ELECTIVE (SSC5b) REPORT (1200 words)

A report that addresses the above four objectives should be written below. Your Elective supervisor will assess this.

1. Sickle cell anaemia is a genetic autosomal recessive haemoglobinopathy which carries significant morbidity and mortality. The prevalence of SCD is thought to be 7% worldwide with the overwhelming burden of the disease, some 75% of cases occurring within peoples of African descent particularly in sub-Saharan Africa. In addition, SCD affects peoples of the Mediterranean and in South Asia particularly India. In the United States there are about 100000 people who have SCD, many of whom are of African descent.

Life expectancy in SCD patients is around three decades lower than in the normal population and in the developing world paediatric mortality before the age of five years of age from SCD is unfortunately very common, with younger patients succumbing to overwhelming sepsis due to loss of splenic function and lack of access to prophylactic antibiotics and pneumococcal vaccination. Patients who reach adulthood are at risk of multi organ damage caused by the accumulative effects of ischaemia and inflammation and fibrosis, hyperbilirubinaemia and iron overload.

Although the genetic mutation which causes this condition has a significantly negative impact on the health of affected individuals and is indeed life threatening in the homozygous setting, it is thought to have been preserved in populations over centuries due to geographical and epidemiological pressures exerted by life threatening parasitic malarial disease, spread by mosquitoes that thrive in tropical climates. A survival advantage is afforded to heterozygous sickle trait individuals of the HbβAβS genotype infected with the plasmodium falciparum parasite. Falciparum propagation is hindered by the presence of ferryl haemoglobin in sickle cells which blocks parasitic modification of actin filaments of sickle cells which is necessary in disease pathogenesis. Additionally, since cell sickling increases the damage to and reduces the lifespan of erythrocytes, there is high cellular turnover which offers improved parasitic clearance from the circulation impeding falciparum propagation, thereby markedly reducing the manifestation of malarial disease.

2. Health provision in the UK differs considerably from the US. The UK employs a public not-for-profit system, free at the point of care, funded through national insurance taxation. The governmental Department of Health allocates public funds to be managed in England by NHS England and other members of the union respectively. NHS England purchases services at the national level and awards funds to general medical practitioner-led clinical commissioning groups (CCGs) to purchase health services at the local level in primary and secondary care within designated trusts. Patient access to services available is governed by primary care general medical practitioners on assessment of patients in clinics. Non NHS private services are available with private insurance policies at cost to policy holders.

Healthcare in the US is, in contrast to the UK system, largely privatised and funded through private insurance policy premiums which are generally provided through employer organisations, which limits access to care for the unemployed of working age. Additionally, standard insurance policies contain excess amounts which must be paid by individuals and can leave patients in debt, which is a leading cause of bankruptcy in America. To foster health equality, help for low income households and vulnerable members of society such as the elderly and disabled has been put in place via two federal health insurance programs called Medicare that provides coverage irrespective of income and Medicaid

for low those on low incomes. This has gone someway to widening access to healthcare in the US, however, there still remain millions of Americans who do not have insurance.

The National Institutes of Health is a unique government tax payer funded research hospital complex outside the realm of the standard private insurance based healthcare system. The NIH is dedicated to translational research into rare, complex and challenging cases, with the aim of improving public health in America. The institutes conduct a varied research portfolio covering mainly phase I & II clinical trials of interventional therapy and natural history studies of disease. Patients seen are volunteers enrolled in studies who are not privately charged for the services they receive at the hospital.

3. SCD manifests when sickle haemoglobin within erythrocytes desaturates to the deoxygenated state which favours polymerisation and in the presence of various potentiating factors favours formation rigid stable structures that distort the familiar normally flexible biconcave disc formation of erythrocytes. Cells become sickle shaped and with increased viscosity are unable to easily pass through microvasculature, which leads to intensely painful ischaemic episodes known as crises, as well as vessel endothelial lining injury and inflammation. With recurring episodes, the accumulative effect of ischaemia can be eventual multi organ failure. The main symptoms of SCD are recurrent episodes of pain from vaso-occlusive crises which can cause life-threatening acute disease as well as lead to multi system damage over time. SCD usually presents in early life as a type of painful crises affecting the hands and feet known as infantile dactylitis. Initial presentation occurs only from around the sixth month of infant life due to onset of the shift between production of fetal haemoglobin present in high amounts in infants which desaturates less easily to adult haemoglobin which destaurates more readily.

Current standard therapies include opiate based analgesia used to manage crises related acute and chronic pain. Additionally long term hydroxyurea therapy which induces expression of fetal haemoglobin is used to reduce the frequency of crises however compliance, efficacy and are toxicity are issues.

Chronic anaemia may be treated with periodic simple blood transfusions which are effective in the short term but are a risk with regard to iron overload. Many SCD patients are iron overloaded and are treated with iron chelating therapy. Where resources exist patients may also undergo exchange transfusions where the sickle cell burden is lowered whilst avoiding an increase in haematocrit which can also help in reducing the frequency of crises.

Preventative strategies such as patient education and genetic counselling are also employed which help patients with family planning and living with chronic disease. As eluded to previously, vaccination and prophylactic antibiotics may protect against sepsis related to autosplenectomy.

4 Standard therapies are used to manage crises and crises related multiple long term sequelae of SCD, however, there is no standard therapy to treat the underlying cause of SCD. My rotation within the sickle cell branch of the haematology department was both enjoyable and educational allowing me a privileged opportunity to learn about and meet the researchers and volunteers involved in NIH studies underway in particular studies looking to target the underlying genetic cause of SCD. Allogenic haematopoietic stem cell transplantation studies which has been shown to be effective in other myeloid diseases is also being investigated as a treatment for SCD with very promising results as well as exciting experimental gene therapy techniques. Obstacles to widespread use of these therapies are also being actively studied at NIH to tackle issues of toxicity and infection related to myeloablation, as

well as the risk of graft rejection and graft versus host disease, however, these studies are very promising and provide curative treatment for patients suffering from this debilitating disease.