BIOGRAPHICAL MEMOIRS

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MONTAGUE MAIZELS

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BY R. G. MACFARLANE, F.R.S.

Montague Maizels (‘Monty’ to all his friends and colleagues) was born in London on 30 September 1899. He was the youngest child and the only boy in a family of four. His father, Joseph Maizels, a silversmith and jeweller, was a Jewish émigré from Prague who had come to Hull and thence to London in the latter part of the nineteenth century. After his arrival in England Joseph married Deborah, one of the nine children of Rabbi N. Lipman, a distinguished Talmudical scholar who was descended from a long line of eminent academics. Deborah became an able and energetic partner with her husband in establishing a successful jewellery business in Whitechapel High Street. The Lipman family was much respected in Jewish circles, and two of Monty’s maternal first cousins became well known medical consultants in London—Dr Walter Levitt, the radiotherapist at St Bartholomew’s Hospital (who was also a barrister), and Dr B. S. Nisse, the cardiologist at the National Heart Hospital. Two of Monty’s sisters married men who later rose to fame and who had both been his friends at school. Miriam’s husband was Professor Samson Wright, the physiologist at the Middlesex Hospital, while Hilda’s was Professor M. Lewis, the Director of Education at Nottingham University. Hilda also achieved her own renown as a novelist. One of her many books (The day is ours) was made into the film Mandy—a touching portrayal of the struggle to establish communication with a deaf-mute child.

EARLY LIFE AND EDUCATION

There was thus a strong academic element in Monty’s family background and, from his early childhood, his parents had ambitions for his future career. The Maizelses were relatively wealthy. They lived in a large house, near Toynbee Hall in Whitechapel, which became the focal point for their children’s many friends. Mrs Maizels was the dominant, matriarchal figure and it was probably her strong character and business ability that ensured financial success. Joseph Maizels was a tolerant, less forceful character, humorous and sympathetic, for whom the children had a deep affection.
With the idea of giving their son the best educational chances Monty's parents sent him, when he was only seven, as a boarder to a private preparatory school run by a Lipman relative at Bedford, called London House. But he was unhappy away from home and made so little progress that after two years he came back to London and went to the nearby Whitechapel Foundation School, later renamed Davenant. Here he soon began to do well and to make friends (including Samson Wright and Michael Lewis) who were clever and ambitious. It was, in fact, a school remarkable for its teaching and academic record, producing a large number of pupils who achieved high positions in the professions, the academic world and business.

Monty did not acquire any outstanding distinctions at school. He refused to enter for scholarships since he disliked competitive examinations. In a brief autobiographical note he wrote: 'I was considered a bright child, though not bright enough in my father's opinion to earn my living in pure science'. Yet it was to science that both Monty and Samson Wright were drawn, and they decided together that medicine offered the best chance of pursuing a scientific career combined with financial security. It was a decision that they both put into effect with highly successful results, but Maizels was always to regret his lack of a sound foundation in higher mathematics and physics that a training in pure science would have given him.

Maizels left Davenant School in the summer of 1916 and entered University College London to study medicine, when he was just 17 years old. He did not, again from his own choice, enter for any of the scholarships that would have been open to him, and there was no financial necessity to persuade him. He already had a grounding in chemistry, elementary physics and biology, and it is possible that his later and predominant interest in chemical physiology was aroused at University College. The department of physiology there was world-renowned under Starling and Bayliss, and any receptive young man must have caught some of the inspiring influence of these creative pioneers. Starling had begun his physiological career at Guy's Hospital in 1889, becoming head of the department a few years later. He then set about to reconstruct the laboratories so that a department that had been considered one of the worst equipped among the London teaching hospitals became one of the best.

Maizels profited from this early energy of Starling, because he himself went to Guy's to complete his medical training in 1917. When he reached the age of 18 he volunteered as a Surgeon Probationer in the R.N.V.R. but was rejected, so he remained to do all his clinical work at Guy's. The laboratory departments there had gained in status with the passing years. M. S. Pembrey, F.R.S., was Professor of Physiology, C. S. Gibson was in charge of chemistry, G. W. Nicholson was the morbid anatomist and Adrian Stokes was the Sir William Dunn Professor of Pathology. But it was the clinicians who dominated the scene, as they did at most teaching hospitals at that time. One has only to look at the Guy's staff list to see name after name that were (and in some cases still are) household words throughout the medical profession: Sir Charles Symonds,
Sir Alfred Fripp, J. J. Conybeare, Arthur Hurst, Sir Arbuthnot Lane and Sir William Hale-White among several others.

It was Sir Arbuthnot Lane who most impressed Maizels, though not quite in a way that the great man would have found flattering. Lane had been at Guy’s ever since he entered the medical school as a student in 1872. He soon established himself, not only as a surgeon with a wonderful manual dexterity, but as a man of forceful and persuasive character and original ideas. The idea for which he became most famous (or notorious) was that the human colon had lost its physiological function and become ‘a useless cesspit’ from which harmful toxins were absorbed. He concluded that many diseases resulted from this ‘autointoxication’ and, being a supremely good operator, he applied the current surgical precept—‘when in doubt cut it out’—and removed the greater part of the large intestine in many of his patients. Maizels, who was one of Lane’s ward clerks in 1918, had already acquired enough critical detachment to be unimpressed by the mere weight of his authority unsupported by facts. Years later, looking to those days, he wrote: ‘He was the original of Cutler Walpole in Bernard Shaw’s The doctor’s dilemma and was typical of the unscientific medicine prevailing at that time. I saw many extensive colectomies performed for goitre, rheumatoid arthritis and even chronic constipation. Many of his younger colleagues strove to emulate this brilliant and enigmatic personality; no-one bothered about statistical analysis of the results. I find all this rather shocking.’

