INTERVIEW WITH PROFESSOR P. L. MOLLISON

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On 4th March 1998 the editor of the BBTS Newsletter (*Dr Frank Boulton*) visited Professor 'Pat' Mollison at his home in London, for the first of what we hope will be an 'occasional series' of interviews with notable British contributors to the field of Transfusion Science and Medicine.

INTRODUCTION

Professor Mollison was born in 1914 and qualified in medicine from Cambridge and St. Thomas' Hospital, London, in 1938. He had just completed a year as resident at St Thomas's when war became imminent. The Dean of his medical school 'posted' recently qualified doctors to various jobs in the District, and Dr Mollison was sent to work at the South West London Blood Supply Depot at Sutton under its Director, Dr J.O. Oliver - a pathologist from St Thomas's Hospital. This was one of four Centres established to supply blood for the expected numerous air-raid casualties. The Depots were administered by the Medical Research Council but were allowed a good deal of local autonomy. Up to that time there had been no blood banks in London or anywhere else in the UK and there were very few people who knew anything about it.

After gaining his Membership of the Royal College of Physicians early in 1940 Dr Mollison was appointed to do research - with the encouragement of Dr A.N. (later Sir Alan) Drury, Chairman of the Blood Transfusion Research Committee. He began to do work on red cell preservation with Maureen Young (later a Professor of Physiology). In 1942, with J.F. Loutit (who was by now Director at Sutton), they demonstrated the value of acidified citrate-dextrose solutions as preservatives. The method of differential agglutination, in which the survival of group O cells transfused to a person of Group A was determined, and which had been originally described by Ashby in 1919, was also used to study red cell destruction in haemolytic anaemias. Prof Mollison collaborated with J.V. Dacie in showing that there was no destruction of normal red cells in hereditary spherocytosis.

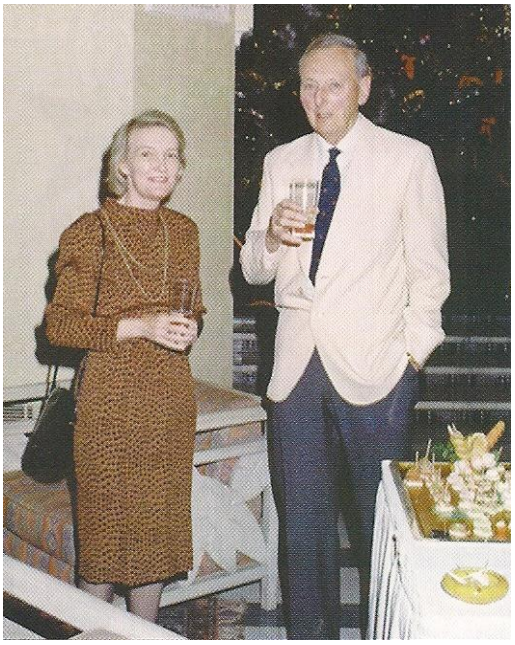
In 1943 he joined the Royal Army Medical Corps, served in a Field Ambulance, and went on to India and Burma as a medical specialist.

After being discharged from the Army he was appointed by the MRC to set up a Blood Transfusion Research Unit. The Unit's initial accommodation was a very small laboratory on one of the Obstetric Wards at the Postgraduate Medical School (PGMS - soon to become 'Royal' or the RPMS) at Hammersmith Hospital. His first assistant was Marie Cutbush (later Crookston) who became a pioneer in red cell serology. Others who worked with him included Nevin Hughes-Jones, who joined him in 1956 and later developed the first quantitative assay of blood group antibodies (in terms of µg/l) and George Jenkins, who studied the components of complement reacting with antiglobulin sera. In 1960 Professor Mollison was invited to set up an independent department of haematology at St Mary's Hospital and his Unit moved with him.

He is best known for his classic text on Blood Transfusion in Clinical Medicine which first came out in 1951 and has now run to ten editions; but I think he merits as much credit for his wartime work in the development of anticoagulant-preservative solutions which enabled blood to be stored for three weeks. He emphasises that many others contributed to this advance, but it was the work at Sutton which was the breakthrough. Interestingly, however, he places more value on his studies on the

patterns of destruction of incompatible red cells in relation to antibody characteristics which were made possible by the introduction of very high specific activity ^{51}Cr. I spent a fascinating afternoon in his company during which he informed me of many interesting background features of his life's work.

