

Historical Review

HAEMATOLOGY AT THE HAMMERSMITH HOSPITAL AND ROYAL POSTGRADUATE MEDICAL SCHOOL 1934–1994

Begun in 1934, the Department of Haematology at Hammersmith Hospital and the Royal Postgraduate Medical School rapidly became the leading clinical and research centre for haematology in Britain and the British Commonwealth. Initially led by Janet Vaughan, it was directed by John Dacie from 1946 to 1977, who stimulated clinical and laboratory research of the highest quality. The department became a model for the training of haematologists internationally, combining laboratory and clinical aspects of the discipline and establishing specialized sections within the field. The Medical Research Council Leukaemia Unit was founded in the department in 1970 under the Directorship of David Galton. In 1981 following Dacie's retirement Lucio Luzzatto became Director of the Department, taking research into the molecular era by introducing the new techniques and science of molecular biology. Many leading haematologists working in Britain, the British Commonwealth and other countries trained in the department and have subsequently established their own Academic Departments along Hammersmith lines. The department has made substantial contributions to the understanding of the biochemical, immunological and molecular basis of many different types of anaemia (e.g. haemolytic, megaloblastic, aplastic, dyserythropoietic). It has also pioneered the characterization of the leukaemias by morphological, immunological, cytogenetic and molecular tests and piloted many new therapies in their management.

IN THE BEGINNING

In 1907 the Local Government Board held an inquiry into the effective bankruptcy of the Hammersmith Board of Guardians caused by the construction of their new Workhouse and Infirmary [now Hammersmith Hospital (HH)] (Fig 1) (Connelly, 1979). The completed building had been formally opened on 5 December 1905 by Her Royal Highness Princess Henry of Battenberg, the youngest of Queen Victoria's children. The institution, which the Guardians had built after Hammersmith separated from Fulham for poor law purposes in 1899, was described as 'baronial', 'a structure which in many of its details was equal if not superior to any nobleman's mansion in the land'. The newspapers called HH the 'Pauper's Elysium' or

the 'Pauper's Paradise'. This view of HH may surprise many who worked at HH during the six decades of this review and found it dingy, cramped and unhygienic, bearing some comparison with the neighbouring Wormwood Scrubs prison, certainly in lack of accommodation and shortage of car parking space.

In 1933 Neville Chamberlain, Chancellor of the Exchequer, laid the foundation stone and The British Postgraduate Medical School on the HH site was formally opened by King George V on June 13, 1935 (Fig 2). It was funded jointly by London County Council, the University of London and the Government. Sir Austen Chamberlain, half-brother of Neville Chamberlain and Chairman of the Governing Body, told the King that the school was to have three main goals: (i) the continuing education of general practitioners; (ii) the training of specialists; and (iii) the pursuit of research and advance of medical knowledge. The King expressed the earnest hope 'that the School, with its happy union of ward and laboratory, University and Local Authority, drawing students and teachers alike from all parts of our Empire – and I trust from regions even more widely spread – may prosper under God's blessing. May it play an imperial role in the relief of suffering among my people in this country and overseas and in enabling the doctors of all lands to come together in a task where all must be allies and helpers' (British Postgraduate Medical School, 1935). An excellent monograph has been published (Calnan, 1985) detailing the history of HH and the first 50 years (1935–1985) of the Royal Postgraduate Medical School (RPMS) (since 1967). A brief history of the Postgraduate Medical School before it obtained its Royal Charter (Newman, 1966) and a major review of medical science at the RPMS over its first 50 years (Booth, 1985) have also been published.

Laboratories dedicated to diagnosis and research in blood diseases have been in existence at HH since 1934 when Janet Vaughan was appointed as Assistant in Clinical Pathology to E. H. Kettle, Head of Pathology. Janet Vaughan had already pursued an interest in haematology at University College Hospital with Cecil Price-Jones and had visited Minot's department at the Thorndike Laboratories in Boston to learn about the treatment of pernicious anaemia with liver. Before joining HH she had continued her haematological researches at the London Hospital with Hubert Turnbull and Donald Hunter, and from these published the first monograph in English on *The Anaemias* (Vaughan, 1934), which attracted both John Dacie and Gwyn Macfarlane into the specialty of haematology. Janet Vaughan's career has been the subject of a previous historical review in this series (Firkin, 2000).

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Fig 1. The Hammersmith Hospital. From a postcard sold in aid of the friends of Hammersmith Hospital (used with permission of the Friends of Hammersmith Hospital).



Fig 2. His Majesty King George V accompanied by the Queen being greeted by Professor Louis Filon, Vice Chancellor of the London University (robed) with Sir Austen Chamberlain. From the *Evening News*, 13 May 1935. Copyright Associated Newspapers Limited, London (used with permission).

R.G. (Gwyn) Macfarlane joined the British Postgraduate Medical School in 1936 as assistant to Janet Vaughan. His interest in haematology arose in 1930, when he was looking after a patient with haemophilia at St Bartholomew's Hospital whose bleeding stopped only after a blood transfusion was given. He spent 3 years learning about haematology, planning and carrying out laboratory research and the standardization of methods. He left in 1939 to join Burroughs Wellcome as Assistant Bacteriologist. His subsequent career at Oxford and his outstanding contributions to the understanding of normal haemostasis, haemophilia and other coagulation disorders has also been reviewed in this historical series (Douglas, 1999).