The infliction of such major mutilations uncontrolled by the proper assessment of the consequences was indeed deplorable—and very prevalent at that time. The trouble was that the ideas on which such treatment was based seemed quite logical. About this aspect Maizels wrote: ‘As a short-cut to success in the early part of the present century it was necessary for a doctor to “shoot a line”. In some cases this line had no factual basis at all; in others—and these the more dangerous—it was based on existing knowledge but was carried far beyond what was justified by the evidence, the criterion being that because an idea was reasonable it was probably true.’ It is significant, perhaps, that although he was otherwise an exemplary student, Maizels was in trouble on several occasions for missing surgical rounds and classes. His interests were directed more towards laboratory work, and in 1919 he won the Beaney Prize for Pathology—an important award. A year later he won the Treasurer’s Medal for Medicine, and he graduated as M.B., B.S. (London) in 1922, with a Distinction in Medicine. During the next five years he remained at Guy’s in a succession of the junior appointments reserved for the most promising of the newly qualified students. It was a large medical school and Maizels—despite his dislike of competing—was clearly marked out as among the best of a numerous class. He became a medical registrar and then held demonstratorships in pathology and in physiology.

During his work in the pathology department, Maizels began a collaboration with A. C. Hampson on what was to become his life-long interest—the chemical approach to the extraordinary biophysical properties of the human red blood cell. Hampson was then the Hilda and Ronald Poulton Research Fellow and he
and Maizels published three papers together (1–3) on the effects of pH on red cell volume, on the distribution of phosphorus between the cell interior and its environment, and on the maintenance of pH differentials between cells and plasma. The work for the first of these papers revealed that the curves relating the osmotic volume changes of the red cell to pH values differed when potassium was substituted for sodium in the buffer solutions employed. Thus, from the beginning, Maizels was confronted by the problem of specific Na–K transport across the cell membrane, though he did not at once take up this challenge. But this work established his choice of a career. If he could earn a living in clinical pathology, he would concentrate on its chemical aspects where most others in the field were more concerned with cytology or bacteriology. There was no immediate opening for such a career at Guy’s. In 1927, Adrian Stokes died of yellow fever while working with infected monkeys during a visit to Lagos, and his successor, R. Donaldson, was mainly interested in morbid anatomy.

INFANTS’ HOSPITAL, WESTMINSTER

In 1928, the post of Clinical Pathologist at the Infants’ Hospital, Westminster, became vacant, and Maizels was appointed. There was a bond between Guy’s and the London children’s hospitals (particularly Great Ormond Street) largely through Sir Arbuthnot Lane’s interest in paediatric surgery, and it was probably this association that influenced Maizels’s appointment. As Clinical Pathologist he was responsible for all the routine laboratory investigations, including haematology, bacteriology, serology, cytology and biochemistry. He was already experienced in the sort of biochemistry needed, and was becoming a competent haematologist. In other subjects in which he had less experience he was able to rely on his assistants.

The clinical problems in the neonatal period are apt to be acute ones, demanding swift decisions and prompt, appropriate treatment. One of these is infantile diarrhoea and vomiting, then relatively common, which had the shocking mortality of almost 50%. Babies could develop a degree of dehydration and electrolyte imbalance within a few hours that soon became irreversible and fatal. Maizels tackled this problem as a biochemist with a main interest in electrolyte physiology. With Catherine McArthur he studied 48 cases during the summer of 1928, determining the chemistry of the blood and urine. One of the technical difficulties was the small amount of blood that can be obtained in such cases, so he adapted or devised methods to work on a micro-scale. It was typical of him that he first carefully standardized all these methods in a series of normal controls. The results of this work, published in 1929 (4), showed the previous reliance on the reaction of the urine to indicate the acid–base disturbance could be dangerously misleading. In 10 out of 20 cases of alkalosis the urine was acid. Other important indicators for appropriate treatment were established in this paper, which emphasized the importance to therapy of a correct understanding of the underlying biochemical position and which helped to institute the régime of investigation and treatment that later proved so effective. Four other papers
Montague Maizels

Two dealt with the biochemical changes in pyloric stenosis in infancy, emphasizing the loss of both plasma and cell chloride, and that the finding of a normal or raised plasma pH and bicarbonate indicated treatment with sodium chloride and fluid. It was also pointed out that persistent vomiting after operations often led to acidosis and a rise in plasma chloride demanding a change from chloride to bicarbonate administration. One of these papers (9) was published with Catherine McArthur of his own department and W. W. Payne, the Biochemist at Great Ormond Street. As a diversion from this predominant interest in electrolyte and acid–base balance, Maizels and Jean Smith published a paper (8) on their finding of a raised plasma phosphatase in rickets and scurvy. They admitted that they could not speculate on the causal relationship of this to the bone changes, but pointed out that increased phosphatase activity persisted for some months after these had been reversed by vitamin therapy. They also considered that the plasma phosphatase was a sensitive indicator of minor degrees of these deficiency diseases.

University College Hospital

In 1931, G. W. Goodhart retired as Clinical Pathologist at University College Hospital (U.C.H.) and Maizels was appointed to succeed him. He found an environment that must have satisfied his desire for a more scientific approach to clinical medicine. Sir Thomas Lewis was the exponent—and a great and inspiring teacher—of a simple, direct and most revealing experimental approach to clinical problems. His influence created a school of pupils who, in their turn, became professors of almost equal eminence. A. E. Boycott, the Professor of Pathology, applied the principles of experimental physiology to hospital pathology (as did his successor, Roy Cameron) and was ably assisted by Goodhart, who was responsible for the actual clinical laboratory investigations. Goodhart had had, as his assistant in haematology, Dr (now Dame) Janet Vaughan whose interest in red cells had led to a Rockefeller Fellowship to study with Minot in Boston. She did not, however, return to University College Hospital, but worked firstly with Professor H. M. Turnbull at the London Hospital and was then appointed Clinical Pathologist at the newly established British Postgraduate Medical School in 1935. Maizels therefore had to widen his interests in applied haematology and he was also, of course, responsible for lectures and practical teaching. Routine laboratory work, consultations with clinical colleagues who took a more intelligent interest in its results than was then usual at other hospitals, and the demands of similarly interested students, took up the greater part of Maizels’s time. But he found, or made, time for a research that was to occupy him for the rest of his working life.

