ABSTRACT

Many developments have occurred in sickle cell disease and care over the last 50 years in Jamaica. The clinic population grew from 50–60 in the mid-1960s to 5500 in late 1999. During this period, the number of staff serving sickle cell patients increased from 2 to 28, comprising physicians, paediatricians, nurses, laboratory technologists, social workers, computer staff and statisticians. The physical facilities have improved greatly, and data management has evolved from the typewritten long narrow paper strips in the late 1960s to sophisticated electronic patient management systems. The many physical resources and the superb opportunities of an ‘island laboratory’ have provided a unique basis for clinical research into the disease.

Keywords: Jamaica, sickle cell disease

Jamaica y la investigación de la enfermedad de células falciformes

RESUMEN

En los últimos 50 años se han producido múltiples desarrollos en torno a la enfermedad de células falciformes y su atención en Jamaica. La población clínica, que a mediados de la década de 1960 era de 50–60, ha crecido a 5500 en las postrimerías de 1999. El personal que presta servicios a pacientes sicklémicos, ha aumentado de 2 a 28 trabajadores, incluyendo a médicos, pediatras, enfermeras, técnicos de laboratorio, trabajadores sociales, personal de computación, y estadísticos. Las instalaciones han mejorado considerablemente, y el manejo de datos de los pacientes, que a finales de la década de los 60 consistía en largas tiras de papel mecanografiadas, ha sido transformado en un sofisticado sistema electrónico de administración de pacientes. La multitud de recursos físicos y las magníficas oportunidades de una ‘isla-laboratorio’ han proporcionado una base única para la investigación clínica de la enfermedad.

Palabras clave: Jamaica, enfermedad de células falciformes

Early Days of the University College Hospital of the West Indies

The story of sickle cell disease in the Caribbean is intimately related to the development of the then University College of the West Indies (UCWI), now University Hospital of the West Indies (UHWI). Following the Second World War, Sir James Irvine chaired a Committee
for Higher Education in the Colonies, which visited Jamaica in 1945 and recommended the establishment of a university starting with a medical faculty because of the shortage of medical practitioners in the area. The UCWI, affiliated to the University of London, was established in October 1948 with the enrolment of the first medical students who had to gain clinical experience in Kingston Public Hospital while awaiting the building of the UHWI on grounds adjacent to the UCWI on the outskirts of Kingston. The foundation stone for the new hospital was laid by the Earl of Athlone, the husband of the first Chancellor of The University of the West Indies (UWI), Princess Alice, but it was not until 1952 that the building was finally available. It was opened officially by Sir Hugh Foot, Governor of Jamaica, on January 15, 1952 and three days later Winston Churchill unveiled a plaque recognizing the contribution of the British Government.

EARLY RESEARCH ON SICKLE CELL

As staff were appointed to the laboratory and clinical services, interest in sickle cell disease started almost immediately. The first published work in 1953–54 was by Derrick Jelliffe (1, 2), who had recently moved from the University Hospital in Ibadan, Nigeria, to the Department of Medicine at UWI, Mona, Jamaica. He surveyed 2116 Jamaican school children of different racial origins with the rather primitive Scriber-Waugh technique, deoxygenating red cells in a sealed chamber, and found positive tests in 5.7% of ‘average Jamaican children of African ancestry’. The early interest was highlighted by a Sickle Cell Symposium on May 28, 1954, chaired by Professor Eric Cruickshank, which addressed the prevalence of the trait, the clinical features, bone and radiological changes and the pathology (3). The arrival of John MacIver and Lodewijk Went in the Department of Pathology led to a fruitful collaboration which introduced haemoglobin electrophoresis enabling the distinction of different genotypes of sickle cell disease (4–6), the characteristics of sickle cell-beta thalassaemia (7–9), a rare variant haemoglobin (10) and one of the first descriptions of hereditary persistence of fetal haemoglobin [HbF] (11). Clinical contributions were also made on megaloblastic change (12) and the aplastic crisis (13), the bone changes by John Golding (14, 15) and outcome of pregnancy by Mavis Anderson (16, 17).