Frank Boulton, *BBTS Newsletter editor*



Professor Mollison and his wife Dr Jennifer Jones

INTERVIEW WITH PROFESSOR P. L. MOLLISON

Editor: "Professor Mollison, what was the background to the development of "Acid-Citrate-Dextrose?"

Prof: "The fact that glucose is a red cell preservative was, of course, described by Rous and Turner in 1916 and applied to the transfusion of human blood by Robertson towards the end of the First World War. Nevertheless a simple citrate-saline solution was used initially in 1939 in the UK, before the merits of glucose were rediscovered. A major problem was that glucose and trisodium citrate had to be autoclaved separately if caramelisation was to be avoided. Glucose was added to citrate by an open method with consequent risk of infection. It was well known that caramelisation could be prevented by acidifying the citrate-glucose mixture. Several groups, including those working at the Army Transfusion Centre at Bristol, had shown that acidification improved preservation *in vitro,* but acidified blood was believed to be toxic and unsafe."

Editor: "Who was working with you at that time on the anticoagulant preservative mixtures?"

Prof: "Originally I worked with Maureen Young, a physiologist. In 1941 we were joined by John Loutit, an Australian Rhodes scholar, who came from being First Assistant to the Medical Unit at the London Hospital to become Director at Sutton. Loutit doubted

whether acidified blood would prove to be toxic and Maureen was given the task of trying out various ways of acidifying trisodium citrate. As a result we started storing blood with various citric acid-trisodium citrate-glucose mixtures. As predicted, there was no evidence of toxicity and, excitingly, preservation was strikingly enhanced as judged by survival *in vivo.*"

"After the War, Loutit was appointed to set up a Radiobiology Unit at Harwell and became very distinguished in that field. His group were in the forefront in showing that the protective effect of screening the spleen, in animals exposed to otherwise lethal irradiation, is due to the repopulation of the bone marrow from stem cells derived from the spleen. He won an award from the USA Leukaemia Society for this work."

Editor: "How did you hit upon the idea of disodium citrate solution?"

Prof: "We had tried a number of acidified citrate-glucose solutions, none of which had been entirely satisfactory in three respects: preventing caramelisation, preventing clot formation and restricting haemolysis on storage. Disodium citrate was one of the acidified citrate solutions which we had tested and we now found that in a slightly different concentration it was better than any of the mixtures we had tested previously."

Editor: "During the Blitz I imagine you were kept busy and that more than one hospital was hit."

Prof: "St Thomas's was very badly bombed and several patients, doctors and nurses were killed; but I don't remember any other hospitals in South London suffering in the same way, although there were large numbers of casualties throughout the region after most raids. Of course, research more or less came to a stop during the winter of 1940-1941, but after the bombing diminished we returned to work on red cell preservation."

Editor: "Who else did you meet while you were at Sutton?"

Prof: "As I mentioned we used differential agglutination to study red cell survival. In reading up the relevant literature I came across the work of Todd and White who had used an almost identical method (differential haemolysis) to study the survival of transfused red cells in cattle. They were working in the Hygienic Institute of the Public Health Department in Cairo before the First World War, many years before Ashby did her work at the Mayo Clinic. I mentioned this to an older friend who pointed out that both these men were living in retirement in Sutton. I went to have tea with them and was given reprints of their work."

"Although most of my studies of red cell survival were related to preservation, I also studied survival in a few patients with haemolytic anaemia. In one, with "acholuric jaundice" (hereditary spherocytosis) normal red cells survived normally. I collaborated with John Dacie, who was at that time a trainee pathologist at King's, in studying five further cases in which the findings were similar. Until the introduction of the Coombs Test, measurement of the survival of normal red cells was the only method of distinguishing between haemolytic anaemias due to intrinsic red cell defects and those due to extrinsic factors, e.g. Auto-Immune Haemolytic Anaemia".

Editor: "What about the work of the blood collection teams - for example, what checks were made on the health and selection of donors at that time?"

Prof: "Very little. I remember that, in the early years of the war, every now and then

somebody would notice that a sedimented bottle of blood in the cold room contained strikingly less than the normal amount of red cells and the Director would recall the donor for investigation. So far as I know, routine screening for anaemia - using the recently described copper sulphate method - came in only after the war. I've looked up the first edition of my book (1951) and the only two topics related to donation are fainting and iron requirements."

Editor: "What happened after your attachment to Sutton?"