It had been known for many years that the non-nucleated mammalian red cell showed a remarkable and unexplained selectivity in its permeability to electrolytes. This situation was complicated by the discordant findings of previous workers, and one of Maizels’s first contributions was to show the important effect of pH
changes on both anion and cation penetration. Such changes, which often occurred spontaneously during manipulation of the preparations, or during storage of the red cells, had in many cases been neglected and uncontrolled. In 1934 and 1935 Maizels published two careful studies (10 and 11) in which the effects of changes in pH and the salt concentrations of the suspending medium were related to the penetration of the cell membrane by inorganic anions and cations and a large number of different organic anions. He found that when red cells are suspended in salt solutions the amount of anion permeating varies with the external pH. If acid is added, hydrogen ions and anions penetrate the cell membrane freely. If the penetration of cations like sodium or potassium were equally rapid, then the amount of anion penetrating would vary with the external salt concentration. But it does not. The conclusion was that human erythrocytes are not readily permeated by cations and that the penetration by chloride is prevented by the electrostatic attraction of the non-penetrating cation. Maizels then went on to study the effect of suspending red cells in an isotonic solution of a non-electrolyte, namely glucose. The result was an outward diffusion of CO₂ so that the external solution became acid. Then cell potassium began to be lost, the rate of loss increasing with time or temperature. But this loss could be greatly delayed if a small concentration of KCl or NaCl were added to the glucose, when the internal K could be maintained at a concentration at least eight times that of the external K. It was difficult to imagine any simple physical explanation for such behaviour.

During the next two years Maizels continued to study this phenomenon by various methods, using not only normal human red cells, but those derived from patients with microcytic anaemia. By these means he was able to show (12–15) that the current supposition that the excess of inorganic cation over anion in the red cell could be accounted for by the function of haemoglobin as an acid was probably untrue, and he used Henderson’s term X⁻ to denote the unidentified cation-binding property of some substance in the red cell interior. He was still pursuing this line of investigation, which was clearly aimed at finding a relatively simple chemical explanation for these diffusion anomalies, when the threat of imminent war after the Munich ‘pact’ changed the direction of his work.

**Blood storage: World War II**

This change was the result of the energy and initiative of Dr Janet Vaughan, one of the leading haematologists in the country. She had given laboratory space (and found a home) for Dr Duran Jorda, a refugee from Franco’s victorious régime in Spain. Duran Jorda had specialized in emergency blood transfusion work during the civil war, and had devised an apparatus for taking, storing and giving blood, which he had been able to bring with him to England. His method was, in fact, too complicated for wide general use, since it involved storing the blood under oxygen at high pressure in glass bottles. But Dr Vaughan saw the potential value of blood storage for transfusion purposes, and after a trial of a simplified method using a gravity drip-feed and of various conditions of storage
(which she published in 1938) she became convinced that 'blood banks' were not only a practical possibility but an absolute necessity if large numbers of air-raid casualties were to be adequately treated. The authorities in charge of the 'emergency medical services' that would operate if war came seemed to be making no attempt to include blood transfusion in their preparations. She therefore took the initiative herself, very fortunately for the thousands of casualties and civilian hospital patients who were later able to receive blood with the minimum of delay.

Dr Vaughan’s first move was to call an informal meeting on 5 April 1939, at her home in Gordon Square, of the London pathologists who might be prepared to set up blood transfusion depots. Maizels was among these, and he was to play an important part, through his experience and interest in red cell chemistry, in the subsequent development of storage technique. At this meeting it was decided that there should be four main depots within 30 miles of London, and it was agreed that the pathologists in charge of these depots should be Dr Maizels, Dr H. F. Brewer, Dr J. O. Oliver and Dr Janet Vaughan, who would be based at Maidstone (or Tonbridge), Luton, Worcester Park and Slough respectively. A report of the meeting was sent to the Group Officers of the Emergency Medical Service for their comment. A second meeting on 11 April discussed and decided details of the necessary equipment and of the techniques to be used.

The immediate official reaction to this private initiative was a reprimand to Janet Vaughan through Professor Dible, the head of the pathology department at the Postgraduate School. He told her, in effect, that she and her committee had no authority and should stop their planning. But meanwhile the obvious value of these plans and the energy behind them had come to the attention of Professor Topley, who was Chairman of the Medical Research Council Emergency Committee. Dr Vaughan’s committee was not, indeed, in conflict or competition with any official efforts to establish a transfusion service because no such efforts then existed and Topley saw the advantage of recognizing officially a going concern. In consequence a special meeting took place at the Medical Research Council on 13 April, attended by the members of Dr Vaughan’s committee, at which they were duly recognized as an official subcommittee of the Council under the chairmanship of Professor G. P. Wright with Professor Topley, Professor Miles and Professor McIntosh as advisers. Thereafter this committee could put its proposals officially to the Ministry of Health and the Group Officers of the Emergency Medical Service. In an astonishingly short time, and as a result of two or three meetings a week, all the practical details of an efficient transfusion service were worked out; medical, technical and nursing staff arrangements, transport, apparatus and equipment, transfusion and storage techniques, location of the main depots and the subsidiary sector depots were all decided and in working order within three months.

Maizels established his depot in a large, four-storied house in London Road, Maidstone. His staff would consist of two senior and three junior medical workers, eight technicians, four office workers, seven nurses, three drivers and a number of ancillary helpers. Some of these would be transferred from his
department at University College Hospital, which would be largely evacuated on
the outbreak of war; and his wife, herself a trained nurse, would take charge of
the nursing staff and supervise the enrolment and care of donors. The Mayor of
Maidstone made an appeal, along the lines suggested by the subcommittee, and
in conjunction with the existing British Red Cross Transfusion Service, for an
additional 16,000 donors, a target that was far surpassed in the course of the next
few months.

To this remarkable and fast-moving creation (how long, one wonders, would
the ‘usual channels’ have taken to produce anything comparable?) Maizels’s
contribution was mainly technical. He could speak with authority on the effects
that storage and various anticoagulant and preservative solutions would have on
the red cells. He was the person best able to devise and carry out the experiments
needed to establish optimum conditions. For example, fears had been expressed
that the potassium lost from stored red cells to the plasma might reach concen­
trations dangerous to a recipient. Problems of this sort were exactly in line
with Maizels’s research interests.