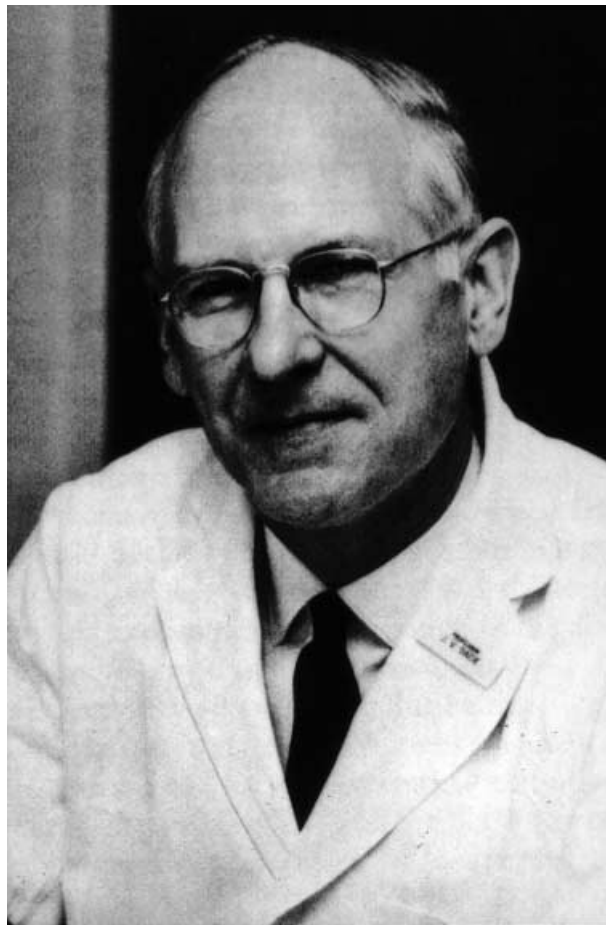


Fig 3. John Dacie. From Vaughan J. (1972) John Dacie. *British Journal of Haematology* 23(Suppl.), 7–15. Copyright Blackwell Publishing (used with permission).

John Dacie (Fig 3) qualified in medicine in 1935 at Kings College Hospital, and gained his Membership of the Royal College of Physicians (MRCP) in 1936. He then began to collect blood films that he stained himself and examined with his own microscope. His first laboratory research at Kings was with R. A. McCance into the effect on iron metabolism of phenylhydrazine-induced haemolysis as treatment for polycythaemia vera. His interest in haematology was further stimulated by reading Janet Vaughan's book. When, in 1937, he received a Medical Research Council (MRC) Studentship, he chose to spend 6 months with her at HH and 6 months in Manchester working with John Wilkinson and Martin Israëls. At HH he learned to perform bone marrow puncture tests and the techniques of diagnostic haematology and undertook research into 'acholuric jaundice'. In Manchester, he encountered a patient with paroxysmal nocturnal haemoglobinuria (PNH) and his interest in haemolytic anaemias was firmly launched (Dacie *et al*, 1938).

He returned to Kings in 1938 and, apart from 3 years spent in the Royal Army Medical Corps (1943–1946),

remained there until, after reading an advertisement in *The Lancet* while in Italy, he applied for and was appointed senior lecturer in clinical pathology in 1946 at the British Postgraduate Medical School. He replaced Janet Vaughan who had left to become Principal of Somerville College, Oxford.

THE DACIE ERA (1946–1977)

Dacie, initially a lecturer in the Division of Pathology, established the first autonomous Department of Haematology in Britain in 1950 when J. H. Dible (who had replaced Kettle in 1936 as Head of Pathology) retired. In 1957, he became the first Professor of Haematology in Britain. His expertise in performing laboratory techniques, emphasis on accurate measurement (acquired partly from Price-Jones via Janet Vaughan) and his outstanding abilities as an observer of morphological abnormalities in blood and bone marrow films (e.g. Dacie & White, 1949) combined in establishing the department as the leading haematology centre in Britain and the Commonwealth. The book 'Practical Haematology' by Dacie was first published in 1950, and from the third edition (now up to nine) with Mitchell Lewis, rapidly became and remains the standard bench book in haematology laboratories worldwide.

Dacie's rigorous scientific approach, whether dealing with a single case or a broad topic, resulted in research of the highest quality being carried out in all major areas of the subject. His growing reputation rapidly attracted postgraduate students mainly from Britain, the Commonwealth and the USA to his department, where they could train in the discipline of haematology and join in or initiate research projects, many stimulated by Dacie and often using relatively simple laboratory techniques to make important advances in knowledge. Firm lifelong friendships were established between workers from different countries and continents. These talented visitors contributed to the department's scientific output and importance and, to what internationally was termed by Wintrobe (1985), the Blossoming Science of Haematology.

Structure of the department

Before dealing with the various strands of research of the department and highlighting individual staff members and research fellows, many of whom subsequently set up their own Academic Departments in Britain and abroad along Hammersmith lines, it is important to record how the department established a structure for clinical and laboratory work, training and research, subsequently widely copied throughout the world.

In response to growing knowledge within the field and the increasing range and complexity of laboratory tests, the department was gradually divided into sections, each with its own clinical and laboratory service and research commitments and led by a senior lecturer/consultant who was responsible not only for the specialized laboratory service but also for dealing with patients and for initiating research activity within that field. The specialized areas included haemolytic anaemias, nutritional anaemias, iso-

topes, blood transfusion, malignant blood diseases and haemostasis. The registrars rotated between these various sections as part of their training, also spending several months in the 'routine' diagnostic section. They were also responsible for providing a night-time and weekend technical service in haematology, cross-matching blood and carrying out simple diagnostic tests including blood counts and coagulation studies. The department established the principle that two junior staff were better employed with one in a full-time service role and the other in full-time research, rather than both trying to combine routine service work with research, a system which had often led to neither function being carried out satisfactorily in other departments.