ARRIVAL OF PAUL MILNER

The next major event was the arrival of Paul Milner and his wife Ann in the Department of Pathology. He quickly took an interest in sickle cell disease which was further stimulated by a visit from Professor Hermann Lehmann, of the British Medical Research Council (MRC) Abnormal Haemoglobin Unit in Cambridge, England. At that stage, it had become clear from the increasing numbers of patients and the research potential that a dedicated Sickle Cell Clinic was justified and this took place every Friday morning in the ‘Gynaecology Clinic’. The UHWI agreed that there would be no charge as it was a research clinic and since Paul Milner was a laboratory-trained haematologist, he requested clinical assistance from the senior registrar to Eric Cruickshank, Knox Hagley. When this post became available in August 1966, Graham Serjeant arrived from England and assisted in the Sickle Cell Clinic, which in those days saw 10 to 15 patients each Friday morning. Meanwhile, Ann Milner, a secretary by training, recorded the haematology and clinical features of individual patients on long strips of paper which were affixed to sheets of cardboard as a filing system. There then began a collaboration of Paul Milner with Graham Serjeant involving Beryl Serjeant, a laboratory technologist, who assisted Paul in the development of laboratory techniques. In early 1967, while touring the Caribbean, Peter Williams, secretary of the Wellcome Trust, arrived in Jamaica looking for research projects and Paul Milner and Graham Serjeant applied and were awarded a grant of £17 000 over two years. This provided Paul Milner with an early Coulter counter (haematology analyser) for the laboratory, paid the salaries of Graham and Beryl Serjeant and provided a Volkswagen minibus as a mobile clinical unit with the rear seats replaced by an examination couch and worktable.

Graham Serjeant was designated a Wellcome Research Fellow in the Department of Medicine and worked from Room 3 of the Rippel Building, a medical research facility at the UHWI. Although officially the Sickle Cell Clinic still operated only on Friday mornings, the patients soon learnt that medical help was available in Room 3 of the Rippel Building which quickly became a daily clinic, even functioning on Saturday mornings. This unofficial clinical facility was invaluable, with one end of a large laboratory being used for patient care, the other end for blood tests and haematology and a side bench for the analysis of newborn screening samples from Victoria Jubilee Hospital (VJH). Painful crises proved to be a problem in management,
and in preference to languishing in the Accident and Emergency Department, Room 4 of the Rippel Building became a day care centre with foam mattresses on the laboratory benches. Although not ideal and far from being currently acceptable, this allowed continuity of patient care until the dedicated Sickle Cell Clinic became available.

The mobile clinical unit (Fig. 1) proved invaluable, and the first project was to locate patients with SS disease who used to attend the Sickle Cell Clinic but had not been seen for 10 years and were then aged over 30 years.

According to the textbooks of that period, patients rarely survived to adult life and so it was natural to assume that they had died. Out of 50 such patients, 5 were found to have died, 5 had emigrated, 17 could not be traced, but 23 (46%) were alive and well and had defaulted from clinic follow-up because they were clinically well. This realization that many Jamaican patients survived to later adult life and actually improved clinically was totally unexpected and, when published (18), led to the assumption by others that either the patients did not have the disease but had the trait or the disease in Jamaica was different.

The reality, of course, was that we were beginning to observe the true natural history of the disease and the assumption of universal severity derived from observations elsewhere resulted from the symptomatic bias in focussing on severely affected patients. This was amply demonstrated following the National Sickle Cell Anemia Control Act in the United States of America [USA] (19) which promoted population screening and led to the detection of unsuspected cases of SS disease on active military service. This was yet another example of the suitability of Jamaica for clinical studies allowing long-term follow-up of patients, and attitudes had changed so much that the description of 102 patients with SS disease aged over 60 years in Jamaica (20) caused little surprise.