Three days before the declaration of war by Britain the four Depot Directors
received a laconic two-word telegram from the Medical Research Council ‘Start
bleeding’, and the carefully prepared machinery began to move. In the event, of
course, the immediate heavy air attacks on London that had been expected did
not materialize, and Britain was given the almost uncannily quiet period of the
‘phoney war’ for the next eight months. But the transfusion depots went into
action, consolidated and improved their arrangements, and provided the civilian
hospitals in their areas with a plentiful supply of stored blood that, for the first
time, allowed patients in need of transfusion to receive it within the half-hour
required for grouping and cross-matching. Thus, when the real blows began to
fall in the spring of 1940, the depots were able to supply all the demands
required of them.

**Original work at Maidstone**

In Maidstone, Maizels had set up a research laboratory in his depot, and he
was able to accomplish a surprising amount of original work in addition to the
administration of an organization that was taking, storing and delivering about
1000 blood donations per week. His area covered S.E. London and the greater
part of Kent. Apart from the local collections in the Maidstone area, mobile
teams went with their equipment and refrigerator vans to outlying districts
where bleeding sessions were organized in local hospitals, village halls or factory
canteens. For the first few months this work went smoothly without the hazards
and disruptions of enemy action, or the necessity to deal with large numbers of
urgent casualties—a period of calm that was soon to change.

Meanwhile Maizels was occupied with several practical problems created by
the use of stored blood. One of these was the formation of shreds of fibrin or
clumped cells that necessitated the use of a filter when the blood bottle was set
up for transfusion. The early filters consisted of a tube packed with glass wool, or
even sand—substances highly surface-active and therefore most likely to cause the adhesion and destruction of platelets and leucocytes and to trigger the many enzyme systems now known to exist in blood plasma. Even at that time Maizels felt that some less traumatic method should be found, but it must also be readily available on a commercial scale. He thus hit on the idea of using ordinary gas mantles (before impregnation) since the small fine-mesh cotton bags were just the right size and shape to be adapted, and they were, of course, easily obtainable. His simple and ingenious gas-mantle filter, which he described in a paper to The Lancet in 1939 (16), proved effective and was in general use for many years.

His main line of research continued to be on the behaviour of red cells under different conditions of storage. In January and March 1940, he published with Whittaker a series of observations on the mean corpuscular volume, degree of haemolysis and escape of inorganic phosphate in relation to time, permeability to cations, pH and the effect of various additives to the suspending medium (17 and 18). It was concluded that the citrate–saline diluent then in use was hypertonic, and in this environment the cells, after an initial decrease in volume, lost their impermeability to cations, swelled and finally haemolysed. These changes could be checked by the addition to the diluent of dextrin, which slowly liberates glucose. Glucose had the effect of delaying the penetration by salts, thus preventing swelling, and it also seemed to cause an extensibility of the cell membrane so that a greater increase in volume could be tolerated without haemolysis. The authors put forward various hypotheses to account for this preservative action of dextrin and glucose, as follows: (1) as non-penetrating substances they might oppose an osmotic pressure to that of the haemoglobin; (2) by maintaining cell metabolism they might help to prevent physical or chemical changes in the cell wall; (3) they might maintain the integrity of the cell wall by some physical process of surface action. Apart from these interesting speculations, which Maizels was later to test by experiment, the practical outcome was the obvious advantage of adding dextrin or glucose to the anticoagulant fluid, and of using an exactly isotonic solution. Another advance was the application of Maizels's own observation, made in 1935 (11) that cation impermeability of the red cell was greatest at low pH values. The storage diluent was therefore acidified and it was found that, at a pH of 6.6, haemolysis occurring during a month's storage was reduced by about 50%. These experiments emphasized the desirability of further tests on acidified and isotonic diluents containing glucose. (The preservative effect of glucose had, in fact, been described, but not explained, in 1916, by Rous and Turner.)

A few weeks after this paper appeared the long-awaited German offensive was launched in Europe. Within a matter of days the German 'blitzkrieg', made possible by air superiority and surprise tactics, had driven a wedge of tanks and artillery between the British and French armies to the north of the Maginot Line, while Holland and Belgium were engulfed by another wave of attacks along their frontiers. With the loss for the British of all channel ports except Dunkirk, the whole British Expeditionary Force of 280 000 men with some thousands of other
nationals were somehow evacuated from the beaches by the makeshift armada of little ships that materialized there as if by magic. The ‘miracle of Dunkirk’ for a time obscured the truly catastrophic facts of defeat, and a threat more daunting than any faced by Britain in many centuries. But the immediate practical result was the arrival in S.E. England between 29 May and 2 June of over 300 000 soldiers without arms or equipment, some thousands of whom were wounded. These casualties were treated in the existing local hospitals and hastily prepared clearing stations. Many of them needed transfusions and the demand for blood far exceeded the amount that Maizels’s own resources could supply. All three of the other London depots came to the rescue, transferring to Maidstone every available bottle of stored blood and arranging special bleeding sessions—as, of course, Maizels did himself. It was a period of the most intense activity for all concerned and the result was a practical triumph for the organization of the transfusion depots and those who had had the foresight to establish them.

After Dunkirk came the Battle of Britain and the blitz, and the Maidstone depot settled down to being in the ‘front line’ with a constant demand for blood for civilian and air force casualties. The blitz not only created this demand but made it physically difficult to supply it. Transport was disorganized, roads might be closed, bleeding centres damaged and donors delayed. The worst-hit areas were those of military importance, such as Chatham and Dover, but even Tunbridge Wells was not immune. Mrs Maizels remembers that during a session at the hospital there, the refrigerator van standing outside received a direct hit, and the blood donors—still with the needles in their veins—had to scramble under the couches in the bleeding room as the ceiling came down. Such conditions persisted throughout the next 12 months, when the opening of the German offensive against Russia in April 1941 relieved the pressure on Britain.