Technical staff were, from the 1930s to 1950s, led by Leslie H. (Jim) Turnbull. Leon Wallett, appointed junior technician by Janet Vaughan in 1936, worked with Macfarlane and Dacie and became Chief Medical Laboratory Scientific Officer (MLSO) in 1955, a post he held with distinction until retiring in 1980. The difficulties recruiting technical staff for the routine service, particularly blood transfusion, together with lack of space were two major problems the department faced throughout the Dacie era, which he fought successfully to improve.

Malignant blood diseases initially were a small component of the department's work. In the mid-1960s the median survival time for patients with, for example, acute myeloid leukaemia was only 8 weeks and the range of treatments available for patients with primary diseases of the bone marrow was limited. Therefore, the need for long periods of in-patient care was much less than in subsequent decades. When, in 1970, the MRC Leukaemia Unit headed by David Galton was established, it soon became a major section of the department.

Blood films were made on all patients, mounted with a cover slip and stored for 5–10 years. The registrar in the diagnostic section was expected to examine all the new blood and bone marrow films, thus gaining knowledge of the variation in normal appearances; this discipline developed the ability to recognize and characterize abnormalities. Interesting cases were presented by this registrar at 5.00 pm, three times a week. This meeting, attended by all staff and research fellows, as well as by clinicians throughout the hospital who cared for patients with difficult haematological problems, was chaired by Dacie. It was his ability to extract the maximum information from the clinical history, the blood count and morphology, to simplify a problem to its core, to suggest where further tests were necessary to arrive at a correct diagnosis and then ask questions focused on areas where new knowledge was needed, that set national and international standards for diagnostic haematology. Previously unrecognized or poorly described diseases (e.g. sideroblastic anaemia, microangiopathic haemolytic anaemia and drug-induced autoimmune haemolytic anaemia) were characterized as a result of careful analysis of all relevant clinical and laboratory findings.

Mitchell Lewis was responsible for the accuracy of the results and increasing automation over many years.



Fig 4. David Galton (courtesy: Professor David Galton).

subsequently transferring this expertise to national and international levels. He established the National External Quality Assessment Scheme and directed it from HH for many years. He was also a founding member and major force in the International Committee for Standardization in Haematology and in the World Health Organization (WHO) work aimed at improving haematology laboratories in developing countries.

One pioneering aspect of the department was the weekly slide session that used a six-headed microscope, attended by registrars and research fellows and conducted by David Galton (Fig 4) in conjunction with one dedicated member of the Department of Histopathology. The blood, bone marrow films and trephine biopsies using the newly introduced plastic (methylacrylate) embedded 2 μ m sections perfected by Anwar Islam were reviewed both for diagnosis and teaching (Islam *et al.*, 1979).

Clinical and laboratory haematology

Unlike many haematology departments in the USA, Scotland and Europe, the department was initially not clinically based, in that staff were not directly responsible for the care of patients with blood diseases admitted to the hospital, although patients were examined in clinics and advice was given on investigations and management to the doctors looking after such patients in the wards.

Christopher Booth worked closely with David Mollin in the care of patients with nutritional anaemias and generously allowed some of his allocated beds to be

occupied by patients with other blood diseases, but left decisions of their investigation and management largely to the haematologists. However, Dacie recognized from the beginning the need for specialized clinical haematologists rather than general physicians to manage patients with blood diseases. Michael Brain was appointed in 1960 jointly as lecturer in medicine and haematology and became the first clinician of the department directly responsible for its in-patients, thus unifying the care of patients with all kinds of blood disease under one haematology department.

Dacie was heavily involved in the training and role of haematologists. His own early acquisition of the MRCP underlay his belief that haematologists should be well trained in general medicine. The question arose whether haematologists could excel both in laboratory and clinical medicine (Dacie, 1960, 1962). Dacie had already discussed this with the distinguished laboratory-based haematologist, Professor Monty Maizels of University College Hospital (UCH) who had been a teacher of Janet Vaughan. Professor Tom Pranker, a 'physician haematologist', was also at UCH and thus the question of haematologists as pathologists or doctors was particularly relevant at UCH (Pranker, 1969). Dacie considered that there could be a laboratory-orientated haematologist and clinically orientated haematologist, but both should work in harmony in the Department of Haematology and not one in Pathology, the other in medicine. Subsequently, as he forecasted, laboratories have become more automated while the clinical work of the haematologist has increased in complexity and volume (Dacie, 1978). Therefore, clinical demands have come to dominate the haematologist's workload. When the Royal College of Pathologists was founded in 1962, haematologists found themselves in one of the main sections. Dacie himself was not involved in the founding of the college or haematologists being included in it. Nevertheless, already a Fellow of the Royal Society since 1967, he became President of the Royal College of Pathologists in 1972.

In Britain, haematologists are now represented by a joint committee of the Royal College of Physicians and Pathologists, initially chaired by the Hammersmith-trained haematologists D. Hoffbrand and then Gordon-Smith. Haematologists are required to pass membership examinations of both these Royal Colleges.