**TAKING THE CLINICS TO THE PATIENTS**

The observation that mildly affected patients defaulted from clinical care confirmed the impression of a symptomatic bias in clinic attendees. This led to an approach to reduce this bias by taking clinical care to the patients, and Sickle Cell Clinics were established attached to six country hospitals at Morant Bay, Annotto Bay, St Ann’s Bay, Mandeville, Black River and Montego Bay, so that no patient had to travel more than about 30 miles. In Montego Bay, the clinic was conducted in a wooden cottage, labelled ‘The Specialist Clinic’, on the grounds of the old St James Hospital (Fig. 2). These were conducted every six weeks between 1967 and 1971 by Graham and Beryl Serjeant and saw large numbers of patients, especially at Black River and Montego Bay in the west of Jamaica. Bus fares were provided, if necessary, and patients failing to attend were visited in their homes (Fig. 3).

All went well and it was assumed that the bias of symptomatic patients had been removed until one day...
on a cottage doorstep in the parish of St James behind Montego Bay. While visiting a family with sickle cell-beta° thalassaemia in which the patient aged 10 years was running a severe clinical course, she was photographed alongside her ‘normal’ sister aged eight years to demonstrate the effects of sickle cell disease on growth, body build and affect (Fig. 4). However, a blood test on the ‘normal’ sister showed that she also had sickle cell-beta° thalassaemia. Therefore, although we had reduced the bias in our observations, we were still unaware of mildly affected cases. To document the disease properly, a population had to be defined without any symptomatic bias and that required newborn screening.

THE FIRST INTERNATIONAL SICKLE CELL CONFERENCE
This took place at UWI on January 8–10, 1969 (21, 22) and was a rather amateur but enthusiastic affair involving most of the small number of people working in sickle cell disease in the days prior to the stimulus of the National Sickle Cell Anemia Control Act in the USA (19). Money was raised locally with excellent support from the bauxite companies which allowed us to offer half of the airfare, and accommodation was provided by colleagues on campus. Attendees from abroad included John MacIver, Richard Huntsman, Ernst Huehns and Hermann Lehmann from the United Kingdom (UK), Lodewijk Went from Holland, Roger Lewis from Ghana, A van der Saar from Curacao, Lemuel Diggs, Howard Pearson, Charles August, William Mentzer, John Bertles and Wallace Jensen from the USA, Wilfrid Dos Santos from Barbados, and many local colleagues from Pathology, Medicine, Paediatrics, Obstetrics, Orthopaedics, Accident and Emergency and the Tropical Metabolism Research Unit (Fig. 5).

INTERLUDES IN MEMPHIS, USA, AND CAMBRIDGE, ENGLAND
In 1969, the Wellcome Trust grant was renewed for a further three years. However, in May 1971, Graham and Beryl Serjeant went for three months to the Sickle Cell Center in Memphis, Tennessee, run by Dr Lemuel Diggs (one of the grand old men of sickle cell disease who had been publishing on the condition since 1932), and then to Cambridge to work with Professor Hermann Lehmann in the British MRC Abnormal Haemoglobin Unit in the Department of Biochemistry in Cambridge, England, intending to pursue a PhD over three years. However, after the first three months sitting in a laboratory in Cambridge while the clinical studies in Jamaica had ceased, it became clear that this was the wrong decision. Negotiations with the British MRC led to the decision to return to Jamaica in November 1972 to start the Jamaican Cohort Study of Sickle Cell Disease.

OTHER DEVELOPMENTS IN THE 1970s
Returning as a staff member to the then British MRC Epidemiology Research Unit (ERU) on the UWI, Mona Campus, the initial work was dominated by several themes. A chance meeting with Richard Huntsman from St Thomas’ Hospital, London, led to a link with Patrick Condon, an Irish ophthalmologist, who during the course of several visits to Jamaica laid the foundation for the work on sickle cell eye disease (23–30). A member of the ERU, Michael Ashcroft, conducted studies on body build in sickle cell disease (31–35), and the Tropical Metabolism Research Unit’s George Alleyne and colleagues addressed acid-base issues in the disease
A meeting with Sir Howard Middlemiss, Professor of Radiology at Bristol, whose postgraduate students were seconded to Mona led to a series of radiological contributions (43–46), and the Departments of Medicine, Pathology and Paediatrics studied renal complications and the general pathology of the disease (47–52).