During this troubled time Maizels still managed to pursue some of his researches. Those of the most immediate and practical importance concerned the conservation of plasma for use as a transfusion fluid. It was found that, in a severely shocked or exsanguinated patient, human plasma or serum which could be transfused immediately without the delay imposed by blood grouping could be a life-saving measure and far superior to the more commonly used saline infusions. The blood transfusion depots could supply surplus plasma drawn off from out-of-date blood. This plasma might, however, contain a few micro­organisms and, if pooled and stored, become dangerously infected. Attempts were made to devise methods for sterilization, but all failed for one reason or another. Filtration through bacterial filters, for example, caused subsequent clotting—a phenomenon that baffled those interested in the mechanism of coagulation (including the writer of this memoir) and rendered the method useless. Maizels took up this problem and sidestepped the obstacle by clotting the plasma deliberately with added serum and calcium chloride, the optimum amounts and proportion of which he determined experimentally with his usual thoroughness. The resulting serum, which was as effective as plasma as a transfusion fluid, could then be filtered and stored indefinitely (21). Later, he collaborated with R. I. N. Greaves at the Low Temperature Research Laboratory
in Cambridge in freeze-drying serum and plasma on a large scale, and he introduced a method for removing the prothrombin and fibrinogen from plasma by treatment with a special grade of kaolin, before filtration and subsequent freeze-drying (23).

But Maizels's main interest continued to be the human red cell, and the chemical basis for its biophysical behaviour. In October 1940 he published with J. M. Paterson a study of the survival and chemical changes in stored red cells after their transfusion into the circulation of a recipient (19). For this study he modified the method of Ashby, devised in 1919 and used by a few workers during the pre-war years, to follow the fate of transfused fresh blood cells. But Maizels seems to have been among the first to apply the method to stored blood, and the first to determine chemical changes in the transfused cell—which proved to be most remarkable. The Ashby technique depended on the fact that group O blood cells can be given to group A, B or AB recipients. After transfusion, therefore, the circulating blood will contain a certain proportion of group O cells which, in samples, will not be agglutinated by the addition of the appropriate isoagglutinins that will clump the recipients' cells. Thus, by differentiating the unagglutinated from the agglutinated cells, the donor cells can be recognized and counted. Maizels and Paterson modified this method to allow a physical separation of the two cell populations. This was by the simple but effective use of filtration through suitable paper. He took great trouble to determine this suitability by a series of experiments, showing that pre-war Whatman's no. 1 paper or war-time no. 4 fulfilled his conditions, which were that single cells should pass freely but that even small clumps should be retained. He also took considerable pains to explore the errors and fallacies of this method, which he was then able to avoid.

Maizels was thus able to put to a realistic biological test the various inferences that had been drawn from in vitro observations on the best methods for storing blood. He found, and reported to the Medical Research Council Blood Transfusion Research Committee in 1941, that 'there was a poor correspondence between the various in vitro tests, that these did not always correspond with the actual survival of cells after transfusion, and that of all the tests used in assessing the value of various diluents for stored blood, methods of testing in vivo are alone conclusive' (22). This particular line of investigation was continued and extended in depth by P. L. Mollison and his colleagues during the next few years, with a consequent great advance in knowledge of the normal life-history of the circulating red cell and its modification in disease. Maizels himself did not pursue this physiological research much further. He was more interested in red cell chemistry, and his observations had revealed a most unexpected phenomenon. His filtration technique allowed the bulk separation of transfused cells, and he was able to study their permeability and electrolyte content in comparison to a pre-transfusion sample and at various periods after entering the recipients' blood streams. In blood that had been stored for many days, the cells had lost potassium and gained sodium to a level from five to eight times the original concentration. But within 24 hours of being transfused these cells had regained
the normal Na–K ratio and they had also regained their original selective permeability (19). Thus their membranes had apparently been biochemically ‘renovated’.

Faced with this situation, Maizels then embarked on a series of experiments, which he published in 1941 and extended in 1943 (20 and 22). To someone (like the writer) who is not a biochemist, these are complex and confusing and give the perhaps unfair impression that the experimenter was himself confused by the complexity of his problem. There were so many variables: changes in pH, osmotic pressure inside and outside the cells, duration of storage and so on, which, combined with the number of natural organic and inorganic constituents to be measured and with those that were added artificially, give an astronomical number of permutations and combinations. Only a clearly visualized hypothesis that could be tested by serial experimental steps would create a comprehensible picture. But, at that stage, no such hypothesis emerged, and Maizels’s experiments therefore present a somewhat random appearance. What did emerge was a confirmation of the non-correlation of in vitro tests of the supposed integrity of the red cells with their subsequent survival in vivo (in particular, the measurement of ‘osmotic fragility’ seemed irrelevant), a lack of correlation which seemed to be due to the renovation of biochemically abnormal cells after they entered the blood stream. Maizels considered various ways in which this might occur. One suggestion involved the supposed formation of lytic substances during storage, such as lysolecithin or soaps, that would damage the red cell envelope in vitro. These, he suggested, might be removed in the normal circulation and the normal K–Na differential mechanism restored, possibly by passage of the cells through the liver or spleen. He therefore investigated the effect of added saponin, lysolecithin and cobra venom, but the results were uninformative (25).

In his speculations on the phenomenon of high K–low Na in the red cells, he wrote: ‘Peters and Van Slyke (1937) remark that no explanation exists for the inequalities of distribution, which must, however, depend on some restraining factor in the cell membrane or inherent characteristics of the cellular and extra cellular media . . . it would appear likely that normal erythrocytes are not impermeable to base, but are continually tending to lose K and gain Na and that the resulting changes are continually reversed by some counter-mechanism. Such a process might take place through the influence of some external factor: it might occur, for example, as the erythrocytes pass through the liver or spleen or other organ.’ He then points out that muscle cells present a similar paradoxical distribution of potassium, and remarks that since these cells ‘are unable to wander in and out of organs’ the mechanism is likely to be a local one, which would support the view that red cells contain their own means for maintaining their ‘paradoxical’ internal constitution. At this point he refers to the recent suggestion by Dean (1941) that a ‘pumping mechanism’ exists (in muscle) which ejects Na and so determines a compensatory entry of K (22).