The department took an active role in training post-graduates, drawn mainly from the Commonwealth countries, for 6 weeks in the year-long Diploma of Clinical Pathology (DCP) laboratory-based course, established in 1947. In 1969, a 1-week (June) annual 'Advances in Haematology' course was established, mainly taught by members of the department, attracting large numbers of haematologists from Britain and abroad. The 35th course in uninterrupted sequence will be given in 2003. The only current British large textbook of haematology (Postgraduate Haematology) based on the DCP course teaching, began its life in 1972 as 'Tutorials in Postgraduate Medicine: Haematology' edited and written entirely by members of the department.

British Journal of Haematology

The British Journal of Haematology was founded in 1955. It was the brainchild of Per Saugman, Chairman of Blackwell Scientific and the publisher's first scientific journal. Saugman put the idea to Gwyn Macfarlane, who was captivated and insisted that John Dacie was the only possible editor. Macfarlane later referred to this as his greatest contribution to haematology. Saugman remained indebted to Dacie for establishing the rigorous attention to accuracy, clear layout and detail which provided a template for Blackwell's subsequent other successful scientific journals (Saugman, 1989). Dacie rewrote or edited each article himself for the first 17 numbers (a total of 170 papers). He then served as Chairman of the Editorial Board for a further 10 years. From HH, Lewis, Galton and Gordon-Smith have been subsequent editors and Hoffbrand has served as Chairman of the Editorial Board.

Haemolytic anaemias

Dacie's own research was primarily into the haemolytic anaemias. P. L. (Pat) Mollison had been appointed during the war to work with the Department of Obstetrics and Gynaecology on Rh immunization. He had been promoted in 1946 to be Director of the MRC Blood Transfusion Research Unit, with an honorary appointment in the Department of Medicine. Dacie, with Mollison and John Loutit, showed how haemolytic anaemias could be divided into those due to an intrinsic red cell defect that were usually inherited and those due to a change in the red cell environment (extrinsic defect), usually acquired (Dacie & Mollison, 1943). Dacie extended his interest into all types of haemolytic anaemia, identifying previously unrecognized syndromes and publishing the definitive textbook on the haemolytic anaemias in 1954, which (by its third edition) had expanded into five books. Particular patients (many of whom he could identify from their blood films) were important landmarks in his contribution to knowledge in the haemolytic anaemias.

Dacie used the recently described acid serum lysis (Ham) test to demonstrate that PNH cells were sensitive to a lysis in normal serum, subsequently shown to be complement. Wendell Rosse (USA) subsequently worked on the details of complement sensitivity among different populations of red cells circulating in patients with PNH (Rosse & Dacie, 1966).

With co-worker John Selwyn, Dacie pioneered the classification of hereditary haemolytic anaemias, using the autohaemolysis test, into those in which the test was corrected by glucose (e.g. hereditary spherocytosis) and those in which it was not corrected (subsequently found to be e.g. pyruvate kinase deficiency) (Selwyn & Dacie, 1954). Although he was keen to discard this test, it helped to focus on a group of haemolytic anaemias with an enzyme deficiency in either the Embden-Meyerhof or hexose-monophosphate pathway, later individually characterized by biochemical and DNA studies (de Gruchy & Grimes, 1972).

The observation of deeply stained red cell fragments in the blood films of patients with such varying syndromes as malignant hypertension, thrombotic thrombocytopenic

purpura and disseminated carcinoma led to the description, with Michael Brain and Dermot Hourihane, of microangiopathic haemolytic anaemia, in which red cells are damaged when circulating through fibrin strands in small blood vessels (Brain *et al.*, 1962). A similar haemolytic anaemia was described in patients with mechanical heart valves and artificial aortic grafts with failure of endothelialization (Sayed *et al.*, 1961).

Although the department in those days did relatively little research into thalassaemia or sickle cell anaemia, as only a few patients with these diseases were then attending, J. C. (John) White, Consultant Haematologist to HH appointed during the Second World War, worked on haemoglobin disorders, particularly the nature of Heinz bodies. An unstable haemoglobin, designated as Haemoglobin Hammersmith was identified from studies of Heinz body haemolytic anaemias. It was subsequently shown to be due to a mutation (Phe → Ser) at position 42 in the β -globin chain (Dacie *et al.*, 1967). J. M. (Joe) White subsequently worked on globin synthesis in haemoglobin disorders, showing a haem defect in sideroblastic anaemia and that haem or its precursors could correct a secondary defect in globin synthesis (White *et al.*, 1971).

Research work into the nature of the cold- and warm-type autoantibodies in the autoimmune haemolytic anaemias was begun in the late 1940s. Carl de Gruchy from Australia was one of the first research fellows in this field and then Marie Cutbush, also from Australia and John Crookston from Canada, who married while in London. Don Tills and Sheila Worledge continued this work. Pat Mollison left the RPMS to become Professor of Haematology at St Mary's Hospital and a few years later, Sheila Worledge became senior lecturer in charge of blood transfusion.

Sheila Worledge was a wonderful teacher, giving the best possible postgraduate training in blood transfusion serology to registrars and other students, working through the blood groups one by one starting with Group A. She analysed in detail the antibodies produced in each type of autoimmune haemolytic anaemia leading to their serological classification as well as to the discovery of autoimmune haemolytic anaemia associated with α -methyl dopa (Aldomet) (Worledge *et al.*, 1966). Morris Blajchman (Canada), Elisabeth Letsky (London), Amiel Cooper (USA) and David L. Brown (Cambridge) were research fellows with her (e.g. Blajchman *et al.*, 1969). Elisabeth Letzky became Consultant at the neighbouring Queen Charlotte's Hospital and continued to provide expertise in obstetrical and neonatal haematology. Like Leon Szur, the Consultant Radiotherapist who worked closely with members of the department, especially Mitchell Lewis and David Galton, Sheila Worledge was a heavy smoker and like Leon, Sheila tragically died prematurely. George Garratty was a lively, innovative, Chief MLSO in Blood Transfusion before joining Lawrence Petz in California to form a major Transfusion Research Centre there.