Prof: "I served in the RAMC from 1943 - 1946, initially as a regimental medical officer and later as a medical specialist. After my discharge from the Army I took up an appointment with the Medical Research Council. Sir Alan Drury who was then chairman of the MRC's Blood Transfusion Research Committee persuaded the secretary of the MRC (Sir Edward Mellanby) to create a Unit for research in blood transfusion. The Professor of Obstetrics at the Post Graduate Medical School (Prof Young) generously found a room for me, and the MRC eventually had a building made for us in the grounds of Hammersmith Hospital. We had our lab on an Obstetric ward partly because of my interest in HDN."

"While still at Sutton I had had some experience of HDN. After reading Levine's classical paper I had taken blood from a woman whose infant was deeply icteric and found that the serum agglutinated 7 out of 10 samples of red cells. Anti-Rh sera which act as good saline agglutinins are, of course, uncommon; so it was lucky that the first one I tested was of this kind. Through the MRC we obtained a sample of guinea-pig anti-rhesus serum from the Rockefeller Institute but it was a very poor reagent, as Landsteiner and Wiener themselves emphasised. The ability to do Rh typing and to test for anti-Rh was a great help in investigating haemolytic transfusion reactions not due to ABO-incompatibility. It also made it possible to show that transfused Rh-positive cells, unlike Rh-negative cells, were rapidly destroyed in HDN."

"At the RPMS in 1947 I started doing exchange transfusions with Rh-negative blood, at first using the method described by Wiener. Infants were fully heparinised, bled from the radial artery and transfused into the saphenous vein. As soon as I heard that Diamond was using the umbilical vein I started to use his method." *(Diamond was a well-known American paediatric haematologist who earlier had been a joint author of a classical paper showing that hydrops fetalis, icterus gravis neonatorum and congenital anaemia of the new-born were all part of the same disease process - Ed.)*

"It was an enormous help when Diamond came to give a lecture in London in 1947 and, before he left, gave me his superior equipment: really well-fitting syringes, 3-way taps and better polythene tubing than any we could get. Over the next two years I gave very many exchange transfusions, not only at Hammersmith, since no one else was doing them initially."

Editor: "It's true, isn't it, that plastic tubing was not used in giving sets for many years after the War?"

Prof: "Yes indeed; the Ministry of Health was reluctant to give up rubber tubing which was cheap and reusable. The change to disposable PVC sets was bound to involve extra expense and was of no proven benefit. The MRC Blood Transfusion Research Committee *(of which Prof Mollison was now Chairman - Ed)* decided that the two kinds of tubing ought to be compared and set up a sub-committee to arrange the work. When the incidence of thrombophlebitis was found to be far higher with rubber, the Ministry agreed to change to plastic."

Editor: "How much was exchange transfusion accepted as a clinical procedure in those days?"

Prof: "There was no difficulty at Hammersmith or at some other hospitals, but at others eminent paediatricians declared that exchange transfusion was an experimental procedure which they would not countenance. The value of exchange transfusion was made less obvious by the fact that, due to technical difficulties, people often failed to exchange more than 200 ml or so. Dr Willie Walker (from Newcastle) and I, with many others, set up controlled trials of exchange transfusion versus simple transfusion, and of premature induction of labour versus spontaneous delivery at term. Although exchange transfusion in prematurely delivered infants was scarcely any better than simple transfusion in mature infants, exchange transfusion in mature infants gave by far the best results and became standard practice."

"We became very interested in assessment of the severity of individual cases of HDN. We obtained evidence that the cord blood Hb concentration is inversely related to the chance of survival. In 1951 Marie Cutbush and I also showed, for the first time I think, that there is a close relation between serum bilirubin concentration and the incidence of kernicterus".

Editor: "While you were at the RPMS at the Hammersmith, who else did you work with?"

Prof: "John Dacie was in charge of the Department of Haematology, which included the Blood Transfusion Laboratory. He generously allowed my Unit to act as consultants to that laboratory, which gave us many valuable opportunities."

"A person with whom we worked closely was Norman Veall, a physicist who had been involved with the atomic bomb project, and who was a member of the MRC Radiotherapeutic Research Unit at the Hammersmith. He had maintained his connections with Harwell. The radioactive chromium which was available in the early 1950s was of relatively low specific gravity; but Veall, using a new method and getting his material irradiated in the Harwell reactor, produced ^{51}Cr with a specific reactivity 100 times higher than that available to Sterling and Gray. It was now possible to label amounts of red cells as small as 1 ml and we proceeded to study the patterns of destruction produced by a wide range of blood group antibodies."