Maizels pointed out that Dean ‘defines the physical conditions under which such a pump would produce a cation distribution conforming with experimental data, but is unable to suggest what motive force drives the pump’. He considered
the possibility of some organic potassium compound within the cell with a lower
dissociation than that of the corresponding sodium compound which, if the
organic ion was indiffusible, might account for the observed distribution ratios.
But though this might be the case for muscle it would not apply to red cells,
since the ‘K combined with chloride and bicarbonate within the erythrocytes is
alone at least eight times greater than external K’. He goes on to argue that a
dynamic process is implied and that ‘the energy required for such a process
might well derive from the active phosphate cycle which is such an important
part of cell metabolism’. In other words, the red cell might be something a great
deal more complicated than the passive, semi-permeable bag of haemoglobin
and salts that most workers then assumed it to be. At any rate, from that point,
Maizels began to take an interest in the organic phosphate of stored red cells,
particularly in relation to its preservation by added glucose though at that time
he could show no correlation between the rate of hydrolysis of phosphoric esters
in stored red cells and the rate of the loss of potassium. Meanwhile, Maizels’s
demonstration of the peculiar properties of the human red cell had attracted
the interest of a number of other workers, so that he had, in effect, opened up a whole
new field of research. J. E. Harris was the first to confirm (in 1941) Maizels’s
finding that stored cells can regain their capacity to concentrate K, since he
showed that this effect could be reproduced in vitro simply by incubating in the
presence of glucose cells that had been stored at 2 °C. Thus there was no need to
postulate specific ‘reconditioning’ by an in vivo mechanism.

Return to University College

During the latter part of his time at Maidstone, Maizels was much occupied
with his work on plasma preservation and then with the preparations for the
return to U.C.H. and the reopening of the medical school there in 1946. His last
two papers from Maidstone were published in 1945 and 1946 (24 and 25). The
first concerned a method for determing the true volume of the plasma trapped
between centrifuged red cells—a factor that could cause errors in computing red
cell volume. The second paper deals with the action of such haemolytic agents as
bile salts, lysolipins and saponin on normal, fresh or stored red cells, and on the
abnormal cells occurring in macrocytic and microcytic anaemia and in hereditary
spherocytosis. The results are rather indefinite and confusing, and the only clear
conclusion is that ‘if experiments on haemolysis are to have any meaning, the
titres of lysins used ought to be referred to the total surface area of the cell
suspensions’.

There was much to be done at U.C.H. (as in central London generally) to
restart an organization that had been interrupted for six years. When the
hospital beds were filled once more, and the staff and students had reassembled
from their evacuation areas or from the forces, it became apparent that clinical
medicine had become increasingly dependent on the laboratory services.
Antibiotics demanded bacteriological control; blood transfusion had become a
routine with serology as an attendant necessity; haematology had developed into a separate discipline, and clinical biochemistry was more than ever before needed in diagnosis and treatment. At U.C.H. most of this extra load fell on Maizels since, as Clinical Pathologist, he was responsible for hospital bacteriology, blood transfusion and serology, haematology and biochemistry. The accommodation was cramped—one main and two smaller laboratories, and three or four still smaller rooms that were used as preparation or store rooms. Maizels had one of the smallest rooms as his research laboratory with an ‘office’ in an alcove in which his desk and a Warburg bath took up all but a few square feet of floor space. The increasing work load demanded an increasing staff, and by 1950 this numbered six graduates and fifteen technicians with Dr F. Flynn in charge of biochemistry, Mrs Stokes in bacteriology, and Maizels (with two registrars) dealing with haematology and serology.

It was not until 1949 that Maizels was able to return to the problem of cation control in red cells. In the meantime he published (26) a study of the value of empirical tests of liver function, with a discussion of their biochemical basis. Then he embarked on an investigation of the spontaneous in vitro restoration of cation control in cells that had lost it as a result of storage at 2 °C. He found that the active expulsion of Na from the cells, with uptake of K which occurred on incubation at 37 °C was energized by glycolosis, and considered that the potassium intake was passive. The result of these changes in electrolyte distribution was the restoration of the physiological Na–K ratio, and the maintenance of a constant cell base and water content. He concludes that ‘any cell unprotected by some external or internal resistant structure would burst because of the osmotic and electrical conditions imposed by its own protein’ (27). He then (28) extended these observations with Flynn. They found that the active output of Na and the passive inflow of K reached a point of balance when the plasma Na concentration was about one-eighth that of the cell Na, and that when the cells are incubated in K-deficient plasma, the output of Na is reduced. They also observed that lithium taken up during cold storage is not expelled during incubation.

Maizels followed up the cation transport aspect of these observations, which he published later in the same year (29). He confirmed that the energy for active transport is an accompaniment of glycolysis, not of respiration. The inhibitors of cytochrome systems, such as cyanide and azide, and other respiratory inhibitors, such as dinitrophenol, malonate, mepacrine and arsenite, were without effect on active transport. But fluoride and monooiodoacetate inhibited glycolosis and active transport.

In 1951 Maizels, with R. Blowers and Evelyn Clarkson, investigated the strange phenomenon of ‘flicker’ in human red cells (30). This appearance of vibratory movements in the cell interior had been described in 1890 by Browicz, and rediscovered by Pulvertaft in 1949, who used phase contrast microscopy. Maizels and his colleagues confirmed these observations and found that flickering was closely correlated with active cation transport, and that both were restrained by agents that inhibited glycolosis but not by those inhibiting respiration.
Glucose, mannose and fructose energized flicker and active cation transport, while galactose, arabinos and disaccharides energized neither activity.

In 1952, Evelyn Clarkson and Maizels turned their attention to red cell enzymes, a natural direction in view of the previous work suggesting an energy-dependent cation transport mechanism. They particularly studied various phosphatase activities in the red cell stroma. They found that the stroma contains enzymes activated by magnesium which convert adenosine triphosphate to adenylic acid and liberate orthophosphate from phosphoric esters and diphosphoglycerate. In stroma-free haemolysate they found enzymes activated by magnesium and inhibited by calcium which hydrolysed diphosphoglycerate and converted inorganic pyrophosphate and triphosphate to orthophosphate, but had no action on ATP. As a result of experiments on stroma, haemolysates and intact cells, they concluded that phosphorylation does not occur at the cell surface and must therefore take place within the membrane or at its inner face (32).