THE JAMAICAN COHORT STUDY OF SICKLE CELL DISEASE

The ability to locate many defaulting but surviving patients in Jamaica raised issues on the variability of clinical course in the disease, and it was becoming clear that although the disease resulted from a single primary gene defect, there was a wide and unexplained variability in clinical course. To understand factors contributing to this variability, it was necessary to define a study population without any symptomatic selection. The best option was at birth, but at that time there were concerns on the reliability of newborn diagnosis in the presence of high levels of HbF. These were largely resolved by the work of Rosie Schneider in Texas, and by combining screening methods using cellulose acetate followed by confirmation of variant bands by agar gel, Beryl Serjeant evolved techniques which reliably made the diagnosis (53).

The stage was set to screen a newborn population, and in collaboration with Leslie Williams, senior medical officer at VJH, screening commenced on June 25, 1973 (Fig. 6). Once again, Jamaica led the world as many researchers still claimed at that time that the diagnosis of sickle cell disease could not be made at birth. The midwives of VJH were superb, and over the next eight and a half years, ending on December 28, 1981, a total of 100 000 non-operative deliveries were screened with the detection of 550 babies with forms of sickle cell disease (54). The first 125 patients with an SS phenotype were matched by age and gender to two controls with normal AA phenotype providing 250 controls, and the entire 800 subjects have been followed up over
periods of up to 43 years. As the children aged, their clinical course was documented, complications defined, and interventions developed for their prevention where possible. Major developments included pneumococcal prophylaxis (55), teaching mothers to reduce mortality from acute splenic sequestration by detection at home (56), the role of parvovirus in the aplastic crisis (57–60), treatment trials for chronic leg ulcers (61–65), the natural history of priapism (66–68), enuresis (69–71), the outcome of pregnancy (72–79), precipitants and features of the painful crisis (80–84), evolution of haematological change (85–91), the causes of death (92, 93) and many others.

Jamaica has been fortunate in collaboration with groups abroad such as David Weatherall and Douglas Higgs in Oxford and with Johns Hopkins Hospital, especially George Dover, which have increased the understanding of molecular changes modifying expression of the disease (94–107). The evolution of ocular pathology in Cohort subjects was carefully documented from 1980 to 2000 by Alan Bird from Moorfields Eye Hospital in London who, with Mrs Sarah Bird, led a team of four to five ophthalmologists who volunteered their services for two to three weeks each year. With measurements of visual acuity, dilatation, retinal drawings and fluorescein angiography, these studies accumulated a unique database on eye complications of sickle cell disease (108–112).

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While the Cohort subjects were waiting to dilate, Tom Walker, a radiologist from the Royal Berkshire Hospital, Reading, UK, also volunteered to do annual ultrasounds for gallstones, renal and splenic features (113–118). The Cohort Study has also taught us much about the clinical variability, the determinants of that variability, the role of genetic factors such as alpha thalassaemia, the persistence of HbF and also of the environment, of skin cooling and the painful crisis, and the milder clinical course associated with improved socio-economic status. The success of the Cohort Study was made possible by the generous and sustained funding from the British MRC, the clinic facilities developed by the Sickle Cell Trust, but above all by the co-operation and enthusiasm of the Cohort patients and their parents.

GEOGRAPHIC COMPARISONS
The development of models of care appropriate to societies with high frequencies of variant haemoglobins and limited resources has made the Jamaican experience of value to other societies. As a result, the Jamaican experience has been sought by colleagues in Brazil, Greece (119), Turkey, Saudi Arabia (120–122), Bahrain, Uganda (123, 124) and India (125–129), and has also contributed to the development of sickle cell care in more developed countries such as the USA and the UK. These collaborations have also provided research opportunities for learning about the variability of sickle cell disease and the determinants of this variability.

