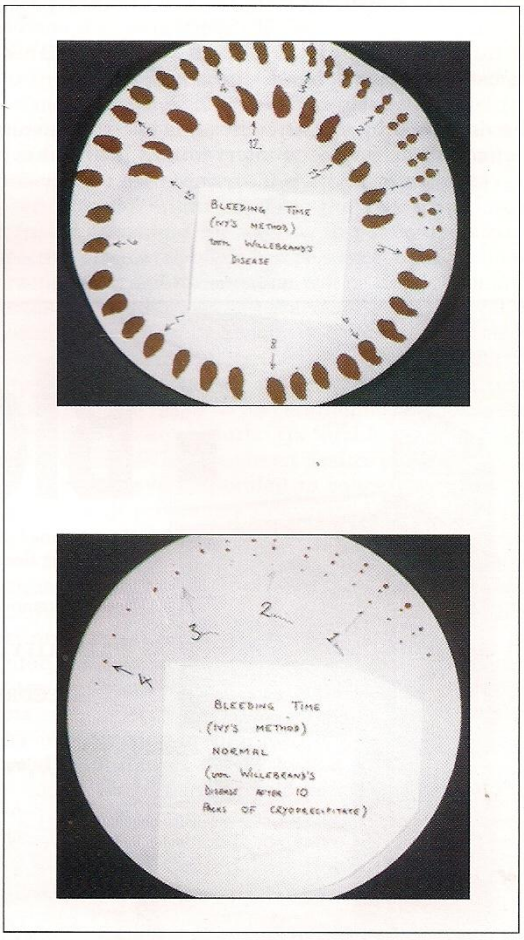

Figure 2 - Bleeding time from incisions on the volar aspect of the forearm (Ivy's method), blotted at 15 second intervals. Recorded in 1973 by the author from a 15-year old women with von Willebrand's syndrome having a severe and prolonged epistaxis, before and after infusion with 10 packs of cryoprecipitate. The pre-treatment timing was abandoned after 13 minutes as it was obviously prolonged and treatment was required.

In 1911 Fleming[18] gave the first English language description of the anti-syphilitic drug salvarsan (compound "606") developed in Germany by Ehrlich in 1906. Ehrlich distributed limited quantities to favoured bacteriologists in Britain including Almroth Wright and Bulloch. Wright passed his source to Fleming who showed the superiority of the intravenous approach in 46 meticulously monitored patients. Any fees Fleming earned went to Wright's Institute. Like Fleming, Bulloch was unwilling to use these precious supplies 'indiscriminately' among the patients of Harley Street, probably earning the dislike of Panton. This was apparently compounded by Bulloch being a mere "salaried" member of the University Staff and not in private practice.

This era saw van den Burgh postulating complement lysis of PNH cells, Moreschi describing the antiglobulin test[19] and the first report of transfusion-transmitted malaria (Woolsey[20], *P vivax* passing to a person with pernicious anaemia). In 1911 Todd and White[21], working in Egypt on cattle, anticipated Ashby by developing adsorbed polyvalent serum for a 'differential lysis' technique. Their estimates of bulls' blood volumes *in vivo* were remarkably accurate and pioneering. Rous and Turner[22] showed human red cells to be more resistant to mechanical and osmotic lysis than those of dogs, sheep or rabbits; and preserved rabbit red cells in trisodium-citrate-dextrose solutions, leading the way to Robertson's 'battlefield transfusions' in 1917-1918[23]. In 1919 Ashby[24], using 'differential agglutination', confirmed that transfusion works through the survival - for at least 30 days - of transfused cells (not so obvious until then).

TABLE 2 - This is a reproduction of the grid in Moss's original paper of 1910. The numbers refer to the some individuals, 1 to 20. The horizontal rows refer to the tubes into which 5% suspension of red cells in saline were placed; and the vertical rows the tubes into which that person's serum were placed. See if you can work out the ABO blood groups of each numbered individual.

No	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20
1					x		x	x	x		x	x		x	x		x			x
2					x		x	x	x		x	x		x	x		x			x
3					x		x	x	x		x	x		x	x		x			x
4	x	x	x		x		x	x	x	x	x	x	x	x	x	x	x		x	x
5																				
6	x	x	x		x		x	x	x	x	x	x	x	x	x	x	x		x	x
7	x	x	x		x			x	x	x	x	x	x	x	x	x	x		x	x
8																				
9																				
10					x		x	x	x		x	x		x	x		x			x
11																				
12																				
13					x		x	x	x		x	x		x	x		x			x
14																				
15																				
16					x		x	x	x		x	x		x	x		x			x
17																				
18	x	x	x		x		x	x	x	x	x	x	x	x	x	x	x		x	x
19					x		x	x	x		x	x		x	x		x			x
20																				

x = agglutination. Empty boxes indicate that no agglutination occurred.

Of greater significance for public health in the UK in 1911 was the passage by Asquith's government, under the Chancellor (David Lloyd George), of the National Health Insurance Act[25]. This provided the fore-runner of the NHS. It had, however, one operational defect. Clinical pathology, being still in its infancy, failed to get proper funding. This severely hampered its progress (for example, Addis's work could not be developed into a service). Even by the 1920s, however, transfusion placed no demand on diagnostic services. Often, selected 'universal donors' were typed just once and -

whenever required - a pint of blood was collected into citrate and used immediately without further compatibility testing or even grouping patients[26].

Finally, in February 1911, an obscure general practitioner – C.A. MacMunn, who was also 'honorary pathologist' at the Royal Hospital in Wolverhampton - died. He was the original discoverer of the cytochromes which he demonstrated in the mid-1880's[27]. His correct interpretations were discounted by the 'great' biochemists of the time, another missed opportunity in the history of science. A month later, in the same town, my father was born. Perhaps that explains the title of this article (which, minus references, the table and captions, has 1911 words).

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Further recommended reading

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