From this demonstration of the importance of glycolysis in active cation transport in the human, non-nucleated red cells it naturally became of interest to discover if similar mechanisms operated in the nucleated erythrocytes of birds and reptiles. Between 1954 and 1956 Maizels published three papers (34, 36 and 38) one being with Evelyn Clarkson, on cation transport in chicken, tortoise and grass snake erythrocytes. The findings showed clearly that in these species active cation transport depends on respiration and that glycolysis contributes little energy for the process. A peculiarity of tortoise cells was their dependence on calcium for normal cation transport. In a calcium-free medium Na and K moved with the concentration gradient, and the erythrocytes swelled and finally hydrolysed. This effect was studied in detail in the 1956 paper, in which it was shown that in calcium deficiency the permeability coefficient for efflux was little altered, whereas influx increased rapidly. Co and Mn can replace Ca.

In 1958, with Mary Remington and R. Truscoe, Maizels widened his investigation of ion transport from erythrocytes to other cells. The first to be investigated were mouse ascites tumour cells, using much the same techniques that had given good results with red cells (39). The rate and temperature coefficients for Na influx and efflux were determined, and the effect of K studied. In a K-deficient medium, the cells could be made to swell or shrink, even at constant osmotic pressure and pH, by changes in temperature and Na concentration. On addition of K to these distorted cells, Na was lost and K gained, but the shrunken cells gained and the swollen cells lost total base, chloride and water, and thus returned to their normal volume. In a second paper (40) the same authors extended these observations, finding that glycolysis as well as respiration was concerned with active cation transport in these cells; and in a third they used (for the first time in Maizels's work) a radioactive isotope, Na*, in experiments to determine rate coefficients and time curves for Na transfer. The distribution of added radiosodium suggested that all cell Na is exchangeable, but it was concluded that the movement of Na* was too fast to make the tracer technique a practical advantage (41).
From mouse ascites tumour cells, Maizels and Mary Remington then turned in 1955 to the cells in rat kidney slices (42 and 43). In these it had been suggested that an active pumping of water occurs without corresponding movements of anions and cations. But, as a result of rather indirect experiments with mercaptomerin, which causes swelling of the cells, it was concluded that increase in tissue water is accompanied by an appropriate increase in anion and cation.

In 1959, with Valerie Bolingbroke, Maizels returned to the effect of calcium on cation transport that he had observed in tortoise erythrocytes. Though he had not been able to show this effect with human erythrocytes suspended in electrolytes, it was now discovered that it did occur if the cells were suspended in a calcium-free non-electrolyte medium, such as isotonic lactose solution (47). Under these conditions salts diffuse from the cells, which then shrink, despite the fact that the external fluid becomes hypertonic. When these lactose-treated cells were transferred to an electrolyte medium, there was a rapid but passive cation transfer; it was concluded that the normal union of calcium with the human red cell is firm and is not broken in Ca-free electrolyte solution. But the bond is broken in lactose solution, and the cell becomes freely permeable to electrolytes. Normal low permeability can be restored by adding calcium, the only cation able to achieve this effect. Deborah McConaghey and Maizels continued this study of lactose-suspended red cells in 1960, using the technique to study the osmotic conditions that allowed the cells to shrink in what would be regarded as a hypertonic solution. This led to an examination of the osmotic coefficients of haemoglobin, which must determine the osmotic balance as its concentration rises during shrinkage of the cell (49 and 50). The same authors published further work on the cation exchanges in lactose-treated cells in 1962. They took advantage of the fact that such cells become highly permeable and lose their natural cation. The latter may then be replaced by any other monovalent cation, and this new cation can then be ‘sealed in’ by adding calcium, which restores membrane function. Such cells do not show active cation transport in ordinary nutrient media, but do so if adenosine is also added. This was an ingenious and fruitful manoeuvre which allowed the study of the transfer of a number of different cations, and it was shown that in systems containing only the cation Na no active efflux occurred, nor did it take place in Na-free systems (52).

Maizels published two further papers on this subject, one in 1965 with Diana Carolin and the other in 1968. The first of these is a long and detailed account of the rates of ion exchange in lactose-incubated cells, and their ‘reloading’ with Li, Na, K, Rb or Cs (54). Selectivity for these was only marked in NaCl media when it followed the series K > Rb > Cs > 24Na > Li, K being three to six times as strongly retained as Na. The second paper was the last that Maizels published on his permeability work (55). It too described observations on lactose-incubated cells and their reloading with various cations, and the exchange of these before and after ‘sealing-in’ with calcium. By these experiments Maizels was able to determine rates for the passive as compared with the active exchanges that could be induced by external conditions.
Looking back over Maizels's work one is struck by the steady progression from the simple to the complex, a process that is almost inescapable during the prolonged investigation of even the simplest-seeming biological phenomenon. When he started his work the red cell was considered to be a lipoprotein envelope enclosing haemoglobin solution. The envelope was semi-permeable, and the cell as a whole behaved like an osmometer. The K–Na differential was difficult to explain, and it was vaguely supposed that the physical structure of the membrane somehow let K in but not out. Maizels had settled down to investigate this problem in depth, and worked on it more or less continuously for nearly 40 years. A number of practical benefits and discoveries derived from this work, mostly in the field of blood transfusion. Maizels was the first, for example, to show that a slightly acid medium favours red cell preservation in stored blood. He also directed attention to the importance of glucose (having begun by using dextrin), which was soon taken up by other workers.

His own assessment of his contribution to the glucose work is given in a letter he wrote to Professor P. L. Mollison in 1975. 'The first person to use glucose was, of course, Peyton Rous in 1916, who did not suspect any chemical action but only a physical effect on the cell surface. It did not take on because (I expect) it needed 92 ml medium for 40 of blood or nearly a litre of medium for 500 ml blood and was hardly practical. Rous only died a couple of years ago; he was Sir Alan Hodgkin's father-in-law. Glucose was used again in 1938. (Gwynne and Alsever, cord [blood]; the Russians, corpse [blood]: hence the purges.) Both of these [uses] were repulsive. I first used acid as a preservative for blood in vitro and it was you and Loutit who put it on the map by use in vivo.'