SICKLE CELL TRUST (JAMAICA)
The British MRC funded the scientific research programmes of the MRC Laboratories, but additional demands had to be met from other sources. This was the background to the formation of the Sickle Cell Trust (Jamaica) as a locally registered charity in 1986 with Graham Serjeant (Chairman), Karlene Mason (Secretary) and 11 Board Members. The Trust received superb support from the private sector in Jamaica and internationally which ensured success of the following projects. The first appeal for US$50 000 to purchase a diagnostic ultrasound instrument (Fig. 7) for studies on gallstones and renal assessment was completed within two months following a major donation from the National Commercial Bank.

The next project was the raising of £100 000 for the construction of a dedicated Sickle Cell Clinic adjacent to the MRC offices on the UWI, Mona Campus. This provided a laboratory, four consulting rooms, treatment rooms and an eight-bed day care centre and was officially opened in August 1988. Since the clinic was to be on the Campus about half a mile from that in the Rippel Building, it was necessary to provide a shuttle service, in a minibus donated by the Dutch Government (Fig. 8) which operated from perhaps the world’s only Sickle Cell Clinic bus stop (Fig. 9). The dedicated centre
provided much better facilities for patient care and the associated research and appeared to have had a profound impact on the features of the disease. Patients were reassured that all staff in the clinic were familiar with sickle cell disease. They saw nurses, doctors and technologists with whom they were already familiar and who already had their records, avoiding the confrontation often encountered in Accident and Emergency departments of hospitals elsewhere. For many patients, this reassurance was a major part of the battle and exemplified by several patients in painful crises who stated that they only had to reach the doors of the Sickle Cell Clinic to start to feel better. In the day care centre, where at busy times of the year, the eight beds may have had to be supplemented by padded benches in the corridor. In the mid-afternoon before the clinic closed, patients were given the option of going home with the same pain-relieving medicines or being admitted to hospital, and over 90% of patients chose to go home. The clinic became an example of the benefits of holistic care in improving the clinical course of many patients.

The next project was the building of an Education Centre for Sickle Cell Disease on the roof of the clinic which was funded by a single donation of J$7 million (£120 000) from the then Telephone Company of Jamaica chaired by Mayer Matalon. The centre opened in 1994 (Fig. 10) and provided an 80-seat seminar room, a laboratory for the Jamaican Government newborn screening programme for sickle cell disease, rooms for presenting and developing educational videos, interactive CD-ROM tutorials, and offices. It was a valuable facility for educational and counselling courses. With the retirement of Graham Serjeant from the MRC in September 1999, these facilities were assumed by UWI, which continues to operate the Sickle Cell Clinic.

Retirement also brought a new phase of the Trust activities, commencing with the organization of illustrated PowerPoint lectures conducted by Karlene Mason to the Fifth and Sixth forms of most of Jamaica’s 160 secondary schools and tertiary institutions, eg teacher training schools, nursing schools and community
colleges, focussing on sickle cell disease, symptoms, complications and genetics. At the end of these presentations, there were questions, but the major request was how students could find out whether they carried variant genes placing them at risk of having a baby with sickle cell disease. The answer was not reassuring as students were told to attend private laboratories where the tests would be expensive and may lack the precision needed for genetic counselling. This programme of public education continued all over Jamaica for eight years (2000–07), and the increasing demand for knowledge of haemoglobin genotype by the students led to the next phase which was the Manchester Project.

THE MANCHESTER PROJECT
In discussion with the Ministry of Health and Ministry of Education, a project was designed to offer free detection of haemoglobin genotypes to the senior students of 15 secondary schools in the Manchester parish. This was part of a larger project associated with education and counselling to determine whether provision of genotype information would influence their choice of partner and reduce the frequency of births affected by sickle cell disease. From 2008 to 2013, screening of 16 636 students in the Fifth and Sixth forms (Fig. 11) found 2432 (14.6%) students with variant genes, placing them at risk of having a baby with sickle cell disease. All students were given haemoglobin genotypes on laminated cards, and carriers of variant haemoglobins were offered counselling.