"An early opportunity arose when a certain Mr Duffy, who was already immunised to Rh (D), became jaundiced after being transfused with 3 units of Rh-negative blood. We found that he had developed a "new" antibody, later called anti-Fy^a. Using ^{51}Cr to label D-positive/Fy^a negative cells and ^{32}P to label D-negative/Fy^a positive cells, we found that anti-Fy^a produced destruction predominantly in the liver; whereas with anti-D, destruction was almost entirely splenic".

Editor: "When you moved to St. Mary's, what direction did your work take?"

Prof: "We became interested in Rh again in the 1960s after Cyril Clarke and colleagues at Liverpool had published evidence that Rh immunisation could be suppressed by passive antibody. Like the American workers (Pollack and colleagues) those at Liverpool had no satisfactory method of determining how much anti-D had to be given to suppress immunisation."

"Nevin Hughes-Jones had been working on estimating the number of sites of antigens - c, D etc. - on the red cell surface. He now devised a way of estimating the concentration of anti-D in µg/ml. This was of great value because it made it possible to

standardise the dose to give to mothers. Under the auspices of the MRC we carried out a controlled trial, in which many hospitals from many parts of the country participated, which indicated that 50, 100, or 200 µg, given immediately after delivery, produced similar results, reducing the risk of Rh immunisation by a factor of ten. We were also able to estimate the least amount of anti-D which would produce measurable destruction of D-positive red cells and found that when a very small dose of D-positive red cells was injected as little as l µg anti-D shortened survival."

Editor: "Was there not some difficulty about deciding whether 1gM anti-D was better, particularly for injecting during pregnancy?"

Prof: "Yes there was. The Liverpool people thought they would have to use IgM if the antibody was to be used during pregnancy, as IgG would cross the placenta and might cause foetal red cell destruction. They then appeared to find that IgM anti-D augmented immunisation although I think, with the benefit of hindsight, that they misinterpreted their data. Anyway, by this time evidence had been produced that transplacental haemorrhage occurred mainly at the time of delivery so, like the American Group, they decided to give anti-D after delivery."

"We thought we had shown that purified IgM anti-D can cause red cell destruction but now I think that this was due to small amounts of IgG anti-D which were present in the preparation."

Editor: "What about your other work with incompatible blood group antibodies?"

Prof: "The improved chromium labelling enabled us to pursue interests into, for example, cold agglutinins. We did experiments to discover whether cold alloagglutinins like anti-P_1 could cause red cell destruction and whether it made any difference whether the injected cells were at 0°C or 37°C. We also did quantitative experiments with anti-D and other warm antibodies to investigate the relation between the number of antibody molecules bound and the rate of destruction."

Editor: "So, apart from your book - which has been an immense influence in the development of Transfusion Medicine - what do you think has been your most rewarding experience professionally?"

Prof: "It's hard to pick on just one thing but if I must I suppose it was being able to make accurate measurements of the survival of very small amounts of incompatible red cells and draw conclusions from the patterns of destruction observed. It was immensely stimulating to work with people such as John Loutit, John Dacie and Nevin Hughes-Jones; and I was particularly lucky to have the support of one or two influential people, particularly Sir Alan Drury but also Professor Albert Neuberger".

Editor: "Thank you Professor Mollison, it has been a real privilege talking to you and I am sure that our readers will be fascinated by this insight into the period of transfusion medicine during the war and up to the period of anti-D prophylaxis. Once again many thanks".

ADDENDUM

A letter in the New England Journal of Medicine of 4th June 1998 (p1699), by Dr Barbara Ulm and colleagues from Vienna, gives added weight to findings first published by Dr Walker and Professor Mollison in the Lancet in 1957. Walker and Mollison had shown

that the neonatal death rate from kernicterus was twice as high in boys as it was in girls. Ulm et al. found that umbilical cord haematocrits before intra-uterine transfusion (corrected for gestational age), were significantly lower in boy foetuses. In their series, 16 out of 17 foetuses with hydrops were male (95% confidence interval 2.2 to 115.4); and that 21% of boys died in comparison with 7% girls (95% CI 0.87 to 10.3). The explanation in not clear, but Ulm speculates that male foetuses are more susceptible to immunologically related “rejection”. This would be in line with other findings such as the greater acceptability of grafted female tissues to male animals than the converse; the presence of “minor histocompatibility antigens” (‘HY’) from the Y-chromosome, and the triggering of strong immune responses to male foetal cells in the maternal circulation of mice.