Maizels, as usual, was rather too modest about his own work. He was the first person to follow the cell chemistry of stored blood after transfusion in vivo, and it was as a result of these observations that he discovered the 'renovation' of cells that had lost their selective cation permeability within a short time of being transfused. Harris then showed that this renovation could occur on incubation with glucose in vitro, thus facilitating Maizels's further studies on glucose and the establishment of the whole concept of an energy-dependent mechanism involved in active cation transport. This he followed into the fields of glycolysis and respiration, showing the importance of the former in non-nucleated red cells and of the latter in the nucleated erythrocytes of birds and reptiles. Parallel with these experiments was the unfolding of the part played by organic phosphates, particularly ATP and DPG, their synthesis and breakdown, and their importance as a source of energy and in controlling the function of haemoglobin. Maizels helped to pioneer this field. In this account it is, of course, his own work that has been described, and this does not imply that other workers were not involved, nor is it intended to belittle their advances. But this is not, for obvious reasons, a general survey of a subject that grew from small beginnings when Maizels first took it up into the vastly complex picture of the red cell that we have today, and to which increasing numbers of people are contributing. The red cell (like the
blood platelet) is now recognized as a ‘living’ organism—despite the absence of a nucleus—with many of the interlocking and counterbalancing enzyme systems to be found in cells in general, plus specially adapted systems of its own.

Professional and personal life

In his professional life Maizels was a most retiring and modest person. He disliked public appearances, congresses, meetings or any social occasion in which he might be caught in the limelight. In consequence he was regarded by many of his contemporaries as very much a ‘lone wolf’ and, since he seldom spoke or appeared on the international stage, his work did not receive the popular recognition it deserved. But those who took the trouble to read his published papers (which demand a good deal of the reader) recognized his merit, and to them it was no surprise when he was elected to the Fellowship of the Royal Society in 1961. Other tributes had already come his way. He was elected a Fellow of the Royal College of Physicians in 1941, and appointed Professor of Clinical Pathology at University College Hospital (University of London) in 1951, and in 1959 he became Sydney Ringer Lecturer there.

In his own laboratory, doing the work he enjoyed and at which he excelled, Maizels seems to have been quite a different person. He was outgoing and friendly and all his many collaborators enjoyed working with him, though he was extremely exacting and demanded the most scrupulous accuracy and attention to detail. All remember his sense of humour and wit. He had read widely, and his remarkable memory allowed him to fit some long quotation from the poets or the classics to almost any situation. Dr Clarkson remembers that when she complimented him on some example of apposite erudition he would shrug it off as ‘Just a little thing of my own’. She also recalls that he used to sing (he had a good voice) appropriate folk ballads, particularly one in which each verse ended with the words ‘six feet of earth makes us all of one size’. He was seldom parted from his pipe, which he sometimes put, still well alight, in his waistcoat pocket—occasionally with dire results. She writes: ‘I well remember him dancing about, shouting “I’m on fire, I’m on fire!” ’ which reduced me to tears of laughter.

His own experimental work was meticulous. Almost everything was done with his own hands. He made and calibrated his own pipettes, standardized all his solutions and usually insisted on washing the glassware himself. His papers show the greatest care in establishing every method used, exploring possible fallacies and sources of error, and laying down a firm base of control observations before moving into the experimental unknown. He trained several generations of pupils in these methods, and they were grateful for the techniques they learned from him, and for his example of careful, steady probing that, from small beginnings, revealed unsuspected mechanisms in wider and deeper fields. But research was only a part of his professional life. He directed a busy routine department, kept its staff happy and its work effective. His clinical colleagues often consulted him, which he appreciated and, since most of them took a more scientific view of
clinical medicine than was usual in other hospitals, these consultations were useful to both sides. Maizels had a profound sense of the value of biochemistry in clinical medicine, which he expressed in a lecture in the *Scientific basis of medicine* series in 1958 (46). He illustrated this by several examples, including the suggestion that if Zuelzer had been able to estimate the blood sugar by an accurate micromethod in 1908 he would have discovered insulin. Another of Maizels’s duties was, of course, undergraduate teaching. This involved practical work and class lectures. Despite his dislike of more formal lecturing, Maizels enjoyed lecturing to students and it is certain that they enjoyed listening to him. Again it was his wit and humour which often ‘brought the house down’ and his facility for apt quotations that carried the subject matter into their minds and helped them to remember it.

In his personal life, Monty’s unpretentious modesty and humour were again predominant characteristics. But they were combined with a warm humanity and a genuine sympathy for other people’s troubles that often led to the practical help which so many of his friends and associates remember with gratitude. He retained his links with the Jewish community and with its continued struggle to alleviate the hardships of the victims of anti-Semitic oppression, and he supported the Zionist work of his brother-in-law, Samson Wright. Laboratory work provided Monty with his main interest in life, and he had few hobbies or deep interests outside it. Though he had played hockey in the Guy’s team as a student he took little interest in sport. But, in his younger days, he was a great walker, spending his holidays exploring Wales and the Lake District on foot. He was fond of classical music, preferring vocal to instrumental works, and he enjoyed opera. But his chief enjoyment came from literature, in particular poetry.

After World War I his family had moved to Willesden, when Joseph’s failing health led to his giving up the business. He died in the mid-twenties and Monty continued to live with his mother until 1934, when he moved to a flat of his own in Hampstead. In 1937, while on holiday at Rustington on the Sussex Coast he met Miss Dulcie Speight, the daughter of a Yorkshire farmer. They soon discovered common interests, but not for some days did they discover that they both worked at U.C.H., she as a staff nurse and he, of course, as Clinical Pathologist. They married on 11 February 1938, against some opposition from Mrs Maizels, since Miss Speight was not of the Jewish faith. But it was an ideally happy union. Monty and his wife worked side by side all through the war, and throughout their life together they shared similar tastes and interests. Their only child, Judith, was born in 1947. Their favourite relaxation was the leisurely exploration of Europe which they carried out by annual motor tours.

After Maizels retired in 1968, his friend Sir Bernard Katz, F.R.S., gave him laboratory space at University College London to continue his experiments. There he worked happily until 1974, when a stroke left him partially paralysed. But he still kept up his interest in his friends and was pleased to welcome and entertain them at his home. He died suddenly on 11 February 1976, the thirty-eighth anniversary of his wedding day.
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The photograph is by W. Bird.

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