To determine any effect on subsequent reproduction, newborn screening was set up with cord blood samples starting with Mandeville Regional Hospital in 2008 and spreading to involve over 15 000 deliveries annually in 12 hospitals in the southern and western regions. The samples were collected on Guthrie cards as blood spots, obtained as the umbilical cord was cut, the samples were dried and then sent to the Central Laboratory in Mandeville. Diagnosis at birth required greater sensitivity to detect low levels of beta chain haemoglobins in the presence of high levels of HbF, and this was most readily achieved by high pressure liquid chromatography (HPLC) in instruments capable of making the diagnosis in three minutes per sample (Fig. 12).

At the end of 2015, an analysis was conducted on 2442 pregnancies to the mothers screened as students failed to show any evidence that the intervention had reduced affected births. Focussing on 898 females with the sickle cell trait, there were five babies with SS disease compared with 5.5 cases predicted from random mating (130). Interviews with the mothers indicated that either their genotype was not mentioned to the boyfriends or the latter declined to be tested. Newborn screening is now well established in the south and west...
of Jamaica and will be continued by the Ministry of Health. Together with the Sickle Cell Unit at UWI which has started screening in the south-east and north-east, the Ministry of Health is finally offering universal screening for sickle cell disease.

**CONCLUSION**

Many developments have occurred in sickle cell disease and care over the last 50 years in Jamaica (Fig. 13). The clinic population grew from 50–60 in the mid-1960s to 5500 in late 1999. During this period, the number of staff serving sickle cell patients increased from 2 to 28, comprising physicians, paediatricians, nurses, laboratory technologists, social workers, computer staff and statisticians. The physical facilities have improved greatly, and the long thin paper strips with patient data employed by Ann Milner in the late 1960s have evolved into sophisticated electronic patient management systems. The research output now exceeds 500 papers in the peer-reviewed press, and Jamaica continues to teach the world much about sickle cell disease. It has been over 40 years since Jamaica became the first country in the world to have extensive newborn screening, and it is gratifying to know that the Sickle Cell Trust was a stimulus to the final development of universal newborn screening in Jamaica. There have also been many other lessons from this brief review of sickle cell research activity since 1952, and foremost among these are the unique opportunities of an island laboratory for long-term studies of the disease. The work has also benefitted from collaborations with many groups worldwide who have recognized these research opportunities. Finally, it is with gratitude to the willingness and co-operation of many of the patients that so much has been learnt about the disease over the last 64 years.

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<tr>
<th>Date</th>
<th>Events/Support</th>
<th>Major Projects</th>
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<td>1952</td>
<td>Inauguration of University Hospital of the West Indies</td>
<td>Early clinical reports</td>
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<td>Improved diagnostic facilities</td>
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<td>Recognition of variant forms</td>
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<td>1965</td>
<td>Formation of Sickle Cell Clinic</td>
<td>Improved data collection</td>
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<td>1967</td>
<td>Wellcome Trust Support</td>
<td>Studies of natural history</td>
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<td>Setting up country clinics</td>
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<td>to reduce symptomatic bias</td>
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<td>1969</td>
<td>First International Sickle Cell Conference</td>
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<td>1972</td>
<td>MRC Epidemiology Research Unit</td>
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<td>1974</td>
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<td>1986</td>
<td>Sickle Cell Trust (Jamaica)</td>
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<td>1987</td>
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<td>1988</td>
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<td>1994</td>
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<td>Built Education Centre for SCD</td>
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<tr>
<td>2000–07</td>
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<td>Illustrated lectures of SCD to secondary schools islandwide</td>
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<tr>
<td>2008–13</td>
<td>Manchester Project</td>
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Fig. 13: Timeline of events.