GROWTH IN YOUNG CHILDREN WITH HOMOZYGOUS SICKLE CELL DISEASE

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ABSTRACT

A prospective study of Jamaican children with homozygous sickle cell (SS) disease, based on a cord blood screening programme initiated in 1973, provided the opportunity for a detailed examination of growth in early childhood. Abnormalities of body shape and size have been previously documented in affected adolescents and adults from the same population. Height,weight and head circumference data from 244 SS and 233 normal (AA) children, matched for age and sex, were available for analysis from birth to five years. The body shape of a sub group of 64 SS and 123 AA children aged 4-6 years was assessed using multiple anthropometric measurements. Bone age estimations based on the X-ray appearance of the wrist were available for 60 of these children (21 SS and 39AA) at age five years.

SS children showed a.significant deficit in weight by one year and in height by two years - weight deficit proportionately greater than height deficit. The features of a slender body build and characteristic chest deformity, noted in affected adults, were present in SS children by age five years when a slight, but consistent, retardation in bone age had emerged. No clear relationship with individual clinical or haematological variables was identified except that better grown SS children tended to have a lower MCV and higher HbF at one year.

These results define the emergence and severity of abnormalities in early childhood growth in an epidemiologically valid population of cases and controls.

CONTENTS

LIST OF TABLES

LIST OF FIGURES

Chapter 1

SICKLE CELL ANAEMIA : INTRODUCTION

1. NOMENCLATURE

The terminology of sickle cell disease, particularly in the earlier literature, has been confusing. Some terms survive from the period prior to the understanding of the genetics and accurate diagnosis of these conditions. In this text, the term 'sickle cell anaemia' applies only to cases of homozygous sickle cell disease (SS disease). The term 'sickle cell disease' applies to cases in which the presence of sickle haemoglobin appears to cause symptoms, but the exact genotype should be used if known. The application of this term to include the sickle cell trait is unacceptable (1) and is not employed here. The normal genotype is abbreviated as AA.

2. PERSPECTIVE

Since the early part of this century inherited disease has assumed increasing importance as a cause of worldwide morbidity and mortality. Better public health services and improved diagnostic and therapeutic techniques have not only reduced the risks of non-genetic illness but have also increased the survival of children born with serious inherited disease or defect.

The frequency of the sickle cell gene reaches levels as high as 40% in some areas of Equatorial Africa but the expected high prevalence of the disease has not, in the past, been recognised in these communities. This has now been attributed to the high mortality seen in affected individuals during childhood, contributed to by infections, especially malaria, poor nutrition, lack of medical care and the general consequences of poor socio-economic conditions. In developed countries, where genotype frequencies are substantially less, for example 7-8% in the USA, increased survival into adult life has revealed the full range of the complications of the disease and imposed an increased burden on health care services. This pattern, as expected with improving socio-economic conditions, is already emerging in developing

countries and sickle cell disease is now recognised as one of the most common and severe genetic conditions throughout the world.

3. HISTORICAL ASPECTS :

Accurate genotyping techniques became available in the early 1950's but many case reports accumulated before this time can, on present day criteria, be considered as authentic SS disease. The clinical entity has long been recognised in West Africa and has been known by several tribal names which are characterised by a repetitive onomatopoeic sound, appropriate to a chronic relapsing disease (2). Apart from one or two earlier case reports retrospectively reminiscent of the disease, the first recognised case was recorded by Herrick (3) from Chicago in 1910. He reported the case of a West Indian student with a history of recurrent hospital admissions for anaemia, jaundice, pulmonary complications and leg ulceration, who had "peculiar elongated and sickle shaped red blood corpuscles" characterising his blood film. This initial report was followed by three more in twelve years, and in presenting the fourth case, Mason (4) reviewed the similarities of all four, using the term sickle cell anaemia for the first time. All patients were of negro origin, all were jaundiced, all had leg ulcers and all had a long history of ill health extending back into early childhood. The haematological findings were all characteristic of chronic haemolytic anaemia and showed the presence of 'sickle cells'.

4. GENETIC ASPECTS :

Mason had concluded that sickle cell anaemia was a new disease entity but a subsequent report (5) of the observation of sickle-shaped cells in the asymptomatic father of one of the previous cases, raised the possibility that this was a familial disease and stimulated investigation into the mode of inheritance. Diagnosis on the basis of a positive sickle preparation caused confusion with further findings of "latent" sicklers among the relatives of patients with sickle cell disease. This was resolved in 1933

when Diggs (6) clearly distinguished symptomatic cases (sickle cell disease) from "latent" asymptomatic cases for which they proposed the term sickle cell trait. In 1949, Neel (7) collected 29 cases of the disease from whom 42 parents were tested and all found to show sickling, evidence which strongly supported the idea of a homozygous-heterozygous form of inheritance rather than, as had been previously proposed, that of a dominant gene with variable expression. Simultaneously Beet (8) presented a similar conclusion based on an extensive study of a large family in Northern Rhodesia. However, calculations of the expected prevalence of the disease according to the observed trait frequency far exceeded the prevalence observed in several African populations and cast doubt on the validity of this theory of inheritance (9-12).

In 1951, Foy (13) argued that the homozygous-heterozygous theory could not fit the African situation unless cases of sickle cell anaemia were being missed and suggested that the most appropriate group to observe would be infants and young children who were known to suffer a high mortality. Shortly afterwards the Lambotte-Legrands (14,15) described 130 young children with sickle cell anaemia from the Congo and recorded their very high early mortality. It became apparent that if a sufficiently young population was examined, cases occurred with a frequency predicted by the homozygous-heterozygous inheritance theory.

The last remaining obstacle to total acceptance of this concept was in the continuing appearance of well documented cases of sickle cell disease in which only one parent showed sickling. In many, the non-sickling parent was of Mediterranean origin and it became apparent that these children were heterozygous for both the sickle cell and β thalassaemia genes. In other cases electrophoretic studies revealed the presence of sickle haemoglobin and another, non-sickling, abnormal haemoglobin. The most common interactions,

HbSC, $HbSD_{Punjab}$ and $HbSO_{Arab}$ have been well documented as causing a similar, but less severe, clinical picture than the homozygous disease.

5. MOLECULAR ASPECTS :

In 1949 Pauling (16) defined an electrical, and hence chemical difference between HbA and HbS by describing different mobility of sickle haemoglobin on electrophoresis. The haem groups appeared identical, suggesting a difference in the constitution of the globin portion of the molecule. Early chemical analysis of the globins failed to reveal distinctive differences, and although Havinga (17) actually demonstrated an excess of valine in the HbS molecule, he considered this an experimental error. In 1956, Ingram, (18)using a new technique of peptide mapping, revealed a peptide fragment from HbS which occupied a different position than in HbA. Further work (19) indicated that this peptide contained less glutamic acid and more valine than the corresponding peptide in HbA. In 1959 Hunt and Ingram (20) were able to conclude that the only structural difference between HbA and HbS was the substitution of valine for glutamic acid at the sixth amino acid position from the N terminal of the β globin chain. This minor change in chemical structure has profound effects on the physical behaviour and function of the HbS molecule, particularly in the deoxygenated state. HbS has an increased tendency to crystalise and to form polymers, factors which contribute to the characteristic deformity of red cell structure.

6. GEOGRAPHICAL ASPECTS :

The highest concentrations of the sickle gene are found in areas of Equatorial Africa. Movement of peoples from West Africa, Zaire and Angola during the slave trade accounted for its distribution to the Caribbean and to North and South America. Subsequent immigration has introduced the gene into Britain and Northern Europe. The finding of areas of gene concentration around the Mediterranean Sea, in Saudi Arabia and in Southern India seemed

incompatible with a theory of a single gene mutation until Lehman (21) suggested that a single mutation occurred in the once fertile Arabian Peninsular and, with changing and increasingly dry climatic conditions, migration towards Africa and India carried the gene outwards. Anthropological evidence supported this concept (22). The theory of multiple gene mutation arising in different areas is now, however, generally considered more likely and although there is yet no report of HbS having arisen spontaneously, spontaneous mutation has been reported in other abnormal haemoglobins (23).

Persistence of a disease-producing gene with, in some places, a prevalence of up to 40% is remarkable, especially when it is seen that the observed number of homozygotes is considerably less than expected. The reports of excessive mortality in childhood discussed earlier explain this loss of sickle cell genes but some factor must then operate to maintain the gene frequency within the population. Two explanations were proposed in the early 1950's - the first, which suggested a high mutation rate, was dismissed as improbable since this would represent a mutation rate up to 3000 times greater than any other naturally known mutation in man (24). The second argument, that gene carriers possess some selective advantage in terms of survival or reproduction, was addressed by several workers. Raper (25) suggested that sickling might have a positive survival advantage against parasites and Allison (24), noting the close geographical association between areas of high gene frequency and the distribution of falciparum malaria, initiated studies into the interaction between malarial infection and the sickle cell trait. A period of controversy followed but Raper (26) demonstrated a lower mortality from malaria in children with sickle cell trait thus establishing that sickling was capable of acting as a selective agent in malarious areas. In summary, there is good evidence that the presence of HbS in the heterozygous state confers some protection against falciparum malaria and that this protection is maximal in young

children at a time before natural immunity has developed (27). The mechanism is not entirely clear but in 1970 Luzzato et al (28) were able to directly demonstrate increased sickling of parasitised cells in vivo.

It is clear that removal from a malarious area would negate this selective advantage - a conclusion illustrated by the introduction of people of Black African origin into the USA during slavery. The frequency of the sickle cell trait in Black Americans is still lower than would be expected by inter-marriage with its resulting admixture of non-black genes (29).and it can be calculated that the difference between the observed and expected gene frequency represents gene loss over a period of 300 years - the approximate duration since the gene was first introduced into the Americas.

THE NATURAL HISTORY OF SICKLE CELL DISEASE

1. THE TRADITIONAL CLINICAL PICTURE :

From the accumulation of published case reports that followed Herrick's original description, a clinical impression of the disease evolved which we can now appreciate as being unrepresentative. The major bias lies with the problem that patients were selected on the basis of symptomatic presentation in a hospital setting. The concept that the disease might exist in a mild form resulting in minimal need for medical care was probably not considered in the early days and the lack of accurate diagnostic techniques before the 1950's precluded effective community surveys. It is unfortunate that the traditional clinical picture based on such observations still survives in many textbooks.

The traditional understanding of the disease is that patients are chronically unwell with intermittent episodes of acute ill health. Haemolysis gives rise to anaemia and jaundice. Symptoms of anaemia are rare but sudden worsening of the anaemia with acute symptoms and even death may result from transient marrow aplasia or acute splenic sequestration. Cardiomegaly and systolic murmurs are common early signs of high cardiac output associated with the anaemia. Gallstones and obstructive jaundice due to acute cholestasis may result from the increased bilirubin load. Compensatory expansion of bone marrow may lead to bone deformity and render it more susceptible to infarction. Most other features of the disease are related to vessel obstruction and tissue infarction - including leg ulceration, pulmonary infarction and infection, dactylitis, and avascular bone necrosis with its consequent risk of osteomyelitis. Splenomegaly is characteristic in early childhood but atrophy secondary to infarction, occurs later. Involvement of the central nervous system and retina may result in hemiplegia and blindness. Growth is impaired, puberty delayed and pregnancy holds hazards in its outcome for both mother and child. In general, life expectancy is substantially reduced and

mortality in childhood is high.

2. EVIDENCE FOR A MORE VARIED CLINICAL PICTURE :

Although the first four reported cases of sickle cell anaemia were all over 20 years of age, emphasis rapidly shifted to the importance of the disease in childhood. The concept of a homozygous-heterozygous form of inheritance stimulated much work in Africa where the high frequency of sickle cell trait suggested that homozygous disease might affect as many as 4% of the population. Only when populations of infants were examined was the expected high frequency noted and their high mortality recorded (30) explaining the relatively few cases seen in adults. Vandepitte (31) estimated a 1% survival to adult life in affected children from the Congo. Several other African studies estimated survival to reproductive age between 20% and 45% (29, 32) but a further study from Uganda (33) of 478 subjects aged over 5 years found a trait frequency of 35% but no case of sickle cell anaemia. Despite this gloomy prognosis, sporadic adult cases were reported from the same environment. Some of the earlier accounts were not confirmed by electrophoresis but Jacob (34) reported three new cases aged 18, 28 and 30 years from a population of 3362 patients attending antenatal clinics in Uganda, calculating a 14% survival rate to reproductive age.

Experience elsewhere was, initially, less well documented. From the United States, Sydenstricker (35) described 10 patients over the age of 30 years and two subsequent reports documented three patients aged 40, 52 and 66 years old (36, 37). There have been few further individual reports of elderly cases but increasingly, clinical studies report older patients and the personal experience of physicians in the United States suggests that survival beyond the age of 30 years is not uncommon.

In Jamaica, Miall (38) studied a random group of over 1500 men and women aged between 35 and 64 years, and found two cases of SS disease - representing a survival rate of almost 40%. Serjeant (39) reported 60 Jamaican cases aged

over 30 years, confirming the impression that the disease in Jamaica is relatively benign - in terms of both morbidity and mortality.

The natural history of the disease varies with the environment. In Africa survival to adult life is infrequent but in the United States and the West Indies many of the deleterious factors in infancy have been removed and survival to adult life is common, although life span is probably reduced. Early mortality, however, even in the United States and Jamaica remains high, and it is likely that the first 2 or 3 years of life are the period of greatest risk. Porter and Thurman (40) reported a 16% mortality in 64 infants during the first year of life. Rogers (41) reporting results from a prospective study of 109 cases of SS disease, diagnosed in the first three years of the Jamaican cord blood screening programme, calculated a 13% mortality at age 2 years - the first epidemiologically valid data available.

3. IMPLICATIONS AND THE NEED FOR A COHORT STUDY

Several factors must be borne in mind when setting up any study to document the natural history of sickle cell anaemia. Studies based on hospital cases include an obvious bias towards those most severely affected and, even in Africa, the relatively benign course of the disease may be more common than is generally expected from the early literature. In Zambia, Barclay (42) found 18 previously undiagnosed cases in a population study of 1707 children aged under four years. In Jamaica, where the concept of a more benign disease was already accepted, Serjeant (43) found 51 unsuspected cases in the families of 220 known sickle cell anaemia patients; several were over 30 years of age. Some of the reports of early mortality pre-date accurate diagnostic techniques and may not be validated. However as the disease may not present clinically until the age of 6 months or more, it is still possible for children to die undiagnosed and Powars (44) reported 7 children presenting as sudden infant death syndrome who were found, on post-mortem blood samples, to have SS disease and pneumococcal septicaemia. The

possibility of such early mortality necessitates diagnosis at birth - a technical possibility only recently achieved - and prospective follow up.

4. SUITABILITY OF JAMAICA FOR A COHORT STUDY

Apart from the technical ability to perform electrophoresis on the newborn, there were several criteria to be satisfied before a natural history study based on neonatal diagnosis could be considered a practical proposition in Jamaica.

Firstly there had to be an adequate level of the sickle cell gene and its distribution homogenously spread throughout the population. Eleven percent of the Jamaican population is sickle positive (38) i.e. approximately 200,000 people. Almost three quarters of the Jamaican people were classified in the 1960 census as being of black african origin, 15% as afroeuropean and the remainder divided into several small groups (East Indians, Afro-East Indians, Chinese, Afro-Chinese, European and Syrian). Africans were brought to Jamaica as slaves, first by the Spanish in the early 16th century and then, on a larger scale by the English in the late 17th and the 18th centuries. These people came mainly from the areas now known as Ghana, Angola, Nigeria and Zaire, where the prevalence of the sickle cell trait ranged from 9-25%. Malaria, introduced to Jamaica from Africa was a problem only at lower altitudes and, although 50% of Jamaican land is above 1000 feet, up to 30% of the population have lived in the low lying area of the capital, Kingston. It was possible that the protective effect of altitude in the rural areas and the placement of people with different levels of the sickle gene in different areas might have resulted in a heterogenous survival of the sickle gene in present day Jamaica. Intense urban migration to the capital and movement between parishes has made heterogeneous survival of the gene unlikely while eradication of malaria was certified by W.H.O. in 1965. It was unlikely therefore that selection of a population from the urban area of Kingston would be unrepresentative of the country as a whole.

The second criterion lay in the ability to collect adequate numbers for study. A trait frequency of approximately 10% will result in cases of SS disease occurring at a rate of 2.5-3.0/1000 live births and a maternity unit with a high delivery rate was required. The government maternity hospital (Victoria Jubilee Hospital) is situated in the centre of the city of Kingston and serves the corporate area of the city, the parish of St. Andrew and some surrounding districts. According to the 1974 census, this area contained 614,000 people (30% of the Jamaican population). In 1973, the year in which the study began, there were 18,375 admissions to the hospital resulting in 13,819 deliveries. Registered births in Jamaica for that year were 61,000, so that 23% of all the births in the country occurred at Victoria Jubilee Hospital (45).

The final criterion was the need for adequate patient follow up. The restricted area and high population density served by the maternity hospital implied that most patients lived within a reasonable distance of the University Hospital, situated in the north eastern section of the corporate area, where the Medical Research Council Laboratories and Clinic were located. Medical, nursing and technical staff were provided by the Medical Research Council for the supervision of all the sickle cell clinics and the resources of the University Hospital were freely available. Communications throughout Jamaica were generally good, permitting follow up of patients who moved away from the city and the relative lack of primary care facilities in the area served to encourage clinic attendance.

PLAN OF THE COHORT STUDY

1. CORD BLOOD COLLECTION :

The majority of women delivered at Victoria Jubilee Hospital present for the first time in labour having received little or no antenatal care. At the time of admission to the labour ward, a special record card was completed with information about the mother (name, age, address, hospital no.) and retained with her clinical notes. At delivery, 2-10 ml of cord blood was collected in a 10ml plastic tube containing lithium heparin. Consecutively numbered, duplicate self-adhesive labels were attached to both the specimen and the mother's record card. Each day a technician from the Medical Research Council Laboratories collected the samples and record cards. The samples received were checked against the number of deliveries recorded and a capillary sample was obtained by heel prick, collected into a small tube with oxalate or dry heparin, from any infant inadvertently omitted. Daily collection of samples was required because of the short duration of mothers' hospitalisation (often less than 24 hours) and the need to contact the mother before discharge if the child was selected for follow up. Between 35-40 samples were collected and screened daily, representing 95% of all non-operative deliveries.

2. DIAGNOSTIC PROCEDURES

As beta chain synthesis accounts for only a small percentage of the total globin chain synthesis at birth, sickle haemoglobin was present only in relatively small amounts in cord blood. Identification of the genotype required a technique capable of detecting small amounts of HbA to distinguish sickle cell trait from homozygous sickle cell disease. Traditional sickling and solubility tests were of little value and although standard techniques of paper electrophoresis could readily demonstrate HbS, they did not give clear separation of HbA from HbF. Agar gel electrophoresis gave good separation of HbA and HbS in the presence of HbF, but would not permit recognition of other

variant haemoglobins with similar mobilities to HbA and HbS. In 1973, Schneider (46) developed an alkali buffer system which would separate Hbs A, F and S on cellulose acetate. Small amounts of HbA, indicative of $S\beta^+$ thalassaemia may still be indistinguishable from the sickle cell trait and other variant haemoglobins may be unrecognised, running in the position of Hbs S and C. Nevertheless, this method provided a technique for preliminary screening after which all samples with abnormal bands could be checked by further electrophoresis on agar gel (47).

(i) Electrophoresis on cellulose acetate

Haemolysates were made by adding one drop of whole blood to 0.5 ml EDTA (tetrasodium ethylene-diamine tetracetate) 10 mg/dl (including KCN 82 mg/dl, to prevent formation of methemoglobin during electrophoresis). Haemolysate strengths were matched visually to give a concentration of approximately 0.25 g Hb/dl, which allowed the major bands to separate without the loss of minor bands such as HbA_2 and Hb Barts. A cellulose acetate membrane was prepared by floating a sheet on the surface of a Tris-EDTA-Borate buffer (pH 8.4) until permeated (to prevent air trapping) before submerging it in the buffer. After soaking, the membrane was blotted and placed with its long axis on a non-absorbable surface (a piece of parafilm). Using a 16-tooth multiple applicator, haemolysates (14 unknowns with an AFS control at each end) were applied to the cathodal side of the membrane. The parafilm reduced loss of haemolysate by preventing absorption into the blotter. The membrane was transferred to a horizontal electrophoresis tank containing 500 ml of the same buffer. A voltage of 350 v was applied for 20 minutes. Curving of the electrophoretic run was prevented by placing a strip of buffer soaked cellulose acetate adjacent to, but not touching, each end of the membrane. The membrane was fixed in 5% trichloracetic acid for 3 minutes, washed three times in 5% acetic acid for 2 minutes each and then stained with benzidine. When all bands were visible the membrane was washed three times with

distilled water and the results read when wet. The sheet was dried before mounting as a permanent record.

(ii) Agar gel electrophoresis

All blood samples showing abnormal haemoglobins, other than Hb Barts, were selected for agar gel electrophoresis. Haemolysates were made as before but strengthened to give an approximate Hb concentration of 3-4 g/dl, and were kept refrigerated until the agar gel electrophoresis was performed. The method used was a modification of that of Metters et al (48). The agar gel was prepared by boiling 0.5 g agar in 50 mls buffer (pH 6.0) until clear, then pouring onto a level, warm glass plate, subsequently stored refrigerated and wrapped in plastic film until used, when it was warmed to room temperature. A horizontal electrophoresis tank was filled with 500 ml citrate buffer pH 6.0 and refrigerated at $4^{\circ}C$. Wicks (1mm x 4mm pieces of Whatman's No. 3 chromatography paper) were dipped into the prepared haemolysates and placed on the surface of the agar plate approximately 1 cm apart, in lines 5 cm apart. After 20 minutes, the wicks were removed with care to ensure no break in the surface of the agar, and the plate placed in the refrigerated electrophoresis tank, with filter paper strips along the edge. A constant current of 50 mA was applied for 60 minutes after which the plate was removed, placed in a shallow tray and the gel fixed in acid methanol for 10 minutes before washing and staining with benzidine. The plate was washed twice with acidified distilled water and left in a third wash overnight. After a final wash, the gel was eased off the plate onto a piece of thin card (previously soaked in acidified water) and slowly dried at room temperature, allowing preservation for a permanent record.

(iii) Diagnostic Criteria

The accuracy of these diagnostic methods has been confirmed by the close agreement between the numbers of different genotypes observed, with the numbers expected from calculations based on gene frequency in the population

(47). The techniques did not however permit detection of the traits for β thalassaemia or hereditary persistence of foetal haemoglobin. The heterozygous condition of sickle cell-β^+ thalassaemia (HbA containing S-thalassaemia) was suggested by the presence of a strong band of HbS and a weak band of HbA, the weak band of HbA frequently best demonstrated on agar gel, whereas the sickle cell trait presented a balanced appearance of Hbs A and S. Sickle cell-β^o thalassaemia (non HbA containing) and heterozygosity for sickle cell and hereditary persistence of foetal haemoglobin (S-HPFH) were indistinguishable from homozygous (SS) disease at birth. Wherever possible the blood of both parents was examined, but family studies were often incomplete or inconclusive. Fathers were reluctant to attend clinic and there was a high incidence of wrong paternity, almost 20% of the fathers tested showing AA genotype. In the absence of a definitive diagnosis by family studies at birth, the diagnosis became apparent from the evolution of haematology over the first year of life. Infants with $S\beta^o$ thalassaemia had higher HbA_2 levels and lower MCV values at one year, and, while the HbF level in infants with SHPFH was often not clearly elevated beyond the range of that seen in SS disease, the degree of haematological severity (evidenced by high total Hb levels and low reticulocyte counts) was much less (45). Electrophoresis on both cellulose acetate and agar gel was repeated routinely on all affected children at the age of 1 year, and at other times when indicated.

Cord blood screening commenced in July 1973 and by May 1980 84,000 infants had been screened, with the diagnosis of 265 cases of homozygous sickle cell (SS) disease, 161 cases of sickle cell-haemoglobin C (SC) disease, 38 confirmed cases of sickle cell-β thalassaemia and 4 confirmed cases of sickle cell-hereditary persistence of foetal haemoglobin (S-HPFH).

3. SELECTION OF COHORTS

When the electrophoretic pattern was compatible with SS disease, the affected infant and the two other infants with normal AA genotype, of the

same sex and born on the same day nearest in time to the affected infant, were admitted to the study. The mothers of all three infants were visited in hospital by the technician collecting the next day's specimens, given a brief explanation of the study and an early appointment to attend special clinics run by medical staff from the MRC Laboratories at the University Hospital in Kingston. These three babies, one SS and two AA, formed the nucleus of each 'cohort' to which was also added any child with other forms of sickle cell disease until the next SS infant was diagnosed and a new cohort formed. After the formation of 125 cohorts with the recruitment of approximately 250 normal controls, collection of AA infants was discontinued but children with all forms of sickle cell disease continued to be entered into the study : each new SS marking the formation of a new cohort, as before.

Any mothers who had already been discharged from hospital before notification of the study or who failed to keep their appointment, were visited at home by a field work assistant and asked to attend.

4. FOLLOW-UP PROCEDURE

At the first visit, the baby's genotype and the reason for further visits was explained to the mother. Relevant family and social data were recorded, the baby was examined by the doctor and weight, length and head circumference recorded. At the start of the study, two frequencies of follow up were used in an attempt to detect any effect of intensive medical observation on the course of the disease. Alternative cohorts (each comprising one SS infant and two AA controls) were seen monthly until six months, at two monthly intervals to one year and three monthly thereafter, whereas other cohorts were seen only six monthly. It became clear that the mothers of infants in the six monthly group were attending almost as frequently, seeking advice for intercurrent illness or for immunization. A mortality rate of 13% by age two years in the whole group (41) reinforced the need for early and frequent follow up. The differential frequency of follow

up was discontinued in January 1976 when 125 cohorts (and the control population) had been collected. All subsequent infants were followed according to the schedule of routine visits shown in Table 3.1. Regular attempts were made to detect and trace patients who defaulted and mothers were strongly encouraged to attend at any time if the child became sick.

Unless clinically indicated, haematological investigations were performed on heel/finger prick samples until the age of 1 year when a venepuncture was performed. This was repeated annually with capillary samples at the intervening visits to the age of 5 years when the frequency of blood sampling was reduced.

The clinic provided a routine service from 8:30 am - 4:30 pm from Monday to Friday and from 8:30 am - 10:30 am on Saturdays. Initially no arrangements were made for out of hours consultation but subsequently the home telephone numbers of the medical staff were issued both to the patients and to the Casualty Department at the University Hospital. This facility was rarely abused and often resulted in appropriate intervention at critical times. At the start of the study, some mothers chose to attend their local clinic or the government Children's Hospital when the child became ill, particularly at nights and weekends. With time, increasing acceptance of the MRC clinic and deterioration of the local health clinic service made this practice rare. The greater part of all reported sickness in this population was observed and treated in the sickle cell clinic. Information about attendance at other hospitals was sought and documented from their medical records.

TABLE 3.1 SCHEDULE OF ROUTINE VISITS

Age	Blood test	Other procedures
First visit	FP	
1 month		
2 months		
3 "	FP	1st DPT and OPV vaccination
4 "		
5 "		2nd DPT and OPV vaccination
6 "	FP	
8 "	FP	3rd DPT and OPV vaccination
10 "	FP	
12 "	VP	Measles vaccination
15 "	FP	
18 "	FP	4th DPT and OPV vaccination
1½ - 5 years	Attendance every 3 months with FP at each visit and VP annually	Booster DT & OPV vaccination
Over 5 years	AA: Attendance every 6 months with VP annually. SS: Attendance every 3 months with FP 6 monthly and VP annually.	

FP = capillary blood specimen by finger (or heel) prick
VP = venous blood specimen by venepuncture.

CLINICAL ASPECTS OF DATA COLLECTION

The importance of prospective follow up after diagnosis at birth in elucidating the natural history of SS disease has been emphasised, and the diagnostic criteria and follow-up schedule have been described in the previous chapter. The procedure followed at each visit to clinic was the same for cases and controls.

1. ROUTINE VISITS :

All children were weighed and measured on arrival. Weights were taken with the children in light clothing without shoes, either on a baby scale read as pounds and ounces accurate to ½ oz, or, when old enough to stand, on a sliding beam scale read as Kilograms accurate to 50g. Weights recorded as pounds and ounces were automatically converted to kilograms during computerisation of the data base. Height was measured as supine length on a supine stadiometer until the child was able to cooperate for standing height measurement on a standing stadiometer; both were accurate to 1 mm. Occipito-frontal circumference (OFC) was recorded with a fibreglass tape. Measurement of OFC was made by the doctor during examination while measurements of height and weight were recorded by the clinic nurse. Weight and height were plotted against local standards (49) and a locally constructed weight for height chart was available for monitoring nutritional status (Tropical Metabolism Research Unit, University of the West Indies).

Every child was seen by a doctor at each visit. The clinics were staffed by Medical Research Council medical staff, usually a specialist paediatrician, and all medical staff had had previous paediatric experience. Most children were brought to clinic by their mothers, more rarely by fathers and on occasion by older siblings. Particular importance was attached to questions about the child's health since his last clinic attendance (especially inquiring if medical advice had been sought from any other clinic or practitioner) and to his current health. A brief physical examination was performed

on each occasion and for the SS children particular emphasis was placed on examination for pallor, jaundice and splenomegaly with inspection of the hands, feet and long bones for signs of local bone infarction. Spleen size was accurately recorded in centimetres along the long axis from the left costal margin to the tip. The presence or absence of a systolic murmur and cardiomegaly was noted at each visit. Physical examination was otherwise directed at evaluation of current symptoms.

Blood tests were performed routinely according to schedule (Chapter 5) or if otherwise clinically indicated.

2. OTHER VISITS :

The policy of the clinic was not only one of prospective observation at pre-determined intervals but also to encourage mothers to bring their children for attention whenever they became ill. Such visits were precipitated either by the occurrence of minor illness, such as scabies or mild diarrhoea, or by significant events such as acute splenic sequestration, pneumonia or meningitis. Many, but not all, were weighed and measured at these visits but blood tests were performed only if indicated. Examination was directed at the reported symptoms but spleen size was noted in all SS children at every visit in view of the value of a record of changing size in assessing anaemic crises.

3. FACILITIES FOR INVESTIGATION & TREATMENT

The clinic provided a full haematology service except for blood transfusion. A biochemistry, microbiology and radiology service was available in the University Hospital where the clinic was sited and at which all sickle cell patients in the cohort study were registered.

Blood transfusion services in Jamaica relied on patients providing donors for all routine transfusion requirements but blood for emergency transfusion was usually available without difficulty.

The department of microbiology provided routine bacterial and viral detection services. Additional requirements, such as typing of pneumococcal

isolates and certain immunological procedures were met by special arrangement. Blood cultures were taken frequently during febrile illness in SS patients.

The department of radiology provided a routine Xray service. At times this was limited, not only by power cuts, but also by shortage of film and chemicals, and a four hour wait for a chest X-ray, even in the absence of such problems, was not uncommon. X-rays were requested only when it was felt that their result would substantially affect the choice of treatment.

Drugs were available on prescription within the hospital without charge to both inpatients and outpatients. The economic difficulties of the country and the overuse of hospital services as a result of diminishing primary health care facilities, often resulted in excessive demand on unreliable supplies. The Medical Research Council therefore provided funding for a limited stock of essential drugs to be dispensed from the clinic, together with other stock items obtained from the hospital pharmacy. The drug stock included oral and injectable antibiotics, paracetamol, antihistamines, cough syrups, iron and folate preparations, antibiotic eye and ear drops, antihelminthics, simple dermatological preparations and a small amount of narcotic analgesics. It was common for mothers to request 'tonics' for their children and although vitamin drops were available in the clinic for the youngest children, brands containing no iron were recommended for mothers who wished, and could afford to buy them. Folic acid supplements were not given routinely to the SS children and a trial of the benefits of folate supplementation was in progress.

The department of child health at the University Hospital ran specialist clinics in paediatric cardiology and neurology and the services of the orthopaedic, dental, dermatology, ENT and ophthalmology departments were available. Referals of SS children were often given priority.

A full immunisation programme was implemented by the clinic giving Diphtheria, Pertussis and Tetanus triple vaccine (DPT) with oral polio vaccine (OPV) at 3, 5, 8, and 18 months with a booster Diptheria and Tetanus (DT) and

OPV at 5 years. Measles vaccine was given at one year and the effectiveness of the antibody response was shown to be as good in SS children as in the controls (Ramlal A. - unpublished observations). BCG vaccination was offered at birth but the early discharge of most babies resulted in many omissions.

4. EDUCATION

At every opportunity clinic staff attempted to reinforce the genetic implications of the diagnosis of sickle cell disease. This was outlined at the first clinic visit and a leaflet, especially written by the clinic staff, was issued to the families of all new patients and other interested parties. The low literacy rate in the population from which the patients came may have reduced the value of these leaflets in some families but the extended family network and communal living style of urban Kingston probably dispersed them more widely. The high degree of impaternity, with as many as 20% of putative fathers showing absence of the sickle gene, further complicated the genetic message. Fathers were notoriously reluctant to attend clinic, to discuss the diagnosis or to have their own genotype checked. The 'absent father' syndrome is well described in Jamaican society where only 25-30% of children are born inside a legal marriage union. Many families may however have stable parental relationships, either as 'visiting' or 'common-law' unions but unstable family patterns are more common in the urban poor, which this population represented (50).

Family planning advice was offered routinely, often with disappointing results. In addition to local government clinics, the gynaecology department at the University Hospital operated family planning clinics to which mothers could be referred.

Nutrition and feeding advice was offered to all mothers, particularly those with children under two years old. Breast feeding was encouraged and the use of supplementary milk feeds and herbal teas actively discouraged. Weaning was not advised before four months, although it often occurred earlier

(51) and the use of cheap, locally available weaning foods was promoted. A series of nutrition education leaflets prepared by the Ministry of Health were available for free distribution.

The importance of early attention to intercurrent illness was stressed to the mothers of SS children. The relevance of critical signs such as pallor and increasing splenomegaly was taught to those mothers whose children seemed particularly at risk of episodes of acute splenic sequestration (52) and the success of this approach was illustrated by timely intervention in several episodes. The management of recurrent episodes of mild dactylitis or painful crisis at home was encouraged with the use of high fluid intake and paracetamol. Alertness to signs of dehydration was taught to mothers of children with apparently mild gastroenteritis.

5. INPATIENT TREATMENT :

There were no beds available for the exclusive use of the sickle cell clinic. Children requiring inpatient treatment were admitted to the paediatric wards of the University Hospital under the care of the Department of Child Health. There was close cooperation between the clinic medical staff and the paediatric residents in supervising treatment. Data from the hospital notes was recorded after all admissions and coded into the computer data base. When it was found that children had been admitted to hospitals other than the University Hospital, details of the diagnosis and treatment were sought and recorded retrospectively.

Children with sickle cell disease formed the largest single diagnostic group of admissions to the University Hospital paediatric wards (Harland P.S.E.G. 1980, personal communication). Details of admissions to all hospitals for the SS and AA children in the first 125 cohorts from the start of the study to January 1980 are shown in Tables 4.1 and 4.2. The high frequency of admission in the SS group reflects not only the severity of the disease but also a greater reluctance to manage these children on an outpatient

TABLE 4.1

Cohorts 1 - 125 : Hospital admissions July 1973 - January 1980

No. of admissions	No. of Children SS	AA
0	41	211
1	29	31
2	18	7
3	6	1
4+	14	0
TOTAL	108*	250

*The discrepancy with the number of cohorts is explained by the subsequent diagnosis of Sβ thalassaemia or SHPFH in children diagnosed as having SS disease at birth.

TABLE 4.2

Cohorts 1 - 125 : Causes of hospital admission July 1973 - January 1980

Diagnosis	No. of episodes * SS	AA
Pneumonia	48	9
Gastroenteritis	22	20
Dactylitis/painful crisis	21	-
Acute splenic sequestration	21	-
Otitis media/URTI	14	4
Aplastic crisis	11	-
Septicaemia	10	-
Measles	9	2
Bacterial meningitis	7	-
Splenectomy	4	-
Malnutrition	4	3
Viral meningitis/encephalitis	2	1
Osteomyelitis	1	-
Cerebral infarction	1	-
Febrile convulsion	1	3
Unknown	3	-
Other	21	15

*many children had more than one diagnosis per admission

basis. Owing to the high demand for beds many episodes of serious illness were managed by daily clinic visits for treatment and reassessment. Admission for dactylitis and painful crisis, and indeed for pneumonia, was uncommon in the absence of complications. The diagnoses given in Table 4.2 are the final diagnoses at discharge and reflect the impact of SS disease on health in early childhood. Many children had more than one diagnosis at each admission.

6. DEFAULTING PATIENTS

Although appointment cards were issued at each visit, many patients failed to attend their next appointment but would subsequently appear spontaneously within a short period. A daily comparison of those attending against those expected in clinic did not provide a practical way of checking attendance and all patients records were periodically reviewed to identify children who had missed appointments. Defaulting patients were visited at home either by a field work assistant or by one of the medical staff. Further contacts were obtained for patients who had moved to another address and it was clinic policy to record the addresses of several close relatives for each family. The deteriorating social conditions and escalating violence found in the Kingston ghettos sometimes interfered with efforts to trace patients, particularly in 1976 and 1980, years of general elections. Attempts to contact patients by letter or telegram were made if home visiting was impractical. The provision of two clinics at the western end of the island (Black River Hospital, St. Elizabeth and Cornwall Regional Hospital, Montego Bay) which were visited regularly by members of clinic staff, gave an opportunity for the review of children whose families had moved to those areas, away from Kingston.

In January 1980, 3% of SS children and 10% of AA children had not been seen for at least one year due to default, although they were thought to be alive and contact addresses were still available, some living in remote country areas. A further 3% of SS children and 18% of AA children had been

recorded as lost to follow up, either through emigration or through lack of further address contacts. A further intensive effort at follow up in 1981/82 resulted in reestablished contacts with many of these children.

HAEMATOLOGY TECHNIQUES

1. BLOOD SAMPLE FREQUENCY :

(i) First year of life : Sampling frequency in the first twelve months was the same for cases and controls but the schedule varied during the study. For the first 125 cohorts a capillary sample was taken within 48 hours of birth and again at each attendance, with a venepuncture at one year. For subsequent cohorts, blood sampling was reduced with collection of capillary specimens at first attendance in the clinic (age 5 - 10 days) and then at 3, 6, 8, and 10 months, with venepuncture at one year.

(ii) Age 15 months - 5 years : Venepuncture was performed at yearly intervals with the collection of capillary samples at the intervening three monthly visits. The same schedule was followed throughout the study and was the same for cases and controls.

(iii) Age over 5 years : Blood samples were restricted to annual venepunctures in all children, with additional capillary specimens at intervening six monthly visits in the SS children.

Additional samples were obtained at other times, either by venepuncture or finger prick, if clinically indicated. This was rare in the AA children.

2. METHODS :

Several methods were modified for use with the small volume of capillary samples. Satisfactory correlation with venous samples has been reported (53).

1) Packed Cell Volume (PCV) : a heparinised micro-capillary tube was twothirds filled, flame sealed at one end and the PCV was measured as the micro-haematocrit after centrifuging at 12000 g for 5 minutes.

2) Haemoglobin and red cell indices : Haemoglobin (Hb), red cell count (RBC), and mean cell volume (MCV) were measured in an electronic

counter (Coulter ZBI 6, Coulter Electronics, Hialeah, Florida) calibrated regularly with a commercial control (4C control, Coulter Electronics). The initial dilution was made using 20µl whole blood flushed into a plastic container with 10 ml Isoton (Coulter Electronics). The mean cell haemoglobin concentration (MCHC) was calculated from the Hb and PCV and the mean cell haemoglobin from the Hb and RBC. Blood films were made for red cell morphology and differential white blood count (WBC).

3) Total nucleated cell count (TNCC) & Nucleated red cell count (NRBC) :

TNCC was measured on the Coulter Counter in the original dilution after haemolysis of red cell with Zappoglobin (Coulter Electronics). NRBC was derived from the TNCC and WBC.

4) Reticulocytes : One drop of whole blood was incubated at $37^{o}C$ for thirty minutes with one drop of brilliant cresyl blue. Counts were expressed as percentage reticulocytes per 500 RBC.

5) Platelets : Platelets were measured on venepuncture specimens using an electronic cell counter (Thrombocounter, Coulter Electronics).

6) Bilirubin : Two methods were used.

(i) Capillary specimens : The plasma of all micro-haematocrits was inspected and any with a hint of colour were placed in the cuvette and read in an optical bilirubinometer (American Optical Corporation). Distilled water was used as the low standard and a special filter supplied by the manufacturer as the high standard.

(ii) Venepuncture specimens : Samples were measured according to the method of Lathe and Ruthven (54). The serum was protected from light and frozen until tested in batches. Commercially available standards (versatol, Warner Diagnostics) were used for each batch.

7) Serum iron and Iron binding capacity : These were measured according to the methods of Beale et al (55).

8) Serum folate concentration : This was measured with an automated

microbiological assay using a chloramphenicol resistant strain of lactobacillus casei, as described by Millbank et al (56).

9) Quantification of HbA_2 & HbF : (i) Venepuncture samples : Standard haemolysates were made from whole blood and used for assessment of HbA_2 (57) and of HbF (58). (ii) Capillary samples : a micro-method for quantitation of HbF based on the method of Singer (59) was established for this study (60).

All data were entered on computer files, incorporating patient identification and date of test (Chapter 6). Data from the control and SS populations have recently been published (61, 62).

Chapter 6

DATA HANDLING & COMPUTING

1. CODING TECHNIQUE AND COMPUTER FACILITIES

A record of every clinic visit, hospital admission and blood test was coded for entry into the computerised data base. The information entered at each entry was preceded by patient identification (incorporating name and genotype) and the date of the visit or test. Although the child's name was recorded in each case, data were listed under mothers' names in order to prevent confusion - many children were not named at their first visit to the clinic and the majority were born outside a legal marriage union but were registered in their fathers' name, hence having a different surname from their mothers. In addition, it was not uncommon for women to have children by two or more fathers.

All information was coded by hand onto ruled sheets of paper, the haematology and clinical data being recorded separately, and the coded information was transferred to punched cards for entry into the data base on an IBM 370/138 computer at the University of the West Indies Computer Centre. Updating of the master file was performed at three monthly intervals when new data and corrections to the existing data were sorted and merged with the existing data base to produce a new master file. Information was maintained on discs and archive tapes held at both the University Computing Centre and the London School of Hygiene and Tropical Medicine. The combined haematology and clinical data for each patient were arranged chronologically and a printout, sorted alphabetically according to genotype, was produced with every update. The computer calculated and printed the child's age at each visit from the date and the date of birth.

These records, together with the patient's clinical notes, allowed review of recent and previous events required at clinic visits and for research purposes. Data extraction and statistical analysis was performed

on the data base either in Kingston or in London, but in order to fulfil the increasing demands on data processing a Burroughs 1815 computer was purchased in 1980 for use at the Medical Research Council Laboratories. This was to be linked to a printer and three visual display units, facilitating immediate update and recall of data in both clinic and laboratories.

2. CLINICAL INFORMATION CODING

The format used for coding of clinical information utilised a sequence of codes represented by a letter and/or a number, to record data under the following headings:

i) height, weight and head circumference values

ii) the presence or absence of cardiovascular changes

iii) palpable spleen size

iv) the nature of the visit - whether attendance was routine, if the visit was precipitated by illness or if the entry referred to birth data or hospital admission

v) treatment given - this entry only broadly differentiated between no treatment, symptomatic therapy only or the use of antibiotics, but coding was specifically allocated for the use of iron and folate supplements

vi) space was allocated for the record of up to six concurrent diagnoses and any radiological, bacteriological or special haematological investigations performed

vii) the final column recorded immunisations given

The data from clinic visits was coded daily and that relating to hospital

admission entered after review of inpatient records at discharge. The sheets were checked for errors before being submitted in batches for card punching.

3. HAEMATOLOGY DATA CODING

The first line entry for each child recorded the reference number of the agar gel electrophoresis on which diagnosis had been confirmed, together with the reference number allocated to the cord blood sample collected at delivery. Haematological results from parents and other relatives, and their genotypes were recorded at the start of each child's entry, thereafter the results of every blood test taken from the child were listed chronologically. The following information was recorded sequentially : % HbA_2 : % HbF (both by the Betke method and the micromethod) : Hb : PCV : MCHC : RBC : MCV : MCH : Reticulocytes : Platelets : NRBC : Red cell morphology : Pitted red cell count : bilirubin (direct and total) : serum iron, binding capacity and % saturation : serum folate. Values for all these indices were not available for every sample, the full range being performed only on venepuncture specimens. In the analysis of haematological data, special arrangements were made for the identification of all results obtained within two months of blood transfusion.

GROWTH IN HOMOZYGOUS SICKLE CELL DISEASE : HISTORICAL ASPECTS

1. THE HABITUS OF ADULT PATIENTS :

The habitus of adults with sickle cell disease was first discussed in detail by Windsor and Burch (63, 64), although some of the features had been noted previously (65, 66). In a mixed study of adults, adolescents and children based on clinical observations, anthropometric measurements and X-ray and photographic data, they concluded that a characteristic habitus was present in patients with 'severe active disease of long duration'. In adults, this was exemplified by a slender build, patients appearing tall although not necessarily of above average height. Shoulders and hips were narrow, necks short and the normal spinal curvature accentuated. The trunk was short and the chest deep and narrow. Limbs were long and the fingers 'spider-like'. Genital hypoplasia, scanty body hair and a high pitched voice suggested hypogonadism. The patients exhibited a 'general appearance of fragility'. While they recognised that some of these anthropometric features were characteristic of normal american blacks, compared to american whites, their conclusions were validated by the use of age and sex matched black controls. The resemblance of adult patients to the eunuchoid habitus was also noted by Sharp and von der Heide (67).

These data were based on small numbers of observations and no new studies on adults were reported until 1972 when Ashcroft and Serjeant (68) described similar results from a study of 121 Jamaican patients with SS disease, all over 20 years of age. A group of 119 control patients from the general medical outpatient clinic, although not individually matched for age and sex, showed similar mean ages and sex distribution, and were selected to exclude conditions which might be associated with unusual anthropometric measurement. Patients with sickle cell disease were taller and thinner than the controls. Although standing height was only slightly

greater in SS subjects, sitting height was significantly less, and leg length was therefore longer. Arm length was greater although arm span was less, as the inter-acromial distance was less. Chest diameter was increased anteroposteriorly giving a barrel or hoop shape. Weight, triceps skinfold thickness and mid-upper arm circumference were all reduced, supporting their clinical observation that obesity in SS patients is rare. However the authors stressed that, although these changes were characteristic, in many patients habitus was normal.

2. GROWTH IN ADOLESCENCE :

Several studies involving adolescents had been reported prior to Ashcroft and Serjeant's data on adult sickle cell patients, and all suggested, perhaps paradoxically, that height was shorter than average. Winsor and Burch's original study included two adolescent boys who showed subnormal weight and height. Whitten (69) included five children over the age of 12 years in his review of 48 children with SS disease. The whole group was shorter and lighter compared with standards for normal caucasian children, a comparison which was not appropriate. Jimenez (70) drew similar conclusions in a study of 38 children, 19 of them over 12 years, compared with black controls.

Ashcroft, Serjeant and Desai (71) reported data in 1972 on a group of 99 Jamaican adolescents (aged 12-21 years) with SS disease, compared with valid local standards. Weight, both in comparison to height and to age, was reduced throughout puberty, but while height was less than average in the younger patients, it tended to increase towards that of the controls with increasing age. This data was cross-sectional and it therefore could not be assumed that the younger children would necessarily develop the physique of the older children, although there was no reason to suppose that the method of patient selection had led to bias. In the light of

their previous findings of increased height in adult SS patients from the same population, they concluded that increase in stature during adolescence was probably greater than average - a feature which might be associated with delay in skeletal maturation.

Two other studies involving adolescents have been reported subsequently. Olambiwonnu (72) studying sexual maturity in SS disease showed that 10/13 boys and 8/13 girls aged 11-16 years had heights and weights below 1 S.D. from the mean for age. McCormack (73) reported that heights and weights were below that of controls in 46 children aged up to 17 years. The median age for this group was 8.5 years and very few patients were over 15 years of age, which would explain why they were unable to demonstrate any trend for height to approach normal with increasing age, as suggested in the Jamaican data. The same criticism also applies to the age range studied by Olambiwonnu. In addition, McCormack's data claimed that weight and height were nearer normal when compared to skeletal rather than chronological age, but the effect was not quantitated.

3. PRE-ADOLESCENT GROWTH :

There have been several reports of growth in younger children with SS disease but the results are conflicting and many studies have involved small numbers of children at different ages making comparisons difficult. The study by Winsor and Burch (63) included 7 children aged 6-12 years. Weight was normal in both boys and girls while height was subnormal only in girls. The study also included anthropometric assessment which revealed consistent shortening of the trunk and increased A-P diameter of the chest, giving the hoop-chested appearance noted in adults. Limb length was longer in boys but not in girls.

Scott (74) reported that the weights of 63 children aged from 3 months to 15 years was consistently below the median for normal children of the same age and commented that many showed "small spindly extremities,

protruberant abdomen, lordosis and poor general nutrition".

Whitten (69) presented the first attempt to quantify the effect of the disease on growth in childhood. He studied 48 children aged 2-13 years, using their siblings as controls. Height and weight were both significantly less in the affected children. Using the Harvard standards (75) he attempted to quantify the effect and showed that the mean percentile for height was 25.5 and for weight 17.1 in the affected children, compared with 39.7 and 41.4 in the controls. Weight was therefore more severely impaired than height and this observation was in agreement with his clinical assessment of body shape, 50% of the children being rated as thin or extremely thin.

Booker, Scott and Ferguson (76) reported a study of 18 infants who were diagnosed and followed during the first two years of life. This is one of the few reports dealing with growth in very young children and they were able to detect weight retardation by the age of six months, the deficit increasing to 2 S.D.'s below the mean of a normal population by the age of 2 years. Height was not measured.

Approximately half of the patients in the study by Jimenez (70) were pre-adolescent, although none were less than 8 years old. Height, weight, arm span and upper:lower body segment ratio were all reduced although the differences were not quantified.

In the first report of growth in Jamaican children (77) data derived from 100 SS children aged 1-12 years was presented semilongitudinally and compared with established local standards. The results suggested that normal height was maintained throughout and that weight tended to fall away after 6 years in boys and after 8 years in girls. The children studied were well distributed throughout the age range and over 30% were aged 5 years or less. This study may be criticised for the use of single measurements in some children and sequential measurements in others as the

characteristics of the children measured more frequently may have biased the results in their direction.

McCormack (73) published growth data on 46 SS children aged 3-17 years from Philadelphia, as part of a study to compare growth potential between AA, AS and SS genotypes. Height, weight, sitting height, upper arm and calf circumferences were all significantly less in both SS boys and SS girls. Triceps skinfold thickness was reduced only in boys. An assessment of body build, using height-$\log_{10}$ weight indices, confirmed their clinical observations of slenderness. These results were compared to those of Whitten (69) and noted to be of the same order.

A further study was reported from Jamaica (78) using cross-sectional data from 99 children aged 2-13 years who were each measured once by a single observer. Established local standards were used for comparison. Mean weights for both sexes were below those of the standards at all ages but the differences were significant only after age 10 years. There was no significant difference in mean height at any age for either sex. The clinic that these children attended undertook regular routine review of all patients and many had been asymptomatic at diagnosis, detected by family studies. It was possible that the clinical severity of the disease was less in this group than in other populations selected on a symptomatic basis.

In the only reported study of growth performance in African children with sickle cell disease, Lesi (79), from Nigeria, concluded that children aged 1-10 years of higher socioeconomic background showed near normal height but poor weight when compared to the Boston 50th centile. Quoting previous workers, he stated that the growth potential of African children of high socioeconomic background was identical to that of caucasian children from developed countries. The effect of sickle cell disease would therefore appear to be predominantly on poor weight gain. Children of

lower socioeconomic status grew less well but also showed a greater deficit in weight than in height. All affected children showed small mid-upper arm circumference compared with data from normal Nigerian children. It is unfortunate that local standards were not available for comparison with the height and weight data.

A recent review of pre-pubertal growth based on work from New Haven where a cord blood screening programme commenced in 1972, was reported by Kramer in 1980 (80). The growth performance of 11 children with SS disease aged 3-6 years, who had been followed prospectively since birth, was assessed. Eleven control children, of normal (AA) genotype, were appropriately matched for age, sex and socio-economic class. Significant impairment of height, weight and skinfold thickness was noted in the affected children, the differences appearing to increase with age. Analysis of growth in infancy suggested that these differences emerged after age six months, but it was not clear if these earlier observations were based on prospective studies in the same clinic. The small number of patients, all studied at different ages, precluded attempts to quantify the severity of growth impairment with increasing age. The predominance of girls in the study group restricted observation of male : female differences.

The most recent published work giving data on the growth performance of SS children came from Birmingham (81). This was the first report describing the natural history of the disease as seen in the United Kingdom. Thirty five children with SS disease were included in a review of 96 children with various sickle haemoglobinopathies. Wide individual variation in height was observed but a significant minority had heights greater than two standard deviations below the mean for the Tanner and Whitehouse U.K. Standards (82), the deviation appearing to increase with age. Weight was reduced to a greater extent, confirming an impression of slender build. The standards used for comparison were of course based on data from white children, but the finding of near

TABLE 7.1

Authors	Year	Country	Nos. & Ages studies		Major Conclusions
1. Winsor & Burch	1944	USA	7	6-12 yr	Subnormal height in girls
2. Scott	1955	USA	63	3/12-15 yr	Subnormal weight
3. Whitten	1961	USA	48	2-13 yr	Subnormal height and weight
4. Booker	1964	USA	18	0-2 yr	Subnormal weight
5. Jimenez	1966	USA	38	0-17 yr	Subnormal height and weight
6. Gray	1971	Jam.	100	1-12 yr	Subnormal weight
7. McCormack	1976	USA	46	3-17 yr	Subnormal height and weight
8. Lowry	1977	Jam.	99	2-13 yr	Subnormal weight
9. Pearson	1978	USA	34	Newborns	Normal birth weights
10. Lesi	1979	Nigeria	268	1-10 yr	Subnormal weight, near normal height
11. Kramer	1980	USA	11 14	3-6 yrs Newborns	Normal birth weight & length. Subsequently subnormal weight, heigh & skinfold thickness.
12. Mann	1981	U.K.	35	3/12-19 yr	Variable reduction in height and weight.

normal growth in the patients with SC and S thalassaemia disease suggested that these observations were pathological and not ethnic.

There are only two reports which discuss the birth weight of affected children (80, 83). Both report it to be normal.

A summary of these reports on preadolescent growth is shown in Table 7.1.

4. SEXUAL DEVELOPMENT

The earliest reference to sexual development in sickle cell disease was by Anderson and Ware (84) who noted infantile genitalia in 26% of a series of patients aged over 10 years.

Jimenez (70) first reported delay in age of menarche in a group of girls with SS disease. Their mean age at menarche was 13.9 (range 9-19 years) compared with 12.2 years (range 11-17 years) in Black American controls. They also demonstrated delayed development of secondary sexual characteristics in both boys and girls. Delay in secondary sexual development was confirmed by Olambiwonnu (72).

Delay in age of menarche in Jamaican patients was recorded by Serjeant in 1971, the mean age being 15.9 (range 12-22 years) compared with 14.9 years (range 10-20 years) in a population attending antenatal clinics. These findings and an additional report of delay in time of first pregnancy, which can only be in part explained by delay in menarche, have recently been confirmed (85).

The average age of menarche in the small group of SS children reviewed by Mann (81) in Birmingham was reported as 15 years. Two girls had not achieved menarche at ages 16.3 and 17.1 years. Data for age at menarche in normal black girls in Britain is not available but these figures are outside the ranges quoted for both European whites and Africans of good socio-economic status (86).

5. SKELETAL DEVELOPMENT

The first reference to bone age assessment is again found in the original work by Winsor and Burch (63). They simply stated that "bone ages were studied in five patients (two were adults) and all were found to be within normal limits".

Whitten (69) reported skeletal age determination in 30 children, scored by the Greulich and Pyle system (87) on X-rays of their left wrists. Seven children, of whom six were over 11 years old had bone ages more than 1 S.D. below the mean for age. He concluded that a relative delay in skeletal development was seen only in adolescence and suggested for the first time that such a delay might provide an explanation for the disproportionately long limbs seen in many adult patients. Danowski (88) reported a five year retardation in bone age in a 17 year old patient.

In 1973, Serjeant and Ashcroft (89) reported the results of a survey of 86 Jamaican patients aged 12-19 years whose skeletal maturity was assessed by the maturity of the distal radial epiphysis using Greulich and Pyle standards. Delay was noted in 81 patients and in the remaining 5 the epiphysis was fused. The study of Jamaican adolescents reported in 1972 (71) compared bone age in 99 patients with a control group. Bone ages of the patients were considerably less than the mean values for the controls, many by more than 2 S.D.'s. Some patients over 20 years had still not achieved skeletal maturity.

Olambiwonnu (72) reported bone age assessments in 15 children between 5 and 16 years. Although bone age was less than chronological age in 13/15 subjects, only in boys was the difference significant. McCormack (73) reported a significant delay in bone age at all ages in a group of 46 children aged 1-17 years but the extent of the difference at different ages was not discussed. Harris (90) attempted to evaluate the change in skeletal

maturity with age by reporting bone age assessments on two groups of children, 62 aged under 11 years and 18 aged 11-18 years. In the younger group only 8% had bone ages less than 2 S.D.'s below the mean for chronological age, compared to 66% of the older children, suggesting that delay in skeletal maturity increased with age. An attempt was made to define the age of onset of skeletal delay in 120 Jamaican SS children aged 2-13 years, comparing their bone ages with local, normal controls (91). Significant delay was apparent in girls from as early as two years and in boys from eight years. The origin of this marked sex difference could not be explained. The prospective study by Kramer (80) on a small cohort of children followed prospectively from birth showed impaired skeletal maturation based on X-ray appearance of the L wrist between the ages 3 and 6 years. The degree of impairment was not quantitated.

6. DETERMINANTS OF ABNORMAL GROWTH

The possible aetiology of impaired growth has been discussed by several authors. Some of the features of the abnormal adult habitus may result from delayed epiphyseal fusion allowing a longer period for longitudinal bone growth in adolescence. This was first suggested by Whitten (69) and supported by the findings of Ashcroft and Serjeant (71). A hypothesis compatible with most observations of height growth in sickle cell disease would be that with the onset of puberty, height growth in normal children increases at a faster rate than in SS children of the same age in whom puberty is delayed. The growth spurt in SS patients would start later and could continue longer if there was sufficient delay in epiphyseal fusion (Fig 7.1). The height of patients could therefore ultimately match that of controls and the prospects for final adult height depend on both the degree of pre-pubertal growth retardation and the length and timing of the pubertal growth spurt.

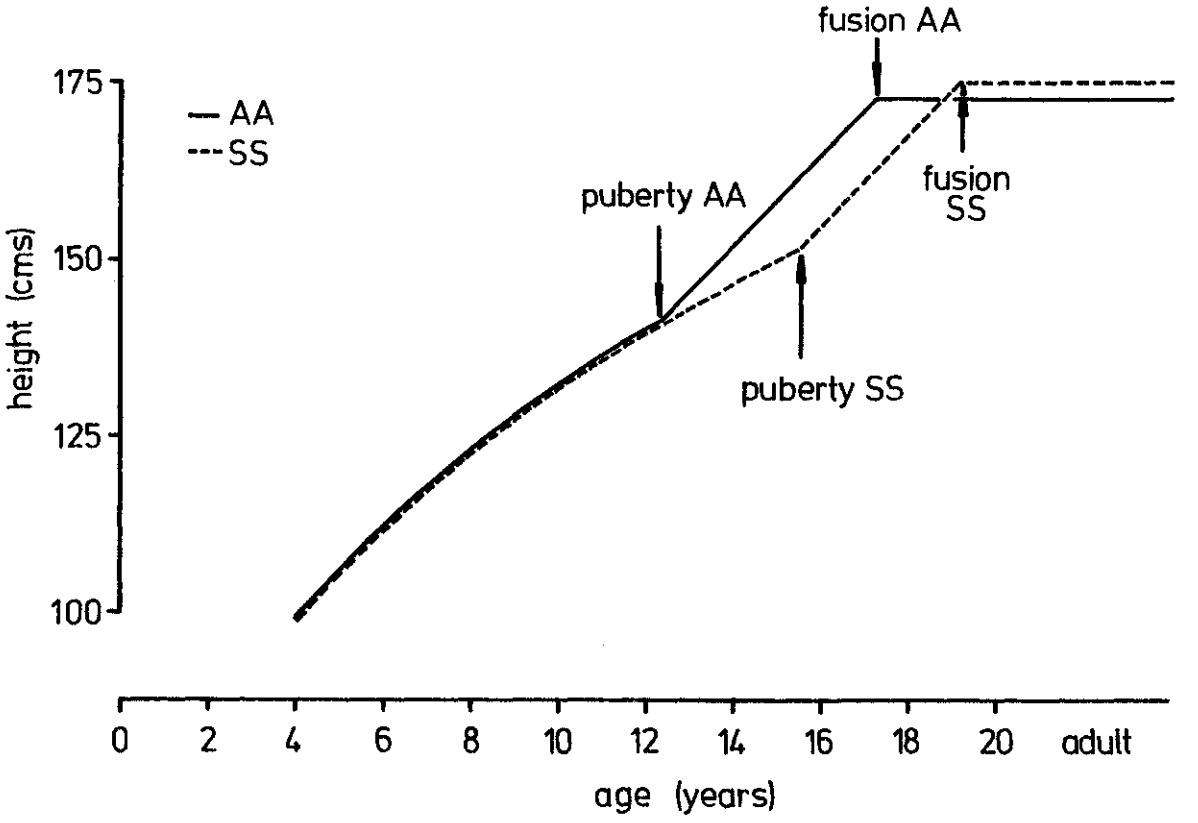


Fig. 7.1 : Suggested pattern of growth in SS disease

Whitten (69) attempted to explore the relationship between pre-adolescent growth retardation and two basic mechanisms which might be implicated in its patho-physiology. He related the degree of peripheral arterial oxygen saturation, as a measure of tissue anoxia, to weight status in 27 children. Although 18 had subnormal levels, no correlation was apparent. Tissue oxygen uptake is in fact likely to be enhanced as a result of the shift of the oxygen dissociation curve to the right in sickle haemoglobin. He was also unable to demonstrate a relationship between the degree of anaemia and weight achieved. Intensive transfusion therapy in two children was associated with a marked growth spurt in one but almost no growth in the other. There was no difference in the clinical severity of disease between children of average and below average weight, although the use of isolated weight measurements is perhaps an insensitive index of overall growth performance.

Serjeant and Ashcroft (68) were able to demonstrate a significant correlation between low HbF and a low ratio of sitting to standing height - one of the most characteristically abnormal features in adults with SS disease - in men but not in women. Other observations in Jamaican patients have shown that lower HbF levels occur in patients with more severe disease (92) and in those with greater delay in skeletal maturity (89). More abnormal habitus is therefore seen in those adult patients with clinical and haematological evidence of increased disease severity. A correlation between HbF and weight achieved was noted by Lowry (78) in children approaching puberty but not at younger ages. They were also able to demonstrate a correlation with total Hb at most ages, but correlations between skeletal maturity and haematological parameters in the same children were inconsistent (91).

Although Watson-Williams (93) observed accelerated growth and initiation of puberty following folic acid supplementation in five African patients with growth retardation and hypogonadism, Liu (94), in a study of folate levels in 33 American SS children, concluded that folate deficiency was common but did not contribute significantly to the pathogenesis of growth retardation. Jimenez (70) reported that 6/8 children with marked retardation in physical and sexual development had low folate levels but did not report their response to folate supplementation. Cyanocobalamin levels were normal in seven of these children. The importance of other nutritional factors has not been extensively investigated but a recent report from Ghana described studies of nitrogen balance in sickle cell disease (95). Nine adolescent SS patients were shown to have a relatively more negative nitrogen balance, with increased faecal and urinary nitrogen loss, at each of three levels of protein intake when compared to data from five normal subjects of a similar age. A very high rate of urea production and recycling was noted in an adult Jamaican man with SS disease (Jackson A, personal communication) in agreement with the Ghanaian observations and suggests an area of further investigation.

Low vitamin A levels are said to be correlated with poor growth in SS children (96), the significance of this observation is unclear.

Delay in physical development in adolescence may be largely secondary to delay in sexual maturation. Jimenez (70) described hypogonadism, delay in oestrogenic stimulation and in onset of menarche. Olambiwonnu (72) reported increased pituitary gonadotrophin levels in both male and female SS patients up to the age of 10 years, implying impaired gonadal function leading to diminished negative feedback on the hypothalamic-pituitary axis. Levels returned to normal by the age of 16 years suggesting that such impairment of gonadal function was transient. They concluded that the growth failure seen in the early pubertal period was consistent with a

deficiency of gonadal steroid necessary for optimal growth, and would be associated with delay in epiphyseal fusion. There is no other published work relating to endocrine function in children with SS disease, except a recent brief reference to somatomedin (96) which was reported to be below normal for age but did not correlate with growth performance.

More recently there has been interest in the relationship between zinc deficiency, which has been documented in adults with SS disease (97) and abnormal growth patterns. A correlation between low zinc status and hypogonadism has been suggested in affected adults (98) but no such relationship emerged in two studies comparing plasma zinc levels and growth performance in SS children (96, 99). The latter study however suggested a relationship between growth delay and carbonic anhydrase activity (a zinc dependent enzyme). The implications are unclear but this area merits further investigation as an opportunity for therapeutic intervention.

There is very little information available on the determinants of the age of onset of growth retardation. Booker (76) noted a clinical association between onset of retardation in growth and the occurrence of infection and appearance of crises. It may be that all these events occur at the time when HbF has fallen to a critical level and the haemolytic features of the disease are fully developed.

7. CONCLUSIONS

The characteristic habitus seen in adults with SS disease is clinically well accepted but its documentation lies predominantly in the work of Ashcroft and Serjeant on Jamaican patients (68). It should be stressed that, while these changes are commonly seen, they are more frequent in patients with more severe disease and in many patients habitus is normal. The normal height of adult patients largely results from increased limb length and an apparent dilemma lies with the fact that this is achieved

despite reports of growth retardation in childhood. The largest, and perhaps best controlled, report on adolescent growth again comes from Jamaica (71) and it is apparent, both from this and other studies, that entry into puberty and its associated growth spurt is delayed. The association of delayed onset of puberty with delayed epiphyseal fusion presents conditions for prolonged growth of long bones and hence recovery of height lost in earlier childhood. Reports of subnormal height in childhood and normal height in adult life are therefore not incompatible, and the final height achieved will depend on both the degree of pre-pubertal growth retardation and on the onset and length of the pubertal growth spurt. The precise determinants of the onset of normal puberty are however not yet clear (100) and the mechanism for the delay seen in SS children remains uncertain.

The onset of prepubertal growth retardation has been recorded as early as six months of age but the subsequent type and extent of growth failure appears variable. While some of the features of adult body changes can be explained by the characteristics of adolescent growth, some are not, for example the findings of low weight, reduction in skinfold thickness and change in chest dimensions. Comparisons between different populations are difficult as social and nutritional factors vary and there is evidence that the pattern of the disease may be different in different areas. Determinants of growth failure may have varying significance in different populations. This suggested a need for a controlled study of growth in early childhood to identify the earliest signs of growth failure, to document their evolution and to relate these to variations in the clinical and haematological severity of the disease.

PLAN OF GROWTH STUDY

1. AIMS :

The aims of the study were to :

i) Document the age at which growth impairment became apparent in children with SS disease.

ii) Quantitate the severity and nature of growth impairment in the first five years of life.

iii) Identify any abnormality of body shape in relation to such abnormalities known to occur in affected adults.

iv) Observe the effect of the disease on skeletal maturation.

v) Relate growth abnormalitiy to indices of the clinical and haematological severity of the disease.

2. POPULATIONS STUDIED :

i) Growth from 0 - 5 years : the structure of the study was designed to utilise the data for growth in height, weight and head circumference which had been routinely collected on all patients since the start of the cohort study. All data was analysed crosssectionally to provide information about growth differences between SS children and the control group.

ii) Anthropometric assessment : a separate project was established to look at detailed anthropometric measurements in the older children from the cohort study. All those who achieved their 4th, 5th or 6th birthdays in the year from February 1979 to January 1980 formed this study group. Arrangements were made for these children to attend individually for measurement within one month of their birthdays.

iii) Skeletal maturity : All five year olds who attended for anthropometric assessment had an assessment of skeletal maturity based on radiological appearance of the bones of the left hand and wrist.

3. HAEMATOLOGY & CLINICAL DATA FILES :

Clinical events and selected haematological indices were extracted for

all patients in the study who had been included in the analysis of cross-sectional data for ages 0-5 years and was based on the master data file updated to June 1980. The use of a later update than that selected for the growth data analysis (January 1980) ensured that the clinical and haematological data files were as complete as possible, there often being some delay in the acquisition of completed hospital admission data and in the coding of certain haematological measurements, notably iron and folate levels which were assayed periodically in batches.

4. PRESENTATION OF DATA

The collection and analysis of data varied between the different aspects of the study. The results are presented in three parts :

i) Growth in AA and SS children 0-5 years

ii) Anthropometric assessment of AA and SS children at age 4, 5, & 6 years

iii) Skeletal age assessment in AA & SS children age 5 years.

The techniques of measurement, data compilation and statistical analysis are described separately for each.

LONGITUDINAL GROWTH DATA : METHODS

1. POPULATION

By January 1980, 706 children had been registered with the cohort study of whom 250 were normal (AA) children and 251 had SS disease (Table 9.1).

The medical records of all AA and SS children were examined for the presence of other medical problems which might adversely influence growth performance. Eight children (5AA and 3SS) were omitted on this basis. A further four AA children, with β thalassaemia trait, who were already excluded from the analysis of haematology data in the control group, were also eliminated (Table 9.2). The remaining children were used for the study but data were not available for 8 AA and 4 SS children and the analysis was based, therefore, on the data from 233 AA and 244 SS children (Table 9.3).

Measurement of height, weight and head circumference recorded at all visits between birth and five years were used for the compilation of a computer stored growth file.

2. COMPILATION OF GROWTH FILE :

The five year span of the study was divided into twenty six age bands, each representing a grouping of ages centered around a "target" age. The target ages were selected to match the ages at which the children were asked to routinely attend the clinic (Table 9.4). For visits at ages up to one year, the precise age at each visit, calculated from date of birth and date of visit, was recorded by the computer in months and days. At ages one year and above, age at attendance was calculated to the nearest month and expressed as years and months. For the selection of the data in each age band, groupings were defined with increasing tolerance for increasing age. For age bands 1-7 (birth to six months) the grouping extended ± 2 weeks around the target age. For age bands 8 and 9 (8 and 10 months) the

TABLE 9.1

CHILDREN REGISTERED IN COHORT STUDY : JANUARY 1980

Genotype	No.
AA	250
SS	251
SC	155
SβThal	38
S variant	12
TOTAL	706

TABLE 9.2

CHILDREN ELIMINATED FROM GROWTH STUDY

AA		SS	
No.	Diagnosis	No.	Diagnosis
1	Short limbed dwarf	1	Congenital heart disease
1	Nephrotic syndrome	1	Athetoid cerebral palsy
1	Congenital Rubella	1	Spastic quadriplegia
2	Congenital heart disease		
4	β Thalassaemia trait		

TABLE 9.3

POPULATION USED FOR GROWTH STUDY

	AA	SS
Registered in cohort study	250	251
Eliminated : medical reasons	9	3
No growth data available	8	4
Children utilised in analysis	233	244

grouping increased to ± 4 weeks and after one year (age bands 11 - 26) the grouping was defined at ± 6 weeks. The age band at one year (10) was asymmetrical because of the change in age recording from months and days to years and months. This grouping ranged from 11 months to 12 months and 14 days. Data recorded during three short periods (1-5 days, 6½ - 7 months and 12½ - 13½ months) could not be utilised in the analysis as these points lay between age bands defined with different tolerance limits. Age index 1 referred only to birth weight.

Measurements recorded for each child were selected at only one visit in each age band. Many children however attended the clinic on more than one occasion during these periods and the visit selected for inclusion in analysis was defined as the routine visit closest to the target age. If no routine visit was recorded then the data available from attendances coded as 'sick' visits were used. Data selected at routine visits was preferred because full measurements were often not recorded when the child presented because of intercurrent illness, notably omission of height and head circumference. The use of data from every visit in each age band would have introduced statistical difficulties : those children attending frequently would have made a greater contribution than those who attended only once.

3. POSSIBLE SOURCES OF BIAS IN THE CONSTRUCTION OF THE GROWTH FILE :

The compilation of the growth file from the computer master file in the manner described raised several questions which affected the statistical validity of the derived data to be used in subsequent analysis.

(i) Bias resulting from age scatter within each age band : Age groupings were defined with increasing tolerance at increasing ages to ensure that, with the exception of the three brief periods of data loss mentioned above, age groupings were continuous. While this ensured minimal loss of data, it introduced extra variability into the distribution of data at each age

TABLE 9.4

DISTRIBUTION OF AGE BANDS

TARGET AGE (months)	AGE BAND	AGE GROUPING ACCORDING TO COMPUTER RECORD	ACTUAL AGE RANGE
0	1	00.00 (months and days)	00.00 (months & days)
1	2	00.15-01.14 "	00.15-01.14 "
2	3	01.15-02.14 "	01.15-02.14 "
3	4	02.15-03.14 "	02.15-03.14 "
4	5	03.15-04.14 "	03.15-04.14 "
5	6	04.15-05.14 "	04.15-05.14 "
6	7	05.15-06.14 "	0.515-06.14 "
8	8	07.00-08.30 "	07.00-08.30 "
10	9	09.00-10.30 "	09.00-10.30 "
12	10	11.00-01.00 (years & mths)	11.00-12.14 "
15	11	01.02-01.04 "	13.15-16.14 "
18	12	01.05-01.07 "	16.15-19.14 "
21	13	01.08-01.10 "	19.15-22.14 "
24	14	01.11-02.01 "	22.15-25.14 "
27	15	02.02-02.04 "	25.15-28.14 "
30	16	02.05-02.07 "	28.15-31.14 "
33	17	02.08-02.10 "	31.15-34.14 "
36	18	02.11-03.01 "	34.15-37.14 "
39	19	03.02-03.04 "	37.15-40.14 "
42	20	03.05-03.07 "	40.15-43.14 "
45	21	03.08-03.10 "	43.15-46.14 "
48	22	03.11-04.01 "	46.15-49.14 "
51	23	04.02-04.04 "	49.15-52.14 "
54	24	04.05-04.07 "	52.15-55.14 "
57	25	04.08-04.10 "	55.15-58.14 "
60	26	04.11-05.01 "	58.15-61.14 "

point : it was possible that the actual age of each group was not centred on the target age. If this were so, the mean weight or height of the group could be biased upwards or downwards by a small amount. Figure 9.1 shows the distribution of the actual age at visit, relative to target age, in selected age bands from 8 - 60 months, in each of the age and genotype groups. There was no change in the distribution pattern with age or between genotypes. There was a slight tendency for visits to be later rather than earlier, but the majority of all visits occurred within 2 weeks of the target age (Table 9.5). Although the one year age band was constructed asymmetrically, nevertheless 80% of all visits at that age occurred within 2 weeks of the target. Any variation due to this factor was considered to be small compared with the overall variation between children and did not interfere with comparisons between the AA and SS groups. As the age groups for target ages 0 - 6 months were already narrowly defined at ± 2 weeks, the same conclusion was applicable.

(ii) Bias resulting from patients defaulting visits : Some children failed to attend at certain ages. Possible explanations were either that they may have been particularly well at that time or that they came from homes with poor parental supervision; it was unlikely that they failed to attend because they were ill. This possibility was assessed by reviewing their growth performance at ages earlier to that at which they subsequently defaulted. Growth at one year was assessed in those who defaulted their two year visit, and at two years in those who defaulted at four years. No significant differences were noted in the height or weight of the children who subsequently defaulted, in comparison to the groups from which they came (Table 9.6). It was unlikely that the data used for analysis was unrepresentative despite the loss of some children who defaulted appointments for the clinic. Defaulting was clearly less common amongst SS children.

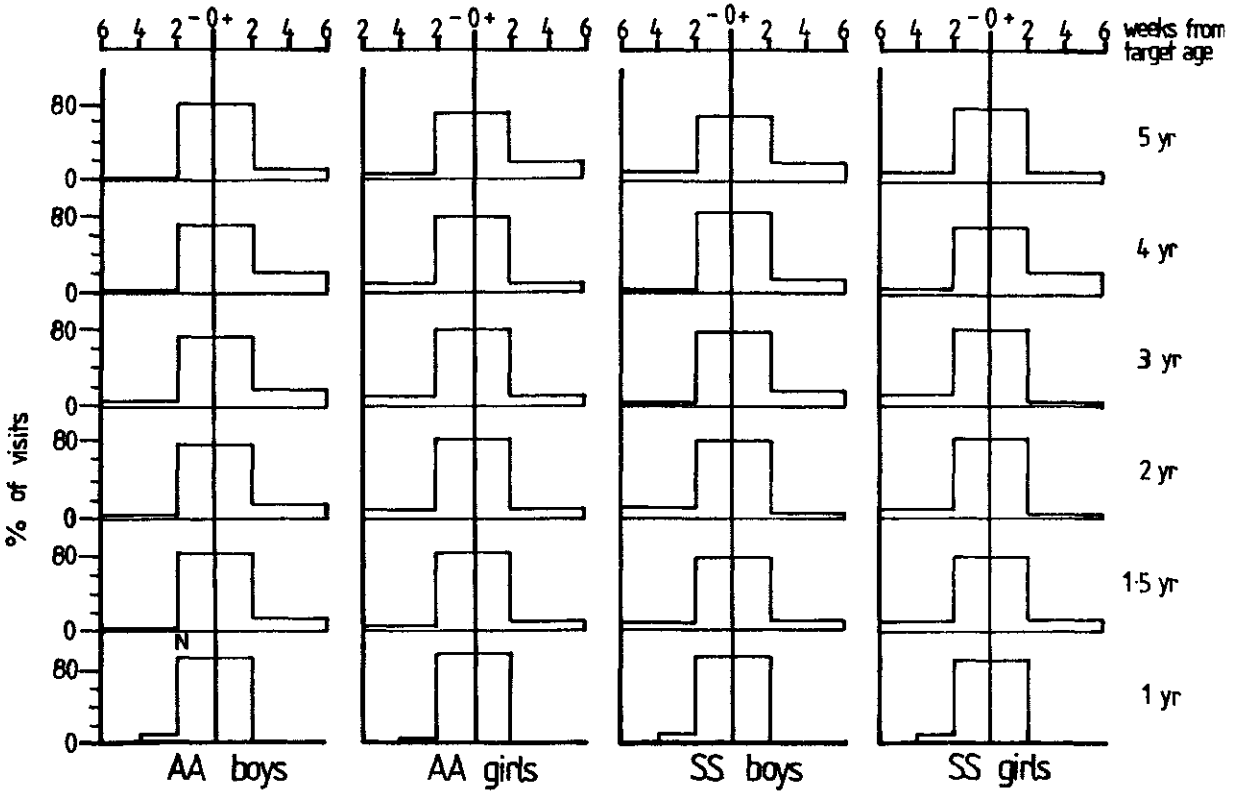


Fig. 9.1: Distribution of visits around 'target age'

TABLE 9.5

PERCENTAGE OF VISITS OCCURRING

WITHIN ±2 WEEKS OF TARGET AGE

AGE INDEX	TARGET AGE (mos)	AA		SS	
		BOYS	GIRLS	BOYS	GIRLS
8	8	82	78	81	74
10	12	93	95	91	70
12	18	82	84	78	78
14	24	79	84	83	85
18	36	74	82	80	82
22	48	74	82	86	70
26	60	83	76	70	79

TABLE 9.6

ANALYSIS OF DIFFERENCES BETWEEN WEIGHT AND HEIGHT OBSERVED AT 1 YEAR AND 2 YEARS IN THE CHILDREN DEFAULTING AT 2 YEARS AND 4 YEARS AND THE GROUPS FROM WHICH THEY CAME

		AA				SS			
		BOYS		GIRLS		BOYS		GIRLS	
		t*	p	t*	p	t*	p	t*	p
AGE 1 YEAR	WEIGHT	-2.01	NS	-1.30	NS	-2.08	NS	-	-
	HEIGHT	-1.14	NS	-0.45	NS	-0.71	NS	-	-
AGE 2 YEARS	WEIGHT	-0.09	NS	-1.02	NS	0.92	NS	-1.66	NS
	HEIGHT	-1.08	NS	-1.57	NS	1.38	NS	0.11	NS

*one sample t test

(iii) Bias resulting from measurements obtained at sick visits : At some ages the only measurements available for some children were those obtained when the child was sick. It was difficult to conceive that measurement of height and head circumference could be atypical but weight might be reduced during illness and this presented a further potential source of bias. The number of weights recorded at sick visits and utilised for compilation of the growth file was investigated at ages six months, two years and four years. The mean of these values was compared with the mean for each group from which these children came (Table 9.7). The differences were slight and not significant. Furthermore the number of measurements utilised from recordings obtained at sick visits were relatively few at all ages (mean = 11% of all readings at each age).

(iv) Bias from secular trends : The recruitment of the control children was discontinued, for logistic reasons, after the first three years of the study, while the recruitment of SS children continued throughout. In January 1980, when the data was analysed, the ages of the control population ranged from 4-6½ years while those of the SS children ranged from 0-6½ years. Any significant change in the nutritional status of the community could therefore have affected differences between AA and SS children at the younger age bands. A comparison of birth weight and weight at two years between children born in each year of the study showed no significant differences (Tables 9.8, 9.9). This was an important source of bias to eliminate as the study was in progress during a period of serious national socio-economic decline.

4. PRESENTATION OF DATA AND STATISTICS

The growth file, compiled from the selected data, was stored on tape and a printout of the information was produced in two forms : 1) Datasort : this provided a listing of all data for each child at every visit. This

TABLE 9.7

ANALYSIS OF DIFFERENCES IN WEIGHTS OBTAINED AT SICK VISITS

COMPARED TO WEIGHTS AT ALL VISITS

FOR AGES SIX MONTHS, TWO YEARS, AND FOUR YEARS

WEIGHT AT AGE	AA				SS			
	BOYS		GIRLS		BOYS		GIRLS	
	t*	p	t*	p	t*	p	t*	p
6 MONTHS	-	-	-0.54	NS	-0.81	NS	-1.10	NS
2 YEARS	-0.80	NS	-0.28	NS	-0.51	NS	-0.60	NS
4 YEARS	-0.84	NS	1.51	NS	-0.34	NS	0.54	NS

*one sample t test

TABLE 9.8

BIRTH WEIGHTS (mean ± SD)

YEAR OF BIRTH		1973	1974	1975	1976	1977	1978	1979
BOYS	AA	3.28±0.48	3.16±0.41	3.13±0.45	-	-	-	-
	SS	3.11±0.62	3.22±0.44	3.25±0.59	3.13±0.54	3.09±0.55	3.39±0.56	3.16±0.62
GIRLS	AA	3.13±0.54	3.22±0.53	3.19±0.44	-	-	-	-
	SS	3.06±0.54	3.37±0.52	3.00±0.47	3.17±0.42	3.48±0.43	2.97±0.64	3.16±0.46

TABLE 9.9

WEIGHT AT TWO YEARS (mean ± SD)

YEAR OF BIRTH		1973	1974	1975	1976	1977
BOYS	AA	11.55±1.13	11.72±1.66	11.85±1.15	-	-
	SS	11.45±1.03	11.55±1.33	11.11±1.11	10.90±1.03	10.93±0.87
GIRLS	AA	10.98±0.66	11.38±1.54	11.56±1.45	-	-
	SS	10.64±1.21	11.01±1.04	10.82±1.12	10.84±1.12	11.72±1.30

was presented first for each child listing data chronologically, and second for each age band listing the name, genotype, sex, weight, height, head circumference, date of birth, date of visit, age at visit, age difference from target age and visit type. 2) Statistics : data for each measurement was analysed separately for each sex and genotype group at every target age to give the frequency, distribution, mean, median, standard deviation and skewness. Values for weight and height velocity were calculated over the periods 1-6 months, 6-12 months, 1-2, 2-3, 3-4 and 4-5 years. Comparative analysis between different sex and genotype groups was calculated individually using Student's t test.

5. MEASUREMENT TECHNIQUES

Weight and height were recorded for all children on arrival at the clinic. This was usually performed by the clinic nurse, but on occasion would have been recorded either by the doctor or a nursing assistant. All members of staff were instructed in the use and maintenance of the measurement instruments and their calibration was periodically checked using standard weights and lengths. The degree of inter-observer error was not assessed. A maximum of 8 people (5 doctors, 3 nurses) had been involved with these recordings since the study began.

(i) Birthweight : Babies were weighed naked in the labour ward within a short time of delivery. The scales were calibrated in pounds and ounces, accurate only to 4 oz intervals, and these values were converted to Kilograms during data coding. Weights were recorded by the maternity staff on the record cards provided for the cohort study. Birthweight was not recorded for 11 AA and 9 SS children.

(ii) Weight was measured in infants using a set of baby balance scales (Detecto Inc., New York) accurate to one ounce (0.03 Kg). Weights obtained were measured in lb and ounces and subsequently converted during data coding to Kilograms. Older children were weighed standing on a platform

scale with a sliding arm balance mechanism (Detecto Inc., New York) accurate to 0.1 Kg. This scale was calibrated directly in Kilograms. All children were weighed without shoes and top clothing but no correction was applied for the weight of the remaining clothes. A sample study to assess the error in weight attributable to retained clothing showed this to be 0.15±0.10 Kgs and there was no significant change in weight of clothing with age.

(iii) Height : was measured as supine length, using a supine stadiometer accurate to 0.1 cms, until the children were old enough to cooperate with measurement on a standing stadiometer. Standard measuring techniques were used (100). The age at which supine length was changed to standing height was not standardised and the method of measurement at each visit was not recorded in the clinical records. There is no published evidence to suggest that the developmental progress of SS children is less than normal and it was concluded that variability due to the change from supine to standing measurement would be the same for both genotypes. The relative advance in motor development seen in black children compared to whites may have resulted in the use of standing height measurements in many children well before the age of two years, the point at which the change in technique is recommended. Supine length averages approximately 1 cm more than standing height (100) and a comparison of supine and standing measurements in 15 children aged 18-30 months from this study confirmed that the difference was of the same order (mean ± 1 SD = 1.1 ± 0.6 cms). Height at two years in this study may therefore have been influenced in comparison to values from standard populations utilising supine length exclusively to two years.

(iv) Head circumference was measured by the doctor during physical examination. A fibreglass tape was used to record the maximum occipito-frontal diameter. The tape was periodically checked for stretch against a steel rule

and replaced as necessary. The characteristic and elaborate hair styles worn by Jamaican children,particularly girls, raised doubts about the accuracy of the measurement and may have contributed to inter-sex differences although the error should have been the same for both genotypes.

COMPARISON OF LONGITUDINAL GROWTH PATTERNS IN AA AND SS CHILDREN

1. DISTRIBUTION OF DATA

The distributions of the weight, height and head circumference data were assessed at each age point by the calculation of values for skewness. These values are shown in Tables 10.1 - 10.4 for boys and girls according to genotype. The interpretation of these data was difficult and lack of significance did not imply absence of skewness. Any distributions which implied significant deviation from normal were inspected visually. No distributions so atypical to warrant either transformation or exclusion from analysis were found.

2. WEIGHT

Means and standard deviations for weight at all age points are shown in Table 10.5 for boys and Table 10.6 for girls. Plots of mean weight at birth, 3, 6, 12, 18, 24, 30, 36, 42, 48, 54 and 60 months, comparing the data for AA and SS children, are shown in Figs 10.1 and 10.2. The significance of the difference between the means was assessed using the Student's t test. One tail values were selected for p on the basis that any difference between the two populations could be predicted to show that AA children were heavier. There was no difference in weight from birth to six months between the genotypes, but thereafter the average weight of SS children began to fall below that of the controls. This difference achieved significance at twelve months in both boys and girls. The extent of the difference increased towards the second and third year after which the divergence lessened, remaining more obvious in girls. Some caution must be used in the interpretation of significance levels obtained by repeated t tests on inter related groups. However numbers were insufficient to permit pure cross sectional analysis on unrelated groups.

The extent of the difference observed between genotypes with increasing

TABLE 10.1

AGE YEARS	AA B O Y S					
	WEIGHT		HEIGHT		OFC	
	n	Skewness	n	Skewness	n	Skewness
Birth	108	0.194				
0.5	78	0.126	77	0.101	78	-0.057
1	80	0.406	78	0.233	74	0.319
1.5	68	0.508	63	-0.107	58	0.578
2	64	0.571	61	0.219	60	0.395
2.5	54	0.791	52	0.107	50	0.533
3	61	1.188	59	-0 111	54	0.474
3 5	47	-0.412	45	-0.361	40	1.166
4	57	-0.202	54	-0.285	55	-0.002
4.5	34	-0.613	32	-0.126	32	0.771
5	36	-0.651	36	-0.499	33	0.226

TABLE 10.2

AGE YEARS	AA G I R L S					
	WEIGHT		HEIGHT		OFC	
	n	Skewness	n	Skewness	n	Skewness
Birth	114	-0.052				
0.5	95	0.641	93	0.146	86	0.026
1	94	0.836	90	-0.115	86	-0 096
1.5	84	1.146	81	-0.382	71	0.188
2	81	0.983	70	0.418	67	0.107
2.5	71	0.629	61	0.324	61	0.011
3	67	0.812	66	0 175	63	0.146
3.5	56	0.465	55	0.182	50	0.425
4	67	0.549	64	0.186	55	0.140
4.5	41	0.374	39	-0.543	37	-0.019
5	33	0.596	33	-0.442	31	0.378

TABLE 10.3

AGE YEARS	SS B O Y S					
	WEIGHT		HEIGHT		OFC	
	n	Skewness	n	Skewness	n	Skewness
Birth	123	-0.299				
0.5	90	-0.187	84	0.265	83	0.068
1	81	0.202	72	0.102	64	0.295
1.5	64	0.248	60	0.406	56	0.225
2	59	0.269	52	-0.021	51	-0.216
2.5	53	0.473	48	0.059	44	0.320
3	51	0.148	49	0.336	47	-0.195
3.5	31	0.386	28	0.046	26	-0.362
4	29	-0.102	28	0.398	22	0.375
4.5	22	-0.056	22	0.052	17	0.215
5	20	-0.385	20	-0.507	19	0.273

TABLE 10.4

AGE YEARS	SS G I R L S					
	WEIGHT		HEIGHT		OFC	
	n	Skewness	n	Skewness	n	Skewness
Birth	112	0.104				
0.5	77	-0.257	75	0.120	74	-0.333
1	73	-0.333	70	-0.625	63	-
1.5	59	-	55	-	47	-
2	58	-	50	-0.739	51	0.107
2.5	44	0.460	40	-0.332	34	-0.007
3	38	0.076	34	-0.064	29	-0-110
3.5	32	0.556	30	-0.572	25	0.066
4	30	0.341	29	-0.626	25	-0.191
4.5	20	0.358	20	-0.178	15	-0.920
5	19	0.500	19	-0.191	15	0.199

TABLE 10.5

WEIGHT (Kgs) BOYS AA:SS

TARGET AGE (months)	AGE BAND	AA			SS			t	p
		n	mean	SD	n	mean	SD		
Birth	1	108	3.18	0.45	123	3.19	0.56	-0.14	NS
1	2	72	4.02	0.55	96	4.18	0.82		
2	3	59	5.38	0.56	92	5.44	0.79		
3	4	42	6.18	0.79	84	6.35	0.88	-1.05	NS
4	5	45	6.83	0.79	76	6 95	0.85		
5	6	34	7.24	0.83	77	7.36	0.93		
6	7	78	7.80	0.95	90	7.68	0.91	0.83	NS
8	8	57	8.43	1.06	84	8.31	1.09		
10	9	47	8.91	1.28	74	8.74	1.00	0.81	NS
12	10	80	9.40	1.11	81	9.07	1.09	1.89	<0.05
15	11	62	9.87	1.09	72	9.71	0.98		
18	12	68	10.57	1.20	64	10.25	1.04	1.62	NS
21	13	50	10.93	1.23	63	10.84	1.09		
24	14	64	11.72	1.29	59	11.15	1.07	2.63	<0.01
27	15	36	12.23	1.32	55	11.59	1.25		
30	16	54	12.91	1.49	53	12.26	1.11	2.53	<0.01
33	17	38	13.26	1.33	48	12.58	1.07		
36	18	61	13.94	1.59	51	13.18	1.19	2.79	<0.01
39	19	29	13.65	1.44	40	13.65	1.23		
42	20	47	14.79	1.56	31	14.14	1.23	1.93	<0.05
45	21	17	14.64	1.69	29	14.26	1.18		
48	22	57	15.46	1.59	29	14.84	1 37	1.68	<0.05
51	23	21	15.81	1.53	25	14.97	1.36		
54	24	34	16.37	1.74	22	15.52	1.65	1.79	<0.05
57	25	9	16.34	1.89	21	15.88	1.70		
60	26	36	17.09	1.78	20	16.44	1.60	1.33	NS

TABLE 10.6

WEIGHT (Kgs) GIRLS AA:SS

TARGET AGE (months)	AGE BAND	AA			SS			t	p
		n	mean	SD	n	mean	SD		
Birth	1	114	3.22	0.49	112	0.51	0.51	0.75	NS
1	2	73	3.92	0.57	84	4.07	0.60		
2	3	58	5.02	0.53	69	5.06	0.70		
3	4	54	5.74	0.52	68	5.79	0.77	-0.40	NS
4	5	53	6.36	0.61	67	6.34	0.83		
5	6	45	6,77	0.76	63	6.84	0 86		
6	7	95	7 34	0.82	77	7.17	0.90	1.29	NS
8	8	63	7.91	0.84	71	7,58	0.93		
10	9	52	8.46	0.93	67	8.18	1.08	1.48	NS
12	10	94	9.03	1.13	73	8.58	1.06	2.61	<0.01
15	11	69	9 60	0.98	68	9.20	1.16		
18	12	84	10 29	1.28	59	9.82	1.21	2.20	<0.05
21	13	56	10.47	1.08	46	10.53	1.26		
24	14	81	11,41	1.39	58	10.97	1.22	1.92	<0.05
27	15	47	11.54	1 48	47	11.61	1.33		
30	16	71	12.46	1.44	44	12.23	1.32	0.85	NS
33	17	32	12 68	1.49	38	12.59	1.52		
36	18	67	13.51	1.84	38	12.69	1.30	2.39	<0.01
39	19	26	13.71	1 17	38	13.07	1.45		
42	20	56	14 52	1,62	32	13.74	1.44	2.23	<0.05
45	21	20	14.00	1 76	30	14.05	1.82		
48	22	67	15.13	2.02	30	14.37	1.70	1.78	<0.05
51	23	18	15 72	1 93	22	14.69	1.95		
54	24	41	16.15	1.88	20	14.83	1.99	2.97	<0.01
57	25	6	17.10	1.17	19	15 45	1.73		
60	26	33	26.83	2.10	19	15.66	1.80	2.00	<0.05

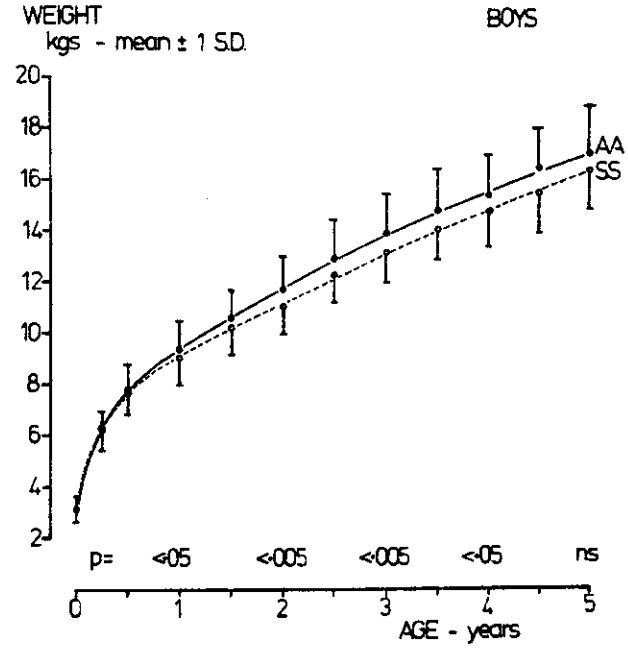


Fig. 10.1 : Mean weight AA and SS Boys

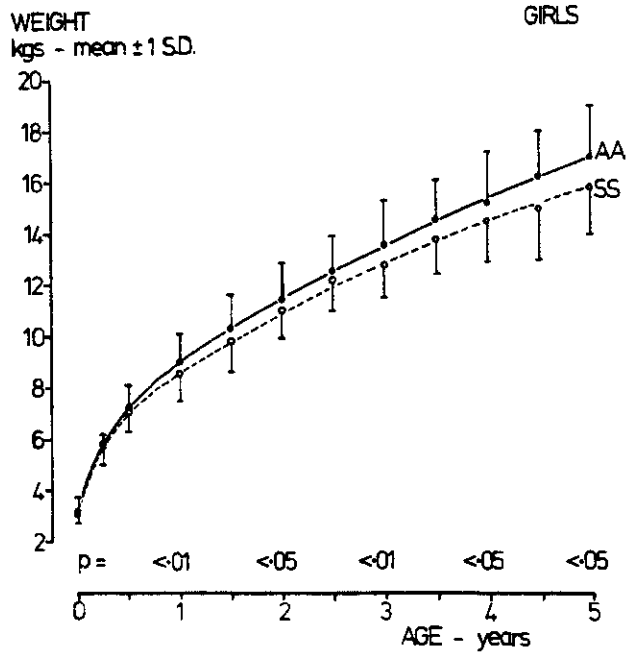


Fig. 10.2 : Mean weight AA and SS Girls

age was examined further by expressing the mean deficit seen in SS children as a standard score. This technique related the weight of each SS child to the mean of AA children at the same age and expressed the difference observed in terms of standard deviation. These individual standard scores (z), derived according to the formula :

$$z = \frac{(x - \bar{x})}{SD}$$ where x = observed weight, $\bar{x}$ = mean AA weight, SD = AA standard deviation, were pooled to give an average deviation seen in SS children at each age point. The results are shown in Table 10.7 and Figures 10.3 and 10.4. The standard scores for boys and girls were of the same order at each age except at 5 years where the greater deficit seen in girls contributed to the increasing divergence of weight in SS children away from the controls.

The clinical importance of the weight deficit was small but significant. Figures 10.5 and 10.6 show the weight curves for AA and SS children compared to data from the National Center for Health Statistics (101), recently adopted as reference standards by the World Health Organisation (102).

A further approach to the difference in weight gain was obtained by comparison of weight velocity. The results are shown in Tables 10.8 and 10.9 and Figures 10.7 and 10.8. Weight velocity was significantly less in SS children throughout the first year in girls and from 6 - 12 months in boys. This accounted for the early deficit in weight seen in both groups but therafter weight velocity was less, but not significantly so, in SS children until the fifth year. The excessive fall in velocity seen in SS girls reflected the characteristics of that group. The possibility that there might be a significant difference in growth potential between SS boys and SS girls required review in the context of other measurements made.

3. HEIGHT

Data for height measurements were treated in a similar manner. Tables

TABLE 10.7

	WEIGHT STANDARD SCORES (mean ± 1.SD)	
AGE (years)	BOYS	GIRLS
0.5	-0.13 ± 0 96	-0.22 ± 1.09
1	-0.30 ± 0.98	-0.35 ± 0.95
2	-0.46 ± 0 86	-0.31 ± 0.86
3	-0.47 ± 0.76	-0.44 ± 0.72
4	-0.37 ± 0.86	-0.37 ± 0.84
5	-0.36 ± 0.90	-0.56 ± 0.85

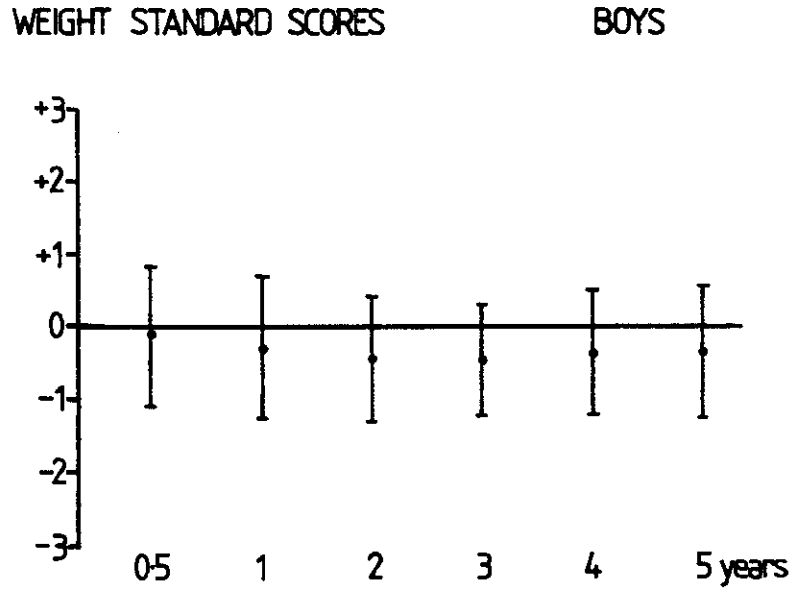


Fig 10.3

Weight standard scores for SS Boys

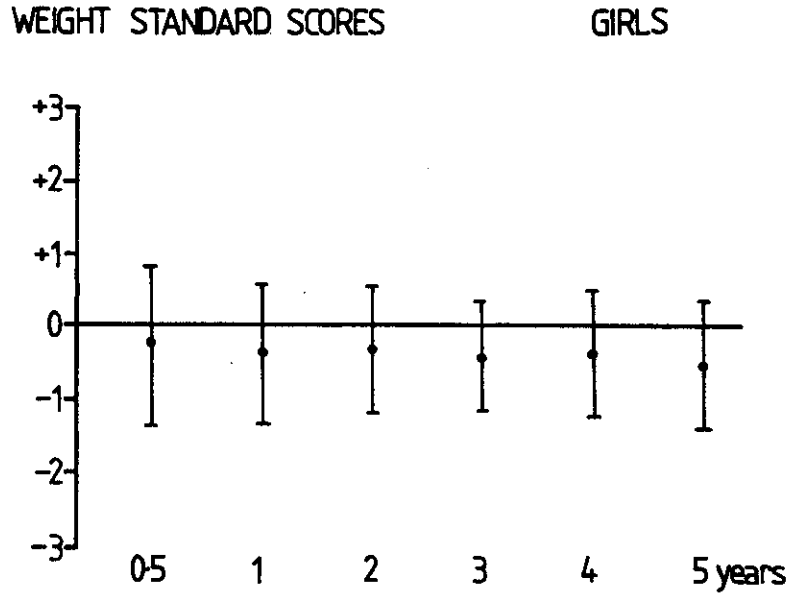


Fig 10.4

Weight standard scores for SS Girls

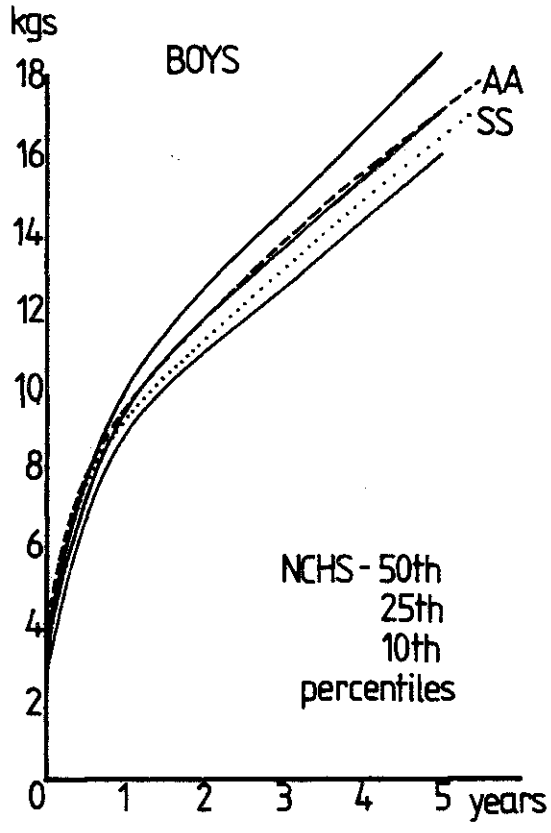


Fig 10.5 : AA and SS Boys - mean weights against NCHS standards

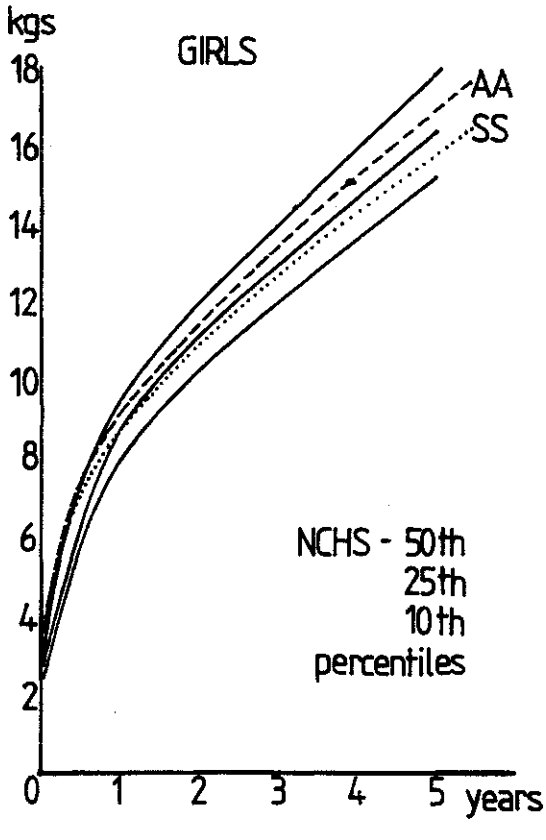


Fig 10.6 : AA and SS Girls - mean weights against NCHS standards

TABLE 10.8

WEIGHT VELOCITY (Kg/month)

BOYS

	AA			SS				
AGE (months)	n	$\bar{x}$	SD	n	$\bar{x}$	SD	t	p
1- 5	47	0.69	0.16	66	0.67	0.14	0.79	NS
6-12	62	0.28	0.09	65	0.21	0.11	3.67	<0.001
12-24	56	0.18	0.05	52	0.17	0.05	0.89	NS
24-36	48	0.18	0.07	43	0.16	0.04	1.01	NS
36-48	45	0.15	0.06	26	0.13	0.06	1.34	NS
48-60	26	0.15	0.06	17	0.11	0.05	1.95	<0.05

TABLE 10.9

WEIGHT VELOCITY (Kg/month)

AGE (months)	GIRLS							
	n	$\bar{x}$	SD	n	$\bar{x}$	SD	t	p
1- 6	56	0.63	0.12	57	0.59	0.12	1.84	<0.05
6-12	84	0.29	0 09	58	0.25	0.10	2.08	<0.05
12-24	71	0.19	0.06	47	0.19	0.05	-	NS
24-36	58	0.18	0.07	36	0.16	0.05	1.49	NS
36-48	50	0.12	0.08	26	0.13	0.06	-0.45	NS
48-60	25	0.14	0.05	15	0.09	0.03	3.53	<0.001

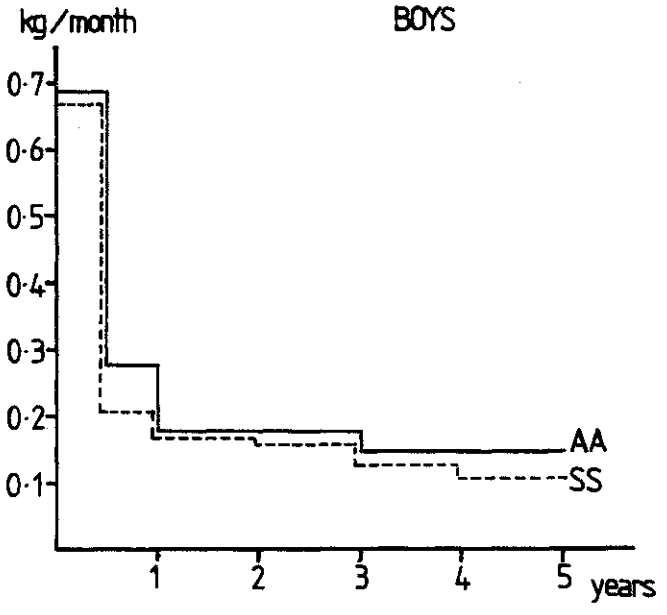


Fig 10.7

Weight velocities for AA and SS Boys

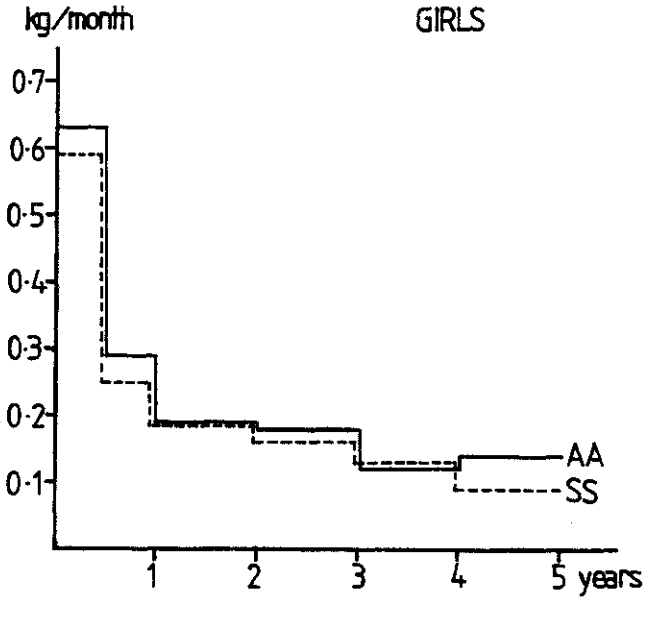


Fig. 10.8

Weight velocities for AA and SS Girls

10.10 and 10.11 show means and standard deviations at all age points to five years. Plots comparing mean heights for AA and SS children are shown in Figures 10.9 and 10.10. Differences in mean height began to emerge in the second year but in contrast to differences observed in weight, their significance was not consistent thereafter. Height deficit in SS children was relatively less than their deficit in weight. The differences observed between boys of different genotype remained unchanged with age after two years, but SS girls appeared to fall further behind AA girls from 3 - 5 years.

These observations were confirmed by inspection of the standard scores for height, comparing the average height deficit of the SS children with the mean height of AA children of the same age (Table 10.12, Figures 10.11 and 10.12). The differences seen between height achieved at 5 years by SS boys and SS girls was attributed to an abrupt deterioration in the position of the girls and improvement in the position of the boys, relative to their controls; neither change was predicted from the trend observed over the first four years and may be attributed to the decreasing sample size at that age.

Height velocities showed the same pattern (Tables 10.13 and 10.14, Figures 10.13 and 10.14). Differences were not obvious during the second half of the first year and were thereafter very slight, except in the older girls.

The clinical relevance of impaired height growth was slight, except in relation to weight deficit with their combined effect on body build. Figures 10.15 and 10.16 show the height curves for AA and SS children compared to WHO standards.

4. WEIGHT FOR HEIGHT

The relatively greater deficit in weight than in height seen in SS

TABLE 10.10

HEIGHT (cms) BOYS AA : SS

TARGET AGE (months)	AGE BAND	AA			SS			t	p
		n	Mean	SD	n	Mean	SD		
1	2	67	53.7	2.6	94	53.4	3.2	0.63	NS
2	3	58	58.1	2.6	88	57.6	2.8		
3	4	37	61.4	2.7	79	61.2	2.9	0.35	NS
4	5	42	63.5	2.6	72	64.1	2.6		
5	6	29	65.8	2 7	66	65.9	2.6		
6	7	77	67.7	2.2	84	67.4	2.7	0.76	NS
8	8	47	70.4	2.9	75	70.2	2.7		
10	9	39	72.2	3.4	61	72.3	2.4		
12	10	78	74.7	2.5	72	74.3	2.5	0.97	NS
15	11	51	77.8	2.9	58	77.0	2.6		
18	12	63	80.4	2.6	60	79.6	2.8	1.63	NS
21	13	41	82.9	3.1	56	81.6	2.8		
24	14	61	85 1	2.8	52	84.1	2.9	1.84	<0.05
27	15	23	87 4	2.9	45	86.1	3.2		
30	16	52	89.9	3.6	48	88.8	3.0	1.60	NS
33	17	32	92.4	3.5	42	90.4	3.2		
36	18	59	94.4	3.8	49	93.1	3.0	1.93	<0.05
39	19	22	94.3	3.3	39	94.7	3.1		
42	20	45	97.9	3.6	28	97.3	3.4	0.70	NS
45	21	9	96.4	4.4	25	98.7	3.3		
48	22	54	101.7	3.7	28	100.6	3.6	1.27	NS
51	23	16	103.2	3.2	25	102.5	3.8		
54	24	32	105.4	3.5	22	103.7	3.6	1.70	<0.05
57	25	8	106.6	4 9	21	105.8	3.9		
60	26	36	108.2	4.0	20	108.0	3.8	0.18	NS

TABLE 10.11

HEIGHT (cms) GIRLS AA : SS

TARGET AGE (months)	AGE BAND	AA			SS				
		n	Mean	SD	n	Mean	SD	t	p
1	2	68	53.0	2.7	80	53.6	2.3	-1.45	NS
2	3	53	57.4	2.1	67	57.4	2.6		
3	4	51	60.3	2.1	67	60.0	3.0	0.60	NS
4	5	51	62.4	2.1	66	62.6	2.6		
5	6	36	64.3	2 5	57	64.7	2.7		
6	7	93	66.6	2.6	75	66.6	2.4		
8	8	56	69.0	2.3	62	68.5	2.7		
10	9	44	71.5	2.4	55	71.1	2.9		
12	10	90	74.1	2.8	70	73.7	2.6	0.90	NS
15	11	49	77.3	3.0	64	76.2	2.9		
18	12	81	80.2	3.2	55	78.9	3.5	2.22	<0.05
21	13	48	82.5	2.9	40	81.8	3.4		
24	14	70	85.0	3.4	50	84.1	3.3	1.46	NS
27	15	36	86.5	3.1	41	87.1	3.5		
30	16	61	89.9	3.9	40	89.2	3.5	0.91	NS
33	17	26	90 7	4.7	32	92.1	3.8		
36	18	66	94.2	4.2	34	92.6	3.9	1.83	<0.05
39	19	17	95.0	4.2	35	94.7	3.7		
42	20	55	98.5	3.9	30	97.0	4.0	1.66	NS
45	21	18	97.8	4.6	24	98.6	4.9		
48	22	64	101.7	4.2	29	100.0	4.4	1.76	<0.05
51	23	16	105.3	4.2	20	101.4	4.9		
54	24	39	105.6	4.1	20	102.3	5.2	2.62	<0.01
57	25	3	107.9	1.3	17	103.6	5.4		
60	26	33	108.7	4.3	19	105.4	5.5	2.35	<0.05

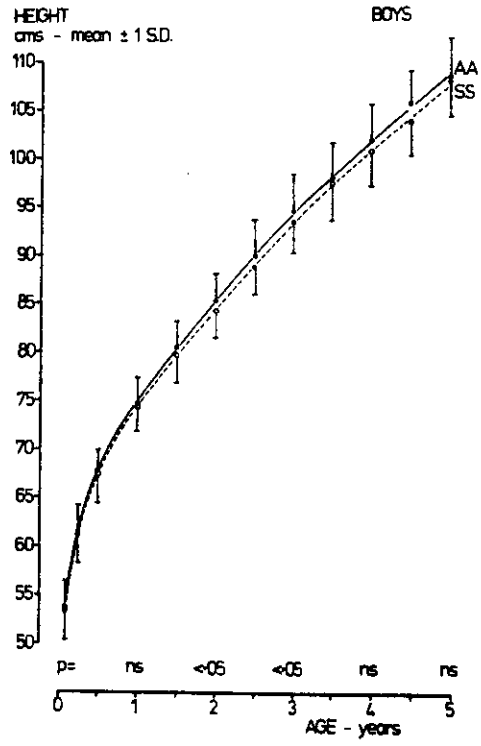


Fig. 10.9 : Mean height AA and SS Boys

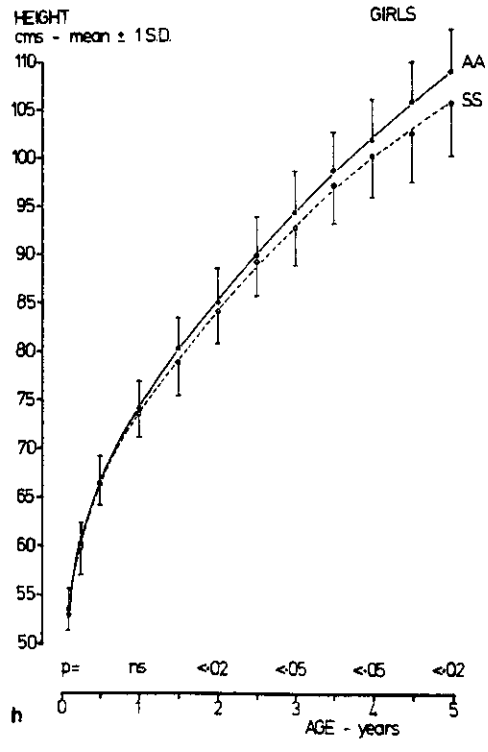


Fig. 10.10 : Mean height AA and SS Girls

TABLE 10.12

AGE (years)	HEIGHT STANDARD SCORES (mean ± 1.SD	
	BOYS	GIRLS
0.5	-0.18 ± 1.21	-0.01 ± 0.93
1	-0.15 ± 1.00	-0.15 ± 0.94
2	-0.33 ± 1.05	-0.25 ± 0.98
3	-0.33 ± 0.83	-0.40 ± 0.92
4	-0.31 ± 0.97	-0.41 ± 1.05
5	-0.01 ± 0.94	-0.78 ± 1.28

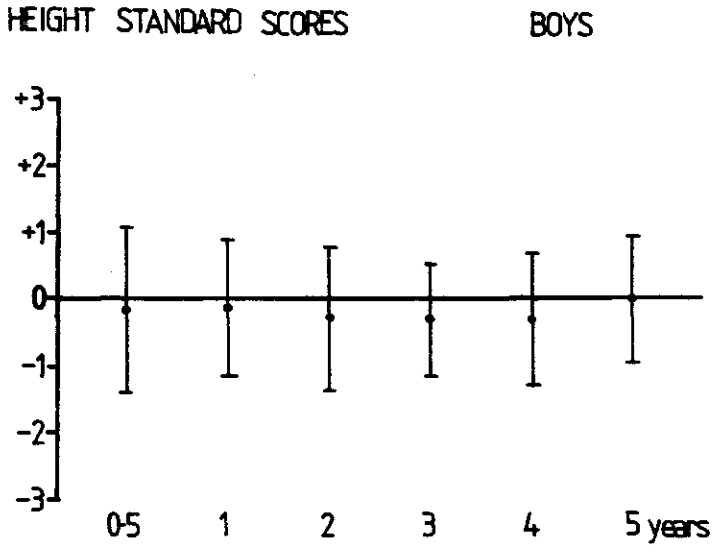


Fig. 10.11: Height standard scores for SS Boys

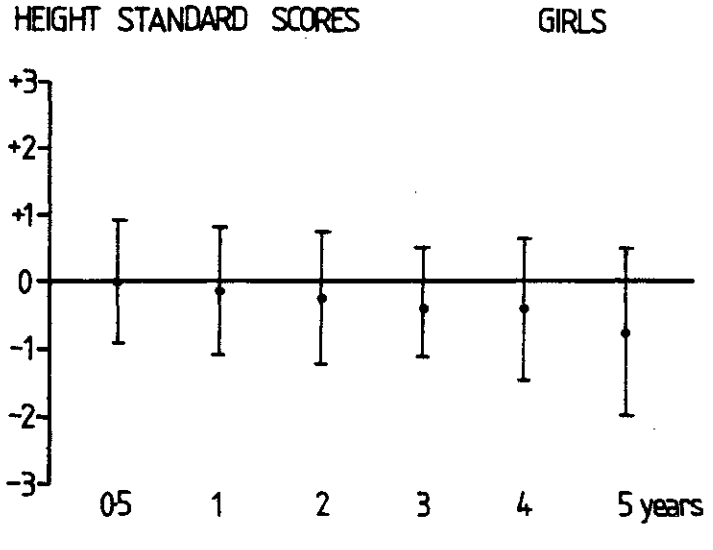


Fig. 10 12 . Height standard scores for SS Girls

TABLE 10.13

HEIGHT VELOCITY (cm/month)

B O Y S

AGE (months)	AA			SS				
	n	$\bar{x}$	SD	n	$\bar{x}$	SD	t	p
1- 6	43	2.62	0.41	59	2.66	0.45	-0.46	NS
6-12	59	1.16	0.31	57	1.07	0.33	1.50	NS
12-24	53	0.79	0.13	43	0.79	0.15	-	NS
24-36	46	0.72	0 17	35	0.71	0 15	0.27	NS
36-48	40	0.59	0.15	24	0.57	0.13	0.53	NS
48-60	26	0.54	0.12	16	0.51	0.09	0.84	NS

TABLE 10.14

HEIGHT VELOCITY (cm/month)

G I R L S

AGE (months)	AA			SS				
	n	$\bar{x}$	SD	n	$\bar{x}$	SD	t	p
1- 6	51	2.48	0.36	53	2.42	0.33	0.88	NS
6-12	78	1.24	0.29	56	1.17	0.33	1.29	NS
12-24	58	0.85	0 16	40	0.83	0.14	0.63	NS
24-36	48	0.73	0.17	25	0.73	0.17	-	NS
36-48	47	0.62	0.12	21	0.56	0.12	1.88	<0.05
48-60	25	0.56	0.12	15	0 48	0 12	1.99	<0.05

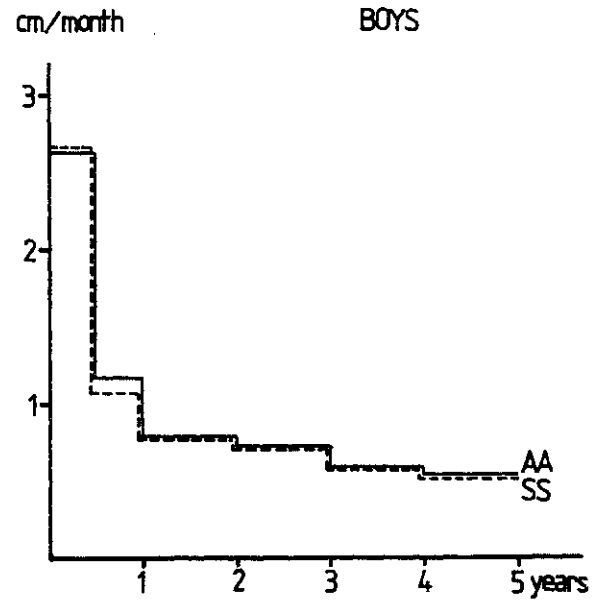


Fig 10.13: Height velocities for AA and SS Boys

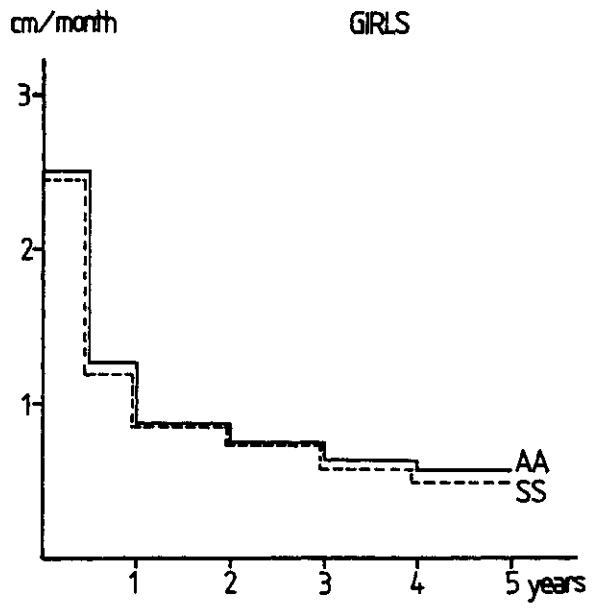


Fig. 10.14: Height velocities for AA and SS Girls

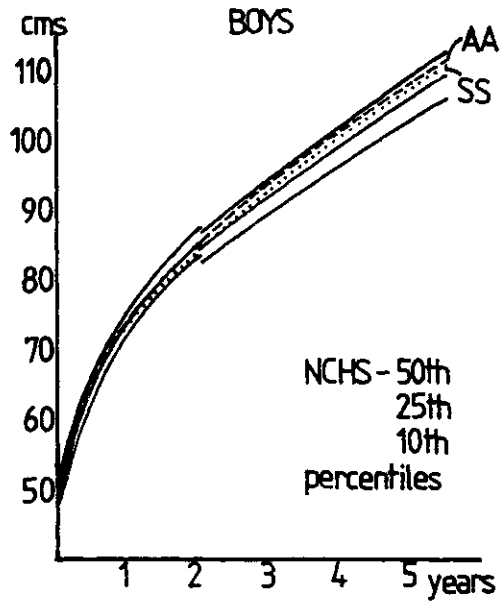


Fig.10.15 : AA and SS Boys - mean heights against NCHS standards

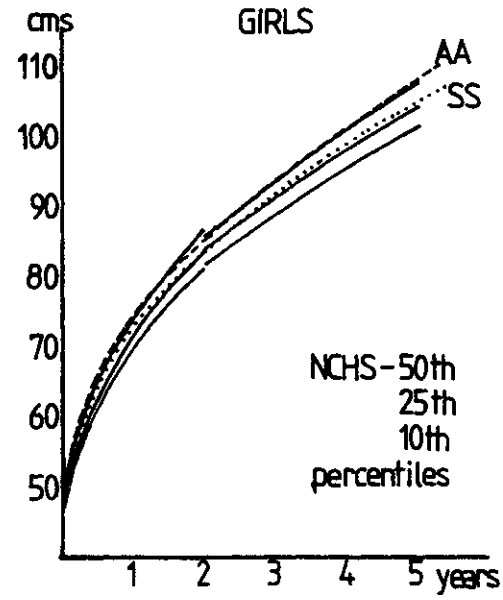


Fig 10.16 : AA and SS Girls - mean heights against NCHS standards

children implied a thinner body build - a deficit of weight for height. A curve of weight against height was constructed using mean weight against mean height plotted at six months intervals from 30-60 months. These lines were compared to the 50th, 25th and 10th percentile lines of weight for height from the NCHS data (101) shown in Figures 10.17 and 10.18. SS children consistently demonstrated a proportionately lower weight for given height than AA children. The difference was less marked in the girls, explained by the relatively greater height deficit seen particularly in the older SS girls, tending to restore height :weight proportions to normal.

5. HEAD CIRCUMFERENCE

Data from head circumference measurements were treated in the same manner. Tables 10.15 and 10.16 show means and standard deviations at all age points to five years. Plots comparing head circumference in AA and SS boys are shown in Figure 10.19 and for girls in Figure 10.20. At one month, head circumference was significantly larger in both SS boys and SS girls, thereafter two distinct patterns emerged. In SS boys, head circumference remained larger, the differences being significant for the first six months but only variably so with increasing age. In SS girls, head size was greater in the first two years, although differences were not significant, and head size was subsequently greater in AA girls.

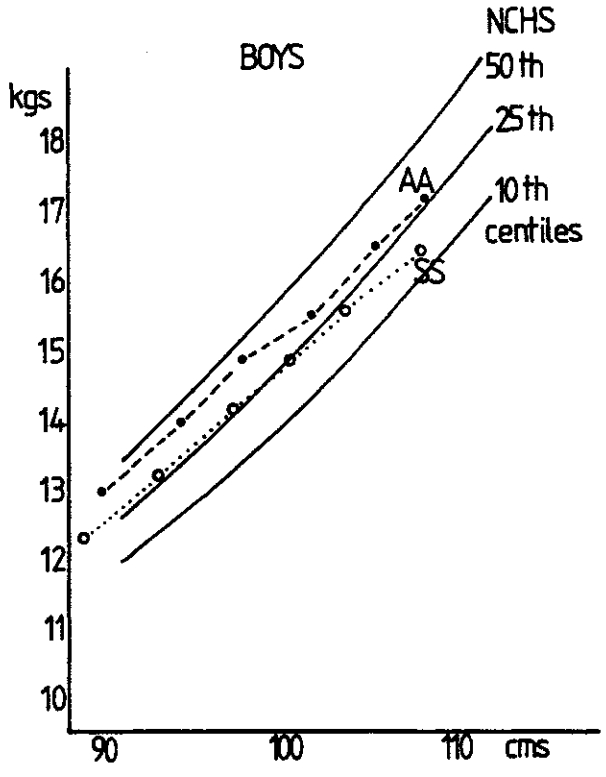


Fig 10.17: Boys - weight for height against NCHS standards

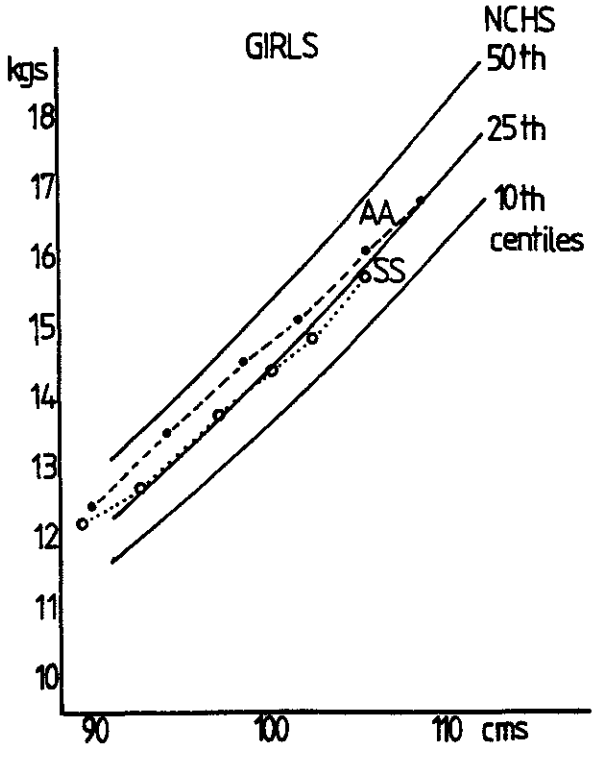


Fig 10.18: Girls - weight for height against NCHS standards

TABLE 10.15

HEAD CIRCUMFERENCE (cms) BOYS AA:SS

TARGET AGE (Months)	AGE BAND	AA			SS			t	p
		n	mean	SD	n	mean	SD		
1	2	62	36.3	1.4	90	37.0	1.8	-2.56	<0.01
2	3	55	38.6	1.2	81	39.3	1.6		
3	4	37	40 2	1.3	74	40.9	1.4	-2.52	<0.01
4	5	41	41.3	1.2	70	42.1	1.2		
5	6	29	42.0	1.4	67	42.8	1.1		
6	7	78	43.0	1.4	83	43.7	1.3	-3.27	<0.001
8	8	48	44.1	1.4	66	44.8	1.4		
10	9	35	44.8	1.4	58	45.6	1.3		
12	10	74	46.1	1.4	64	46.3	1.2	-0.89	NS
15	11	54	46.8	1.3	58	47.1	1.3		
18	12	58	47.5	1.4	56	48.0	1.2	-2.00	<0.05
21	13	42	47.9	2.1	53	48.2	1.2		
24	14	60	48.6	1.5	51	48.7	1.3	-0.37	NS
27	15	25	48.8	1.7	41	49.5	1.3		
30	16	50	49.2	1.5	44	49.8	1.4	-1.97	<0.05
33	17	32	50.0	1.6	43	49.7	1.2		
36	18	54	50.1	1.4	47	50.3	1.4	-0.71	NS
39	19	20	49.7	1.6	35	50.3	1.3		
42	20	40	50.3	1.3	26	50.9	1.4	-1.75	<0.05
45	21	8	49.7	1.7	18	51 1	1.1		
48	22	55	50.7	1.5	22	50.8	1.4	-0.27	NS
51	23	13	51.0	1.7	21	51.2	1.4		
54	24	32	51 1	1.1	17	51.1	1.5	-	-
57	25	8	52.1	1.8	17	51.3	1.7		
60	26	33	51.3	1.5	19	51.7	1.8	-0.84	NS

TABLE 10.16

HEAD CIRCUMFERENCE (cms) GIRLS AA:SS

(months)	AGE BAND	AA			SS			t	p
		n	mean	SD	n	mean	SD		
1	2	65	36.0	1.3	76	36.6	1.4	-2.60	<0.01
2	3	52	38 2	1.1	63	38.6	1.3		
3	4	50	39.6	1.1	65	39.9	1.3	-1.30	NS
4	5	49	40.5	1.1	60	40.9	1.2		
5	6	36	41.4	1.1	55	42.0	1.3		
6	7	86	42.3	1.3	74	42.5	1.3	-0.96	NS
8	8	55	43.7	1.2	55	43.6	1.2		
10	9	42	44.4	1.1	55	44.6	1.4		
12	10	86	45.1	1.4	63	45.2	1.3	-0.44	NS
15	11	48	46.3	1.4	52	45.9	1.4		
18	12	71	46.8	1.4	47	46.8	1 4	-	
21	13	45	47.3	1 3	35	47.1	1.5		
24	14	67	48.1	1.3	51	47.8	1.4	1.19	NS
27	15	32	48.4	1.6	36	48.1	1.7		
30	16	61	48.7	1.4	34	48.7	1.5	-	
33	17	26	49.5	1.5	27	48.9	1.5		
36	18	63	49.6	1.6	29	48.9	1.5	1.97	<0.05
39	19	16	49.1	1.3	29	49.6	1 7		
42	20	50	49.9	1.3	25	49.4	1.5	1.47	NS
45	21	12	50.0	1.8	22	49.9	1.7		
48	22	55	50.2	1.6	25	49.8	1.7	1.00	NS
51	23	14	50.0	1.5	16	50.1	1.5		
54	24	37	50.8	1.4	15	50.2	2.1	1.18	NS
57	25	2	51.2	0.3	15	50 5	1.4		
60	26	31	50.8	1.5	15	50.7	1.3	0.21	NS

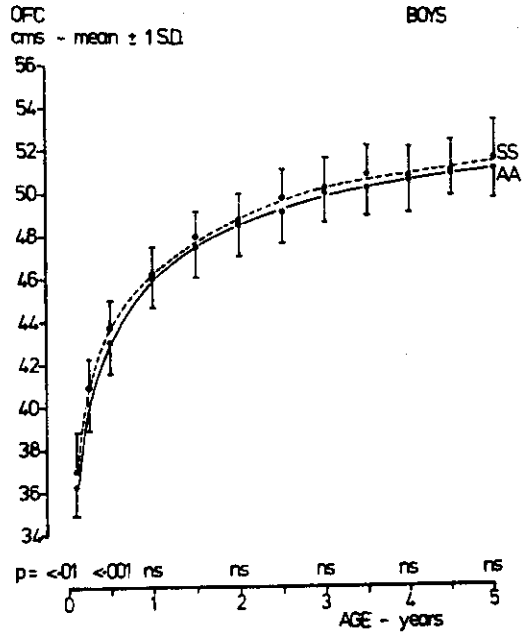


Fig.10.19: Mean OFC AA and SS Boys

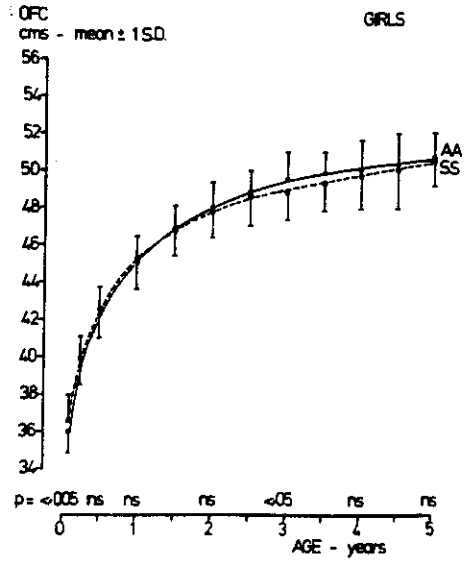


Fig 10.20: Mean OFC AA and SS Girls

Chapter 11

GROWTH PERFORMANCE, CLINICAL DISEASE SEVERITY AND SOCIOECONOMIC STATUS

1. METHODS

Although SS children demonstrated statistically significant growth retardation, the average deficit in both weight and height was unlikely to be of importance in the clinical assessment of the whole group. Nevertheless, certain children were striking in the degree of the growth retardation and the possibility that this could be related to evidence of disease severity was explored.

The clinical records of all SS children were examined to ascertain the frequency and nature of all episodes of illness in the first five years of life. The data were collected into several groups which were thought to represent an index of clinical severity of disease in each individual. This analysis was undertaken with the recognition that many of these factors were interrelated and any study on an individual basis was an imprecise guide to an overall clinical evaluation of disease severity.

i. Frequency of episodes of major illness. The diagnoses included in this category were clearly defined (Table 11.1). Many of these clinical events were treated entirely on an outpatient basis because of the heavy demands on in-patient beds. Any attempt to categorise disease severity in relation to hospital admission patterns would therefore have been inappropriate.

ii. Frequency of episodes of minor illness. The diagnoses considered are also listed in Table 11.1. Episodes of other minor illness, notably treatment of minor skin lesions or intestinal parasites - which were endemic in the community - were not included. If any of these defined minor diagnoses resulted in hospital admission, for example, unusually severe painful crisis, this was categorised as a major illness. If an illness included both major and minor diagnoses, only the major illness was recorded.

TABLE 11.1

DIAGNOSES DEFINED AS: MAJOR ILLNESS	MINOR ILLNESS
Acute splenic sequestration	Upper respiratory infection
Aplasia requiring transfusion	Bronchitis
Septicaemia	Gastroenteritis
Bacterial meningitis	Dactylitis
Pneumonia	Painful crisis (other than episodes severe enough to warrant hospitalisation)
Osteomyelitis	
Convulsions	
Urinary tract infection	
Hospitalisation, other than for routine surgery or blood transfusions	

iii. Frequency of 'sick' visits to clinic. The number of nonscheduled extra visits initiated by parental anxiety or obvious illness might be a measure of disease severity although it was recognised that such visits were likely to occur in proportion to the attentiveness and anxieties of the family. No relationship appeared to exist in the frequency of 'sick' visits between children who were regular or irregular attenders for routine appointments.

iv. Frequency of early splenomegaly. The importance of early splenomegaly, defined as a spleen palpable at, or before, the age of six months has been emphasised in assessing the risk of serious infection and early death in this population (103). It has also been correlated with increased haematological severity as represented by a faster decline in foetal haemoglobin levels (104).

v. The early growth pattern of children who subsequently died. The major causes of death in SS children from this study were sepsis and acute splenic sequestration. Although deaths from such causes are sudden and unexpected, both diagnoses can be related in their pathogenesis to splenic and/or immune dysfunction and might relate to previous evidence of a more severe disease process. There was an unexplained predominance of girls among the children who died (18/119 girls, 7/132 boys. $X^2 = 6.74$ $p < 0.01$) but death was most frequent in the first two years of life in both sexes (mean age at death = 15 months, range 4-33 months in girls, and 21 months, range 3-54 months, in boys) and there was therefore little data on earlier growth performance for many of these children.

It was inappropriate to use weight as an index of chronic ill health relating to growth failure in view of the marked variations in weight observed over short periods in acute illness. Height achieved was more

likely to represent growth progress over a prolonged period and the patients were divided into two groups, those above and those below mean height for their age and sex, labelled respectively 'good' and 'poor' growers. This allocation took no account of any familial influence on height growth as such information was not available. Greater sensitivity in dividing 'good' from 'poor' growers would have been obtained by looking at groups drawn from the extremes of the observations at each age, for example comparing those children lying outside one standard deviation above or below the mean. This however would have significantly reduced the number of children eligible for analysis, particularly at the older age groups where patient numbers were less. Assessments of growth performance, on that basis, were made at ages six months, one, two, three, four and five years. A comparison was made at each age between the good and poor growth groups, the figures for frequency of events being cumulative and not related only to the period between two observation points; this was because the overall impact of continuing good or poor health was the question under review. The number of children in each group at each age is shown in Table 11.2.

2. GROWTH AND THE FREQUENCY OF ILLNESS

The results of comparison between the good and poor growth groups are shown in Tables 11.3 to 11.5 for the mean number of episodes of major illness and minor illness and the frequency of sick visits. The mean of each observation tended to increase steadily with age as the frequencies were cumulative although the groups at each age point were themselves independent, varying according to the number of children who attended and were measured at that age. No consistent differences emerged. Episodes of major illness were more frequent amongst the smaller boys at all ages but differences did not achieve significance and this pattern was not seen in girls except in the first year of life.

TABLE 11.2

AGE (years)	BOYS		GIRLS	
	GOOD	POOR	GOOD	POOR
0.5	35	40	35	36
1	34	36	35	28
2	28	23	28	22
3	23	24	18	16
4	12	16	15	13
5	8	10	11	8

TABLE 11.3

AGE (years)	MEAN NUMBER OF EPISODES OF MAJOR ILLNESS SEEN IN:									
	BOYS					GIRLS				
	GOOD		POOR			GOOD		POOR		
	n	$\bar{x} \pm SD$	n	$\bar{x} \pm SD$	t	n	$\bar{x} \pm SD$	n	$\bar{x} \pm SD$	t
0.5	3	0.09 0.28	5	0.12 0.40	0.37	4	0.11 0.32	8	0.21 0.50	0.99
1	15	0.44 0.75	22	0.61 0.87	0.86	6	0.17 0.57	17	0.61 0.87	2.38*
2	30	1.07 1 39	29	1 26 1 39	0.49	32	1.14 1.32	19	0.86 1.08	-0.79
3	30	1.30 1.72	47	1.96 2.30	1 09	28	1.56 1.76	28	1.75 1.95	0.29
4	28	2.33 2.10	41	2.56 2.78	0.23	35	2.36 1.95	24	1.85 2.51	-0.58
5	19	1.90 2.00	31	3.10 3.84	0.84	32	2.91 2.47	18	2.25 2.55	-0.55

*p <0.05

TABLE 11.4

AGE (years)	MEAN NUMBER OF EPISODES OF MINOR ILLNESS SEEN IN: BOYS					GIRLS				
	GOOD		POOR			GOOD		POOR		
	n	$\bar{x} \pm SD$	n	$\bar{x} \pm SD$	t	n	$\bar{x} \pm SD$	n	$\bar{x} \pm SD$	t
0.5	65	1.85 1.48	67	1.67 1.74	0.47	30	0.86 0.96	55	1.53 1.40	2.31*
1	108	3.18 2.55	125	3.47 2.56	0.47	70	2.00 1.61	85	3.04 2.60	1.91
2	178	6.36 4.87	129	5.61 3.07	0.63	144	5.14 4.25	104	4.73 2.95	-0.38
3	169	7.35 4.38	190	7.92 5.11	0.40	134	7.44 5.19	107	6.67 3.70	-0.48
4	104	8.67 5.60	170	10.62 6.92	0.77	125	8.36 4.53	106	8.15 4.18	-0.12
5	82	8.20 3.60	109	10.90 7.10	1.02	107	9.73 4.34	59	7.37 4.27	-1.11

*p <0.05

TABLE 11.5

	NUMBER OF SICK VISITS SEEN IN:												
	BOYS							GIRLS					
	GOOD			POOR				GOOD			POOR		
	n	$\bar{x}$	± SD	n	$\bar{x}$	± SD	t	n	$\bar{x}$	± SD	n	$\bar{x}$	± SD	t
0.5	45	1.29	1.42	58	1.45	1.60	0.45	25	0.72	0.97	35	0.97	1.13	0.98
1	97	2.85	2.55	117	3.25	2.50	0.65	44	1.26	1.29	81	2.89	2.66	**3.14
2	174	6.21	5.40	136	5.91	3.63	-0.22	125	4.46	3.63	82	3.73	3.24	-0.72
3	175	7.61	4.02	219	9.12	7.67	0.82	141	7.83	2.80	109	6.81	4.74	-0.75
4	126	10.50	7.23	218	13 62	10.83	0.83	148	9.86	4.54	115	8.85	5.93	-0.49
5	110	11.00	6.20	141	14.10	11.70	0.70	126	11.45	6.23	68	8.50	6.00	-0.98

**p <0.01

This difference was mirrored in the increased frequency of minor illness in the first year in the same groups of girls, but achieved significance only in the first six months. The rate of minor illness tended to be less in the better grown boys but the differences were not consistent and did not approach a significant level. After the first year of life, frequency of minor illness was in fact higher in the good growth girls. The possibility that the early differences seen amongst the girls could be attributed to the presence in the poor growth group, of the relatively larger number of girls who subsequently died, was not supported by examination of the growth performance of this particular group (see below). The pattern of sick visits appeared to mirror the pattern established for the frequency of both major and minor illness, in boys and girls.

The observation that SS girls appeared to deviate further away from AA girls with increasing age, while the established growth differences remained constant in boys (Chapter 10) prompted examination of the differences in illness frequency between SS boys and SS girls. The t values for comparisons of rates of major and minor illness and sick visits are shown in Tables 11.6 and 11.7 for good and poor growth groups. Negative t values imply greater frequency of illness or visits in girls. No consistent differences emerged and only isolated comparisons achieved significance. In general, the frequency of all events was greater in boys but the mean number of episodes of major illness was consistently, but not significantly, greater in the good growth girls. Minor illness was significantly more common in good growth boys during the first year of life. The explanation for the apparent difference in growth performance of SS girls over the age of 2 years does not obviously lie with evidence of increased clinical severity of the disease, as judged by these criteria.

TABLE 11.6

"GOOD GROWERS" M:F COMPARISON : t VALUES

AGE	MAJOR ILLNESS	MINOR ILLNESS	SICK VISITS
0.5	-0.27	3.27**	1.93
1	1.66	2.27*	3 23**
2	-0.19	0.98	1.40
3	-0.46	-0.06	-0.19
4	-0.04	0.15	0.27
5	-0.97	-0.83	-0.16

TABLE 11.7

"POOR GROWERS" : M:F COMPARISON : t VALUES

AGE	MAJOR ILLNESS	MINOR ILLNESS	SICK VISITS
0.5	-0.86	0.38	1.48
1	-	0.65	0.55
2	1.05	0.96	2.07*
3	0.29	0.82	1.05
4	0.64	1.05	1.32
5	0.51	1.17	1.16

(negative t value = frequency greater in girls)

*p <0.05

**p <0.01

3. GROWTH AND THE SIGNIFICANCE OF EARLY SPLENOMEGALY

The prognostic importance of early palpable splenomegaly in terms of risk of serious clinical illness and death and in relation to evidence of haematological severity, has been established. It was possible therefore that this physical sign might serve as a marker for those children who were also found to show poorer growth progress. A comparison of the frequency of early splenomegaly in the good and poor growth groups for both sexes is shown in Table 11.8. There were no consistent or significant differences seen, implying that poor growers were not over represented among those apparently high risk children with early splenomegaly.

4. GROWTH IN CHILDREN WHO SUBSEQUENTLY DIED

The cause of death in the 25 children who died are listed in Table 11.9. The heights and weights of these children at age six months and one year are compared with the mean value for all children of the same age in Tables 11.10 and 11.11. The numbers are too small for statistical comparison and whereas the boys who died were consistently smaller in height and weight at all ages, the girls who died were larger at six months and marginally smaller at one year. Weight achieved was used for this comparison as it may be of greater relevance to growth performance in the first year of life than length attained.

5. GROWTH AND ASSESSMENT OF SOCIAL STATUS

The population from which the children in this study came was substantially from the lower socioeconomic areas of the city of Kingston and its environs. Slums and shanty town conditions were common in these areas, with their sequelae of unemployment and unstable family patterns. Nevertheless, a spectrum of relative affluence and domestic stability was apparent in the families attending the clinic. Information about factors reflecting socio-economic conditions was not consistently recorded

TABLE 11.8

HEIGHT ACHIEVED AT AGE: (years)	NUMBER WITH EARLY PALPABLE SPLENOMEGALY					
	BOYS			GIRLS		
	GOOD	POOR	χ^2	GOOD	POOR	χ^2
0.5	12	15	<0.01	12	15	0.16
1	13	7	2.71	6	11	2.83
2	8	6	0.01	8	5	0.02
3	8	4	1.19	3	7	1.83
4	6	3	1.80	6	6	<0.01
5	4	2	0.70	5	5	0.07

TABLE 11.9

PRINCIPAL CAUSES OF DEATH	
Acute splenic sequestration	10*
Pneumonia	7
Gastroenteritis	4
Meningitis	1
Septicaemia	1
Unknown	2
TOTAL	25

*5 with proven septicaemia

TABLE 11.10

HEIGHT AT AGE:	SIX MONTHS			ONE YEAR		
	n	$\bar{x}$	SD	n	$\bar{x}$	SD
Boys subsequently dying	5	65.4	1.4	3	71.2	2.6
All SS boys	84	67.4	2.7	72	74.3	2.5
Girls subsequently dying	10	67.7	3.1	7	73.3	2.5
All SS girls	75	66.6	2.4	70	73.7	2.6

TABLE 11.11

WEIGHT AT AGE:	SIX MONTHS			ONE YEAR		
	n	$\bar{x}$	SD	n	$\bar{x}$	SD
Boys subsequently dying	6	6.58	0.43	3	7.91	0.82
All SS boys	90	7.68	0.91	81	9.07	1.09
Girls subsequently dying	10	7.54	1.17	8	8.03	0.65
All SS girls	77	7.17	0.90	73	8.58	1.06

in the clinical notes, except at the time of diagnosis and the child's first attendance. A comparison was made between the good and poor growth groups to assess the frequency of certain factors selected to represent aspects of domestic stability and socio-economic status.

Almost 75% of children born in Jamaica are born outside a legally recognised marriage union (50) but many are born to common law unions which may be long lasting and stable. The conjugal state of the mother, whether single or living with the child's father, was recorded. Many women however, move from one union to another with successive children, and a further influence on the stability of the family is the number of previous conjugal partners (or "baby fathers") by whom the mother has born children. The number of children in the family reflects the economic burden on the mother. Maternal age at the time of the child's birth may have a significant effect on child rearing skills. Finally, the area in which the home is sited reflected in part the economic well-being of the family, those living in the 'downtown' urban areas being generally more deprived than families from the 'uptown' suburbs or adjoining rural areas. Analysis of these factors (Table 11.12) indicated that the poor growth groups did not show an excess of potentially adverse factors, namely, single mothers, young mothers, large family size, multiple 'baby fathers' or worse housing areas.

TABLE 11.12

SOCIAL FACTOR	B O Y S		G I R L S	
	GOOD (n=36)	POOR (n=36)	GOOD (n=39)	POOR (n=31)
Marital State:				
Single	14	12	23	14
Together	22	24	16	17
Family Size:				
<2 older siblings	23	21	26	20
>3 older siblings	13	15	13	11
Maternal Age:				
<20 years	9	13	19	13
>21 years	27	23	20	18
No. of 'Baby Fathers':				
1 only	21	18	22	17
>1	15	18	17	14
Housing Area:				
'Downtown'	29	32	29	24
'Uptown'/Rural	7	4	10	7

GROWTH & HAEMATOLOGICAL DISEASE SEVERITY

1. METHODS:

All haematological values considered to be in 'steady state', that is, excluding those taken within two months of blood transfusion or associated with acute sequestration or aplastic crises, and obtained within the age band limits (Chapter 9.2) defined at six months, one year, three years and five years were used for the construction of an haematology data base. Only rarely was more than one result available for a child at one age point but if this were so the average was taken.

Data was collected for values of Fetal haemoglobin (HbF), total haemoglobin (Hb), mean cell volume (MCV), percent reticulocytes, serum iron and serum folate. The number of children who had HbF and folate levels measured at six months was small: these were not included in the analysis. Delay in the laboratory resulted in a rather small number of serum folate results at the other age points but these were analysed.

Height and weight achieved at each age point were related to the haematological indices using Standard Linear Correlation to calculate Correlation Coefficients. Analysis of variance was used on data at age one year to explore the combination of haematological variables which would best correlate with growth performance.

2. RELATIONSHIP WITH INDIVIDUAL HAEMATOLOGICAL FACTORS:

The results of multiple correlations between height and weight and the individual haematological factors are shown in Tables 12.1 - 12.4. There was no consistency in the relationships between the sexes or within age groups, for either weight or height. Isolated correlations achieved significance but distribution plots were constructed (using data from both sexes together) to assess the strength of these relationships. Three examples are shown in

TABLE 12.1

BOYS

Weight

	HbF			Total Hb			MCV			Retics			Iron			Folate		
	r	n	p	r	n	p	r	n	p	r	n	p	r	n	p	r	n	p
6/12	-	-	-	0.24	79	0.04	0.04	80	0.73	0.08	79	0.46	0.56	10	0.09	-	-	-
1 Yr.	0.30	64	0.01	0.41	67	0.001	-0.02	67	0.89	0.01	67	0.97	0.17	61	0.19	0.35	39	0.03
3 Yrs.	0.30	43	0.05	-0.11	46	0.44	-0.05	46	0.76	0.26	45	0.08	0.36	45	0.01	0.01	34	0.98
5 Yrs.	0.08	18	0.74	-0.06	18	0.80	0.17	18	0.49	0.33	17	0.19	-0.14	17	0.60	-0.68	13	0.01

TABLE 12.2

BOYS

Height

	HbF			Total Hb			MCV			Retics			Iron			Folate		
	r	n	p	r	n	p	r	n	p	r	n	p	r	n	p	r	n	p
6/12	-	-	-	0.21	75	0.06	0.07	76	0.56	0.04	73	0.76	0.36	10	0.30	-	-	-
1 Yr.	0.19	61	0.13	0.29	62	0.02	0.04	62	0.73	0.08	62	0.52	0.04	58	0.76	0.14	39	0.40
3 Yrs.	0.03	41	0.86	-0.12	44	0.43	-0.01	44	0.94	0.22	43	0.15	0.29	44	0.05	0.01	33	0.96
5 Yrs.	-0.05	18	0.83	-0.20	18	0.43	0.10	18	0.68	0.43	17	0.09	-0.16	17	0.53	-0.72	13	0.005

TABLE 12.3

GIRLS

Weight

	HbF			Total Hb			MCV			Retics			Iron			Folate		
	r	n	p	r	n	p	r	n	p	r	n	p	r	n	p	r	n	p
6/12	-	-	-	0.10	67	0.44	-0.21	68	0.08	-0.13	66	0.29	0.35	6	0.50	-	-	-
1 Yr.	0.09	58	0.48	0.07	65	0.57	-0.23	65	0.06	-0.14	65	0.26	-0.06	52	0.65	0.13	36	0.46
3 Yrs.	0.01	30	0.98	0.07	33	0.69	0.12	33	0.51	0.03	32	0.85	-0.03	32	0.88	-0.12	21	0.60
5 Yrs.	0.52	16	0.04	0.64	17	0.005	0.05	17	0.85	-0.24	17	0.36	-0.18	17	0.49	0.16	14	0.59

TABLE 12.4

GIRLS

Height

	HbF			Total Hb			MCV			Retics			Iron			Folate		
	r	n	p	r	n	p	r	n	p	r	n	p	r	n	p	r	n	p
6/12	-	-	-	0.29	66	0.02	-0.22	67	0.08	-0.26	65	0.04	-0.04	5	0.95	-	-	-
1 Yr.	0.14	57	0.31	0.08	64	0.50	-0.16	64	0.22	-0.17	64	0.17	-0.02	52	0.91	0.12	36	0.48
3 Yrs.	0.19	27	0.35	0.09	29	0.66	0.12	29	0.52	0.15	28	0.45	0.08	28	0.68	0.15	18	0.56
5 Yrs.	0.29	16	0.27	0.32	17	0.20	-0.05	17	0.83	0.09	17	0.72	-0.24	17	0.35	0.19	14	0.52

Figures 12.1-12.3. The distribution of weight against Hb at one year is shown in Figure 12.1. There were few children with low weight and high Hb, although some children had high weight with low Hb. Figure 12.2 shows weight vs.HbF at the same age. There was a tendency for children with low height to have low HbF. Figure 12.3 shows height vs.MCV at one year where those with the lowest height had the highest MCV. Each of these plots suggested a relationship which demonstrated some evidence for the anticipated effect of the haematological variables on disease severity. None, however, achieved significance. One of the difficulties in interpreting these results lay with the fact that none of the chosen haematological variables could be considered to be acting independently. Further analysis to look at combinations of haematological factors was indicated.

3. ANALYSIS OF VARIANCE:

It was possible, indeed likely, that any specific effect imposed by haematological factors in modifying growth patterns would become distorted by other factors (illness, environment and inheritance) with increasing age. The use of analysis of variance to explore combinations of haematological factors and their effects on growth was therefore restricted to children at the age of one year. In order to increase the size of the groups for analysis, data on Serum folate was initially omitted and all children who had complete data for the other variables were included. Analysis was performed separately for weight ($n = 112$) and height ($n = 109$).

As sexes were combined, the first step was to look at the dependence of weight on sex alone. The t value was -2.60 ($p < 0.01$). That is, girls were significantly lighter than boys at one year (an observation already established). Further analysis showed that the model which best predicted weight was (sex +) HbF + MCV - the combination of these variables being highly

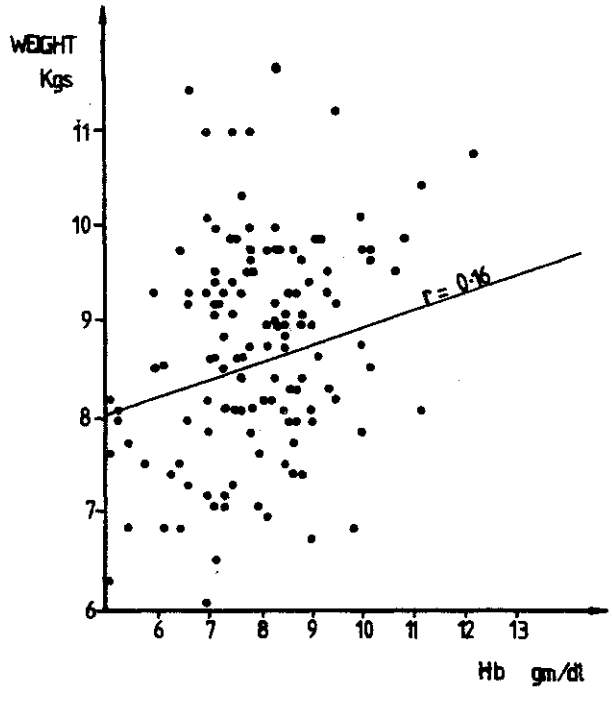


Fig. 12.1 : Distribution of weight against total haemoglobin at one year

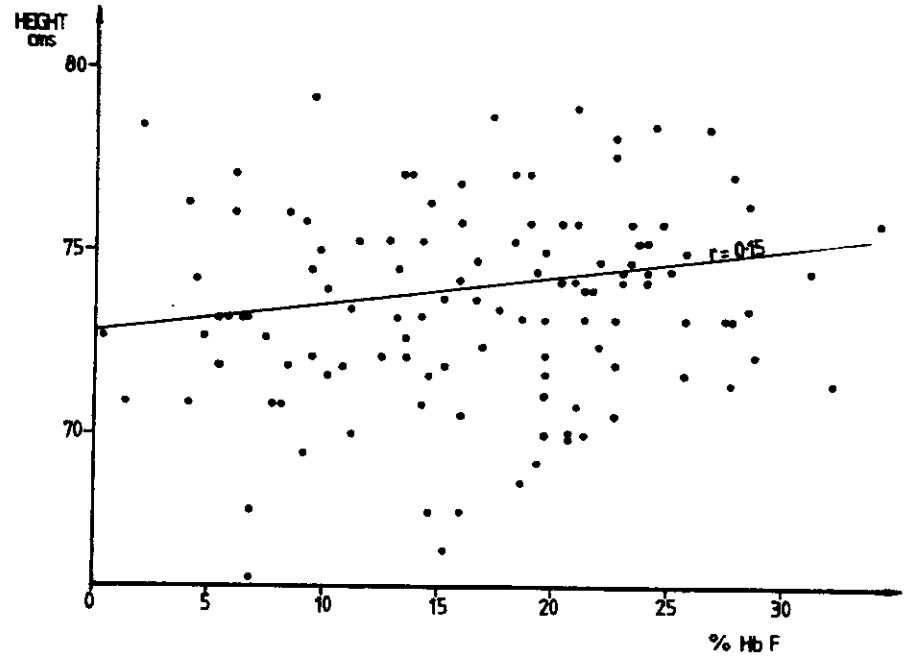


Fig 12.2 : Distribution of height against Hb F at one year

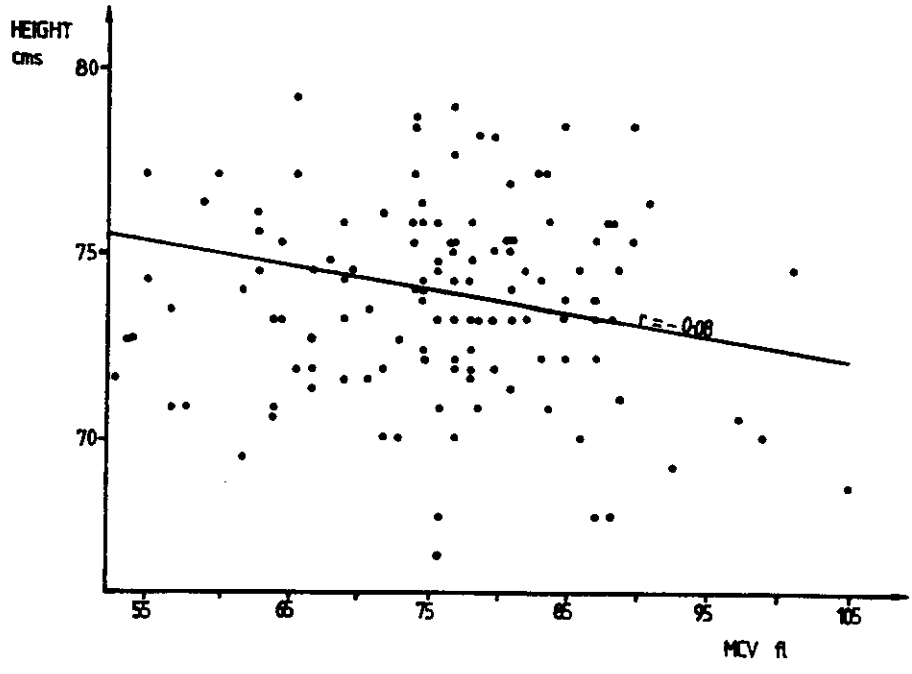


Fig 12.3 : Distribution of height against MCV at one year

significant (t = 3.25 + -2.64; $p < 0.01$). A similar computation using data for height showed that while dependence of height on sex was not quite significant (t = 1.68; $p > 0.05$), the same two haematological values (HbF + MCV) together provided the best model for predication of height (t = 2.40 + -2.22; $p < 0.05$). In conclusion, "good" growth at one year appeared to be associated with high HbF and low MCV - both shown to be beneficial in reducing the clinical and haematological severity of the disease (104(a)). However, it was observed that this model actually accounted for only a small proportion of the variability in weight and height (13.2% for weight and 6.5% for height). Even at this early age, haematological factors appeared to only one small aspect of the variables determining growth.

When the smaller group of children with complete data for all factors plus folate (n = 72 for weight and n = 71 for height) was analysed, the contribution of the MCV was no longer significant. The best model for the prediction of weight became (sex+) HbF + Folate (t = -2.68, 2.42 + 2.14; $p < 0.05$), while none of the haematological variables seemed to contribute significantly to the prediction of height. This lack of consistency emphasised the difficulties inherent in assessing the effect of haematological factors in isolation.

ANTHROPOMETRY STUDY: METHODS

1. POPULATION:

The oldest children in the cohort study were selected for a detailed assessment of body shape using multiple anthropometric measurements. All children still attending the clinics who reached their 4th, 5th or 6th birthday in the year 1.2.79-31.1.80 were included in this study. The use of this age scatter increased the number of children in the study group : if all had been measured at the same age, for example at 5 years, the numbers would have been restricted to the survivors of the 30-40 SS children (and hence 60-80 AA children) who had entered the cohort study over one year, five years previously. All children were measured within four weeks of their birthday.

Of the 248 AA and 108 SS children who would have qualified for the study, 123 AA (49%) and 64 SS (59%) were actually measured (Table 13.1). Twenty-one children had died (19 SS and 2 AA) and strenuous efforts were made to trace all the remaining children, including those who had previously been lost to follow up. One hundred and fifteen home visits were made by myself and a field work assistant during the course of the study, in attempts to trace lost patients or to encourage those who defaulted appointments to attend again. Fifty-seven AA and 7 SS children either could not be traced or were known to have left the country. Forty-nine AA and 12 SS children, all known to be alive and to have attended the clinic in the previous twelve months, failed to attend for measurement despite being sent appointments for the Study. Many of these children lived in isolated rural areas where a follow up visit at home was impractical; a few lived in barricaded areas of urban Kingston where it was at times unwise to go. Fourteen children (9 AA and 5 SS) who, despite attending the clinic within four weeks of their birthday, were not measured because they had attended on the wrong day. The study had to be abandoned in one child

TABLE 13.1

	AA	SS
Number of children who would have qualified	248	108
Died	2	19
Lost to follow up	57	7
Defaulted study	49	12
Missed study	9	5
Unsuccessful study	1	0
Omitted from study	7*	1+
Number measured	123	64

*Congenital heart disease (2)
Short-limbed dwarf (1)
β thalassaemia trait (4)

+Congenital heart disease

through lack of cooperation. The same medical criteria for exclusion from the study applied as in the analysis of the longitudinal growth data (Chapter 9) and eight children were eliminated.

The study was explained to all parents who accompanied their children to the clinic and verbal consent for the procedures was obtained. It was emphasised to the parents of the AA children that the data collected was to be used to assess the growth performance of the children with SS disease. No parent declined to cooperate.

Table 13.2 gives details of the number of children measured in each age, sex and genotype group. The numbers of children measured at age 6 years are less because the oldest children in the cohort population did not become 6 years until July 1979, half way through the year of the growth study.

2. MEASUREMENT TECHNIQUES

All measurements were made by myself and the same technique was used for all children, cases and controls.

Weight was recorded with the children in light clothing (for example, sundress or shorts and T-shirt) without shoes. A sliding beam balance scale was used which recorded weight to ±0.1 Kg. The scales were intermittently calibrated with a standard weight.

Height was measured using a standing stadiometer (Holtain Instruments Ltd.) whose calibration was checked daily with a standard measuring rod. The child was placed with his head held in the Frankfurt plane and an assistant (usually the child's mother) ensured that his heels were not raised from the ground while he was encouraged to "make himself tall". The counterbalanced headboard was brought down on the child's head whilst gentle upward pressure was exerted below the mastoid processes (100). The digital gauge gave a reading accurate to ±0.1 cm.

TABLE 13.2

	AA		SS	
AGE (years)	BOYS	GIRLS	BOYS	GIRLS
4	25	29	12	10
5	22	25	8	15
6	15	7	13	6

Sitting height was measured on a sitting stadiometer (Holtain Instruments Ltd.) The child sat with his knees comfortably flexed over the edge of the table while the sliding back piece was brought forward against his spine and advanced until he was sitting perpendicularly without lifting his buttocks from the table. With the head elevated in the same plane and upward traction on the mastoids, the head board was lowered and the digital gauge read to ± 0.1 cm.

Head circumference was measured using a flexible steel tape held to record the maximum occipito-frontal diameter. Hair slides were removed and wherever possible plaits and knots displaced. As discussed in Chapter 10.5, the intricate "cane row" braiding of the hair in girls presented a source of some inaccuracy. Measurement was recorded to the nearest 0.1 cms.

Arm span was measured with the child standing with his back against a wall using a horizontal scale constructed from graph paper ruled in 1 cm divisions. Arms were held at 90^{o} to the trunk and measurement was made with the child encouraged to stretch out as far as possible.

Mid-upper arm circumference was recorded on the left arm after the mid-point between the olecranon and the acromion had been identified and marked with the elbow held in 90^{o} of flexion. Arm circumference was then measured using a flexible steel tape with the elbow extended. Measurement was made to the nearest 0.1 cm without indenting the skin with the tape.

Chest circumference was recorded with the steel tape held horizontally at the level of the nipples and the measurement was made with the child in expiration. Most children were unable to forcibly expire and hold their breath in expiration while the measurement was made. Inevitably measurements were recorded at different degrees of expiratory effort. Readings were taken to ± 0.1 cm.

Anteroposterior and lateral chest diameters were measured in the

horizontal plane at the level of the 4th sterno-costal junction during expiration, using an Harpenden Anthropometer. The digital gauge recorded to ± 0.1 cm. The instrument was calibrated regularly against a standard measuring rod.

Intercristal distance (pelvic diameter) was measured with the tips of the anthropometer held firmly against the crests of the anterior superior iliac spines, indenting the subcutaneous tissues if necessary.

Interacromial distance (pectoral diameter) was measured with the tips of the anthropometer held on the lateral aspects of the acromium processes, with the child standing erect.

Triceps skinfold thickness was measured at the posteriorly marked mid-point of the left upper arm, with the elbow extended, using a Holtain Skinfold Caliper according to the technique described by Tanner and Whitehouse (105). Measurements were recorded to the nearest 0.1 mm.

Subscapular skinfold thickness was measured just below the angle of the left scapula using the same calipers (105).

The mean of three consecutive readings was taken for all measurements except for weight, head circumference and arm span which were only measured once.

3. DATA ANALYSIS AND STATISTICS

(i) Data Base: All results were coded for computerisation with the children listed according to age, sex and genotype grouping. Certain derived values were computed for incorporation into the data base:

Arm length = (Arm span - Interacromial distance) ÷ 2

Leg length = Standing height - Sitting height.

Means and standard deviations were calculated for each variable.

(ii) Data Distribution: The statistical methods used for the analysis of the data assumed that variables were normally distributed. Their actual distributions were therefore examined prior to analysis. It was difficult to form a good impression of the distributions from examination of the individual age, sex and genotype groupings because of the small sample sizes. The data were therefore pooled to permit an overall assessment of the distribution of each anthropometric variable. Using the data in each of the twelve separate subgroups, the mean ($\bar{x}$) and standard deviation (S) of each variable was calculated and then used to standardise each observation ($x_1 \ldots\ldots x_n$) in the group according to the formula:

$$Z_i = \frac{x_i - x}{S} \qquad (i = 1, \ldots, n)$$

The standardised values (Z) had the same distribution as the observed values (x) but were scaled to have zero mean and unit standard deviation and the Z's for each variable from all twelve sub-groups could be pooled. A histogram of the pooled data was constructed to give an overall impression of the distribution of each variable. The distributions of all measurements were approximately normal, except mid upper arm circumference and the skinfold thicknesses, each of which were positively skewed.

The Transformation 100 $\log_{10}$ (reading in 0.1 mm - 18) is in general use for skinfold thickness (106) and was found to be suitable (Fig 13.1, 13.2) but no transformation is generally discussed in publications presenting data on arm circumference. The transformation $\log_{10}$ (arm circumference) was applied to the data and found to be suitable (Figure 13.3).

DISTRIBUTION OF LOG_{10} [Triceps skinfold -18]

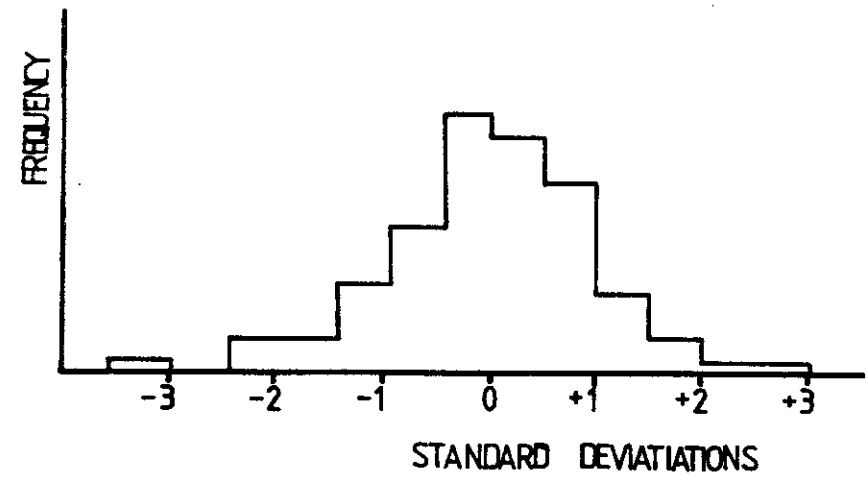


Fig.13.1

DISTRIBUTION OF LOG_{10} [Subscapular skinfold - 18]