Nutritional anaemias

David Mollin joined John McMichael in the Department of Medicine in 1947, but his meeting with Dacie, when he wished to perform laboratory research, led to a career in

haematology at HH until he was appointed to the Chair at St Bartholomew's Hospital in 1966. With G. I. M. (Innes) Ross from the Department of Microbiology, he showed that, using *Euglena gracilis*, the concentration of vitamin B₁₂ could be measured in serum and that this was an accurate guide to the vitamin B₁₂ stores of patients (Mollin & Ross, 1952). Barbara Anderson subsequently perfected this assay. Israel Chanarin (Chan), joined Mollin in 1955 and worked on vitamin B₁₂ and folate metabolism (e.g. in pregnancy) until 1960. He subsequently set up his own major units at St Mary's and Northwick Park Hospitals and wrote the definitive textbook on the Megaloblastic Anaemias. With Alan Waters, visiting from Australia, Mollin established the first serum folate assay (simultaneously with that of Victor Herbert in Boston, MA, USA) in 1961 using *Lactobacillus casei* as the test organism (Waters & Mollin, 1961). The first reliable red cell folate assay was developed in Mollin's laboratory in 1966 (Hoffbrand *et al.*, 1966). With J. E. (Jim) Kohn, a convenient thin layer chromatography assay of formiminoglutamic acid, then used as a test for folate deficiency, was established.

Mollin, with Christopher Booth, also used radioactive B₁₂ to study vitamin B₁₂ absorption. They demonstrated for the first time that B₁₂ was absorbed in humans through the terminal ileum (Booth & Mollin, 1959). Using a combination of all these tests the megaloblastic anaemias could now be confidently divided into those caused by vitamin B₁₂ deficiency and those caused by folate deficiency. The incidence of these deficiencies in various gastrointestinal and other diseases was established. Mollin and Booth joined with Norman England in Malaya, Selwyn Baker in Vellore, Henry Foy in East Africa and Fred Klipstein in Haiti in studying tropical sprue, showing folate deficiency in the acute phase, vitamin B₁₂ deficiency in chronic tropical sprue.

Stuart Douglas and Dacie had earlier described the distribution of iron granules in normal red cells pre- and post-splenectomy and in erythroblasts (Douglas & Dacie, 1953). Mollin and Dacie showed that 'sideroblastic anaemia' was characterized by the presence of ring sideroblasts in the bone marrow (Dacie *et al.*, 1959). Barbara MacGibbon then showed that these anaemias could be divided into inherited and acquired types and that the acquired cases could be further subdivided into primary (now recognized as a subtype of myelodysplasia) and secondary when another bone marrow or extramedullary disease was present (MacGibbon & Mollin, 1965).

Mollin's section, funded from 1963 for 5 years as an MRC Group, existed in a converted Nissen hut that had previously been occupied by Mollison's MRC Blood Transfusion Unit, and was situated between one of the surgical blocks and one of the obstetrical blocks at the front of the hospital. Space was extremely limited and the atmosphere was charged with Mollin's enthusiasm, scientific originality, sense of humour and irascibility. The laboratory was supervised with extreme efficiency and dedication by Barbara Anderson. Her attention to detail was illustrated when she gave all the test tubes for the *Euglena* assay purple, rather than the usual white cotton wool, plugs on the day in 1966 when the Queen was to visit.

In 1968, I became responsible for the work of this group, moved since 1966 with the rest of the department to splendid new quarters on the fourth floor of the Commonwealth Building. Here we worked on vitamin B₁₂ and folate inter-relations (Lavoie *et al.*, 1974), the DNA defect in megaloblastic anaemia (Hoffbrand & Pegg, 1972; Hoffbrand *et al.*, 1974) setting up the first assay of the immediate DNA precursors, the deoxynucleoside triphosphates, in human cells. Tim Peters from the Department of Medicine collaborated closely in studies of vitamin B₁₂ and folate absorption. Kshitish Das joined from the Postgraduate Medical School in Chandigarh (India), where I was seconded to help establish an autonomous Department of Haematology (on Hammer-smith lines).

Isotope studies and aplastic anaemia

Mitchell Lewis joined the department as a registrar in 1953, having previously worked in the South African Institute for Medical Research. He remained in the department until his retirement in 1989 and, through his work as Consultant in Laboratory Medicine to the WHO and as Director of the WHO Collaborating Centre for Haematological Technology, has continued to maintain an office in it. His early work concerned the use of isotopes in measuring erythropoiesis and tracking sites of red cell destruction in haemolytic anaemias. Closely associated with Leon Szur in this work, he also worked with Szur on polycythaemia and myelofibrosis, including the use of isotopes in blood volume studies and the management of these patients by venesection, busulphan or radioactive phosphorus. John Pettit (New Zealand) performed research studies both with Lewis and with the Leukaemia Unit.

Lewis's laboratory work in isotopes, haemolytic and other anaemias led to an interest in aplastic anaemia (Lewis, 1965). This was subsequently to become a major interest of E. C. (Ted) Gordon-Smith in the department. Lewis's interest in erythropoiesis also led to studies of congenital dyserythropoietic anaemias. The department described the first recognized cases of hereditary erythroid multinuclearity with a positive acidified serum (Crookston *et al.*, 1969).

Gordon-Smith succeeded Michael Brain (who had left to join McMaster University in Hamilton, Canada) as clinician in the department. However, with the creation of the MRC Leukaemia Unit in 1970, patients with malignant haematological disorders were now cared for by the 'white cell' team. Gordon-Smith focused his clinical effort and research on aplastic anaemia (Gordon-Smith *et al.*, 1971, 1982) as well as continuing research in haemolytic anaemias. He acquired the techniques of bone marrow transplantation from visiting Seattle and introduced this to HH, specializing initially in aplastic anaemia. J. M. (Jill) Hows became a mainstay of the programme (Hows *et al.*, 1981; Yin *et al.*, 1984). Judith Marsh was one of the pioneers of treatment of aplastic anaemia with antilymphocyte globulin (Marsh *et al.*, 1987). Gordon-Smith's transplant programme also became linked closely to that led by John Goldman of the Leukaemia Unit. His laboratory studies into the nature of the marrow defect in aplastic anaemia were carried out with Myrtle

Gordon, now professor in the department (Gordon & Gordon-Smith, 1981; Gordon *et al.*, 1983).

Haemostasis

Following the departure of Gwyn Macfarlane, haemostasis remained a minor section of the department, although Dacie (with his Oxford colleagues) published the first report of Christmas disease (Biggs *et al.*, 1952). W. R. (Bob) Pitney was a Research Fellow in the department when Christmas disease was described and subsequently joined the department in 1966 to head the Haemostasis Section until 1970, when he returned to Australia. Studies were carried out into thrombotic and haemorrhagic diseases, the department becoming recognized as a Haemophilia Centre. Jack Hirsh from Australia was a distinguished Research Fellow in 1963, working on platelet age and the influence of splenectomy on the platelet count in haemolytic anaemias (Hirsch & Dacie, 1966). He then settled at MacMaster University, heading the major haemostasis research group there. Subsequent consultants in charge of this section included Jack McBride and then Reuben Mibashan, an outstanding graduate of Witwaterstrand University of South Africa, who ran the section from 1971 until 1976. Mike Laffan was appointed in 1992 and linked with Ted Tuddenham when Tuddenham's MRC Group moved from Northwick Park to HH. Tuddenham's work on the structure and function of proteins involved in haemostasis, beginning at the Royal Free Hospital in 1974 with the cloning of the Factor VIII gene, has been of major importance in elucidating at a molecular level the normal mechanisms of blood coagulation and how these are altered in disease.

MRC Leukaemia Unit

Following discussions between Dacie and Galton on the one hand, and the MRC and Department of Health and Social Security (then the Ministry of Health) on the other, begun in 1966, the MRC Leukaemia Unit was established in 1970 primarily to investigate and treat acute leukaemia in adults. Clinical facilities for out-patients and in-patients (later called the Dacie Ward) were built at HH, and laboratory and office space was provided on the fourth floor of the Commonwealth Building. A special feature was the provision of a four-bedded day ward for the administration of blood products or drugs.

David Galton had joined the Chester Beatty Unit and the Royal Marsden Hospital in 1947 to begin studies of drugs developed by Alexander Haddow's group. He had, for 15 years, attended HH for two sessions each week to perform out-patient clinics and supervise the in-patient care of patients with leukaemia, lymphoma and myeloma. David Galton's teaching of postgraduates on this material was memorable for the detailed accurate record keeping, including haematological charts, sometimes stretching across the room, recording the blood counts, lymph node, spleen and liver size, and treatment of each patient. Galton, like Dacie, was an expert in morphology and shared his open minded and inquisitive approach to areas where research was needed to elucidate the pathogenesis of disease and new therapeutic possibilities. He was

appointed the first Director of the Leukaemia Unit in 1970 and moved full time to the HH, becoming University Professor in Haematological Oncology in 1976. The first MRC-appointed staff included John Goldman, Daniel Catovsky and Alexander Spiers.

Galton's careful scientific approach led, with his talented assistants, to the development of the unit into one of the most important centres for leukaemia research and treatment worldwide. Their research in the unit led to the proper characterization, using newly developed immunological, cytochemical and cytogenetic markers, of different leukaemia subtypes. Diseases defined and characterized included B- and T-cell prolymphocytic leukaemia (Catovsky *et al.*, 1973; Galton *et al.*, 1974), splenic lymphoma with villous lymphocytes (Melo *et al.*, 1987), adult T-cell leukaemia/lymphoma (T-ALL) (Catovsky *et al.*, 1982), hairy cell leukaemia variant (Catovsky *et al.*, 1984) and Philadelphia negative chronic myeloid leukaemia (CML). Participation in the MRC Adult Leukaemia Trials, chaired by David Galton, led to the department piloting new therapeutic protocols prior to their incorporation into the national randomized trials.

Alexander (Sandy) Spiers aimed at improving chemotherapy for patients with acute and chronic leukaemias. A military man by inclination, he produced 'heavy artillery' regimens, aiming to gain efficacy without increasing toxicity by combining drugs with different modes of action and toxicities (e.g. Spiers *et al.*, 1974, 1977). He was also, with John Goldman, one of the first at HH to perform research on CML (Spiers *et al.*, 1975).

Daniel Catovsky came to specialize in the lymphoid leukaemias, making major contributions to the knowledge of diagnostic and prognostic features and management of diseases such as chronic lymphocytic leukaemia, hairy cell leukaemia and its variant, adult T-cell leukaemia/lymphoma, prolymphocytic leukaemia as well as of the acute leukaemias and myelodysplasia. He was one of the first to characterize hairy cell leukaemia as a clonal B-cell disease and to explore the relation of the human T-cell lymphotropic virus type 1 to T-cell diseases (Catovsky *et al.*, 1982). He was a pioneer in the uses of cytochemical, immunological, electron-microscopic and biochemical markers to correctly classify acute and chronic leukaemias. He worked closely, where necessary, with research workers in other institutions, with expertise in the relevant techniques (e.g. Greaves *et al.*, 1977; Hoffbrand *et al.*, 1977; Catovsky *et al.*, 1979; Binet *et al.*, 1981). In 1974, Galton and Catovsky became the two British founding members of the French, American and British Group, which standardized diagnostic criteria for the various types of leukaemia and myelodysplasia so that haematologists generally would use the same criteria based on relatively simple morphological and other laboratory findings (Bennett *et al.*, 1976). Estella Matutes, who moved with Catovsky to the Royal Marsden in 1988, first joined him at HH and Robin Foa (Rome) was another of his outstanding research fellows.

John Goldman focused his clinical work and research on CML. He showed that stem cells with marrow repopulating capacity were present in the peripheral blood of patients

with CML (Goldman *et al.* 1977). He developed one of the first major marrow transplant programmes for this disease (Goldman *et al.* 1982, 1986) and pioneered treatment with autologous transplantation (Goldman *et al.* 1981), interferon and, more recently the ABL-specific signal transduction inhibitor, Imatinib. John (A. J.) Barrett, already a Professor of Haematology at Charing Cross Hospital, joined the unit in 1988, playing a major role in its transplant programme until he joined the National Institutes of Health in the USA in 1993. Goldman's laboratory, subsequently run by Nick Cross and Junia Melo, has made substantial contributions to the understanding of molecular aspects of this disease and to the use of molecular techniques for monitoring its response to therapy. The Leukaemia Unit was renamed the Centre for Adult Leukaemia in 1992 in recognition of the major expertise in the biology and treatment of CML. Goldman became Professor of Leukaemia Biology in 1987 and Director of the Leukaemia Research Fund Centre for Adult Leukaemia Unit from 1988. In 1987, he became Medical Director of the Anthony Nolan Bone Marrow Trust and succeeded Lucio Luzzatto as head of the Department of Haematology in 1994.

JOHN HUMPHREY (1977–1981)

After Dacie's retirement in 1977, the chair was advertised but none of the applicants was appointed. John Humphrey (FRS, Head of Immunology) was asked to be the Acting Head of Haematology. He was a distinguished scientist and a father figure in Immunology. Recognizing the need for the department to be headed by an outstanding clinical scientist with knowledge and skills in molecular biology, he recruited Lucio Luzzatto. Negotiations began in 1979, but the appointment only took effect from September 1981. Sheila Worlledge, a previous co-worker of Luzzatto in Africa (Worlledge *et al.* 1968, 1974) was one of the moving figures in inviting him to the chair. Unfortunately she died before Luzzatto arrived.

THE LUZZATTO ERA (1981–1994)

Lucio Luzzatto (Fig 5) had qualified in 1959 at the University of Genova Medical School. He trained in haematology and soon developed an interest in G6PD and learned early molecular techniques with Paul Marks in New York (Luzzatto *et al.* 1964). He worked in Ibadan from 1964 to 1974, producing research of the highest scientific quality in difficult technical conditions, particularly on G6PD and sickle cell disease. He first published studies on PNH in 1970, showing this to be a clonal disease (Oni *et al.* 1970). During a 7-year period as Director of the International Institute of Genetics in Naples, he continued to work in Ibadan on the relationships between variants of G6PD deficiency, sickle cell anaemia, other haemoglobin disorders and malaria in the African population, until his appointment in 1981 at HH. By then, the MRC Leukaemia Unit was flourishing, but the rest of the department, suffering from the retirement of Dacie, the departure of Joe White as Professor of Haematology at Kings College Hospital, the



Fig 5. Lucio Luzzatto (courtesy: Professor Lucio Luzzatto).

death of Sheila Worlledge and financial stringencies had, to some extent, stagnated.

The arrival of Luzzatto began the regeneration of the department, especially the 'Red Cell Team' and began its application of the new recombinant DNA techniques to clinical problems. Luzzatto brought with him a considerable intellectual approach, talent for selecting major, achievable research goals and practical as well as theoretical abilities in research. His warm personality and support of the less gifted and privileged also helped to inspire those around him and gave them a sense of their own worth and purpose.

His laboratory was refurbished adjacent to his office, a pattern that was to become common in clinical academic departments engaged in molecular research. He performed the first Southern blots, not only in the department, but probably in the whole of the RPMS. He held weekly informal evening sessions for Senior House Officers/Registrars/Research Fellows. These covered different aspects of molecular biology, including features of the genetic code, regulation of gene expression, clonal origin of the leukaemias, gene rearrangements in lymphoid cells and other new developments as they appeared in the journals. By 1982, he had obtained an MRC 5-year Programme Grant for research into the molecular genetics of G6PD and the laboratory

began to be populated with students and postdoctoral scientists from the UK, Italy, Nigeria and elsewhere.

Major research arising from Luzzatto's laboratory included the cloning of the human *G6PD* gene, the first human enzyme to be cloned (Persico *et al.*, 1986). Human red cell G6PD was shown to be encoded only on the X-chromosome (Mason *et al.*, 1990). In collaboration with Margaret Adams' Laboratory, the three-dimensional structure of G6PD was elucidated (Naylor *et al.*, 1996). Knockout of the *G6PD* gene was achieved (Pandolfi *et al.*, 1995) and between 1987 and 1994 the largest number of G6PD mutations to be identified from any one laboratory were found (Vulliamy *et al.*, 1993; Luzzatto & Mehta, 1995). The molecular explanation for the cooperation of two mutations in causing the commonest form of G6PD deficiency, the A variant, was discovered (Vulliamy *et al.*, 1991). Philip Mason and Tom Vulliamy helped set up the first molecular diagnostic haematology unit in the country.

With Peter Hillmen and Monica Bessler, the first cell lines with the PNH phenotype were produced (Hillmen *et al.*, 1993a) and Luzzatto's group then showed the site of the block in the biochemical pathway of synthesis of glycosylphosphatidyl inositol responsible for the phenotype (Hillmen *et al.*, 1993b). In Japan, Kinoshita first cloned the *PIG-A* gene in 1993 and in the following year, in association with Kinoshita, the genomic structure of the gene was demonstrated and *PIG-A* mutations were established as the molecular basis for PNH (Bessler *et al.*, 1994a). The group then reviewed the evidence that the basis for PNH was somatic mutations and cellular selection, favoured by an aplastic marrow (Bessler *et al.*, 1994b). A New England Journal of Medicine publication in 1995, co-authored by five key players in the PNH story at HH, described the natural history of PNH based on up to 50 years of follow-up (Hillmen *et al.*, 1995). This appeared 57 years after Dacie's first publication in this field (Dacie *et al.*, 1938).

Letizia Foroni, Simon Wagner and Mike Laffan, working with Lucio Luzzatto, were among the first in Europe to use clonal gene rearrangements of the immunoglobulin and T-cell receptor genes for diagnostic purposes (e.g. Foroni *et al.*, 1987). The biological significance of clonality in the leukaemias became apparent and the use of these techniques in the analysis of skin tumours was pioneered within the department (Whittaker *et al.*, 1988).

Luzzatto substantially developed red cell work at HH and, with Mitchell Lewis and Ted Gordon-Smith, set up the first MSc Course in Haematology. Luzzatto examined a student's MSc project report with the same enthusiasm, thoroughness and scientific rigour he used in preparing publications for Nature or Science. He ran a busy haemoglobinopathy clinic and fostered the amalgamation of the bone marrow transplant programmes of Gordon-Smith and Goldman.

During this era a batch of new professors was created. In 1980, Joe White had become professor at King's College Hospital; Catovsky, Goldman and Gordon-Smith held personal chairs in the department. Gordon-Smith became head of the department at St George's Hospital in 1987,

and in 1988 Catovsky was recruited as Professor of Haematology and Cytogenetics by The Institute of Cancer Research and Royal Marsden Hospital.

When Galton retired in 1987, Luzzatto was invited by the MRC to become Director of the Leukaemia Unit. Goldman also obtained Leukaemia Research Fund support, which subsequently was to be the dominant source of funding for the unit when the MRC withdrew support in 1992. A large number of talented post-doctoral scientists joined the department during this era, some to work initially with Luzzatto and to gain their first experience of recombinant DNA techniques and then to apply their new expertise in molecular biology to other areas, particularly the malignant diseases.

Senior members of the department included Tim Cox, subsequently to be a Professor of Medicine in Cambridge, who worked in iron metabolism and haemochromatosis. Irene Roberts, now Professor in Paediatric Haematology, set up marrow transplantation for thalassaemia and sickle cell anaemia. David Swirsky, a direct descendant of the Hayhoe-Dacie-Galton generation of morphological experts, became the National Health Service consultant in the department in charge of the diagnostic section. Current senior members of the department Jane Apperley, Amin Rahemtulla and Inderjeet Dokal (who, subsequently with Phil Mason, first cloned the dyskeratosis congenita gene; Dokal *et al.*, 1992) were initially junior research fellows. Atul Mehta, now at the Royal Free Hospital, was one of the first to explore mutations in mitochondrial DNA in haematological diseases (Mehta *et al.*, 1989). Professors Ghulam Mufti and Swee Lay Thein (King's College Hospital), Barbara Bain (St Mary's Hospital), John Porter (Royal Free and University College Hospital), David Oscier, (Southampton) and Charles Craddock (Birmingham) all received training at HH during this period. The technical staff of the department were led during most of Luzzatto's years at HH by Eleanor Lloyd, who supervised laboratory work and took on many administrative duties. She received the Order of the British Empire in recognition of her immense contribution, but unfortunately died early of cancer.

In 1994, Luzzatto left HH to set up and become the first Professor of the Department of Human Genetics at the Sloan-Kettering Institute in New York. He was recruited by Paul Marks, with whom he had been a Research Fellow at Columbia University 30 years earlier. Monica Bessler and Pier Paolo Pandolfi moved with him and have become, in the USA, internationally recognized independent investigators. John Goldman succeeded Luzzatto as Head of Department and has continued to lead the department's outstanding scientific output and contributions to clinical research. The story after 1994 will have to be recorded with the value of perspective by a future historian. A major event that should be recorded here has been the demise of the Royal Postgraduate Medical School as an independent Institution in 1997 and its merger, with the Institute of Obstetrics and Gynaecology, into Imperial College within London University. Nevertheless, the ethos of the School expressed in 1935 by Austen Chamberlain lives on in the

various Academic Departments at HH, not least in Haematology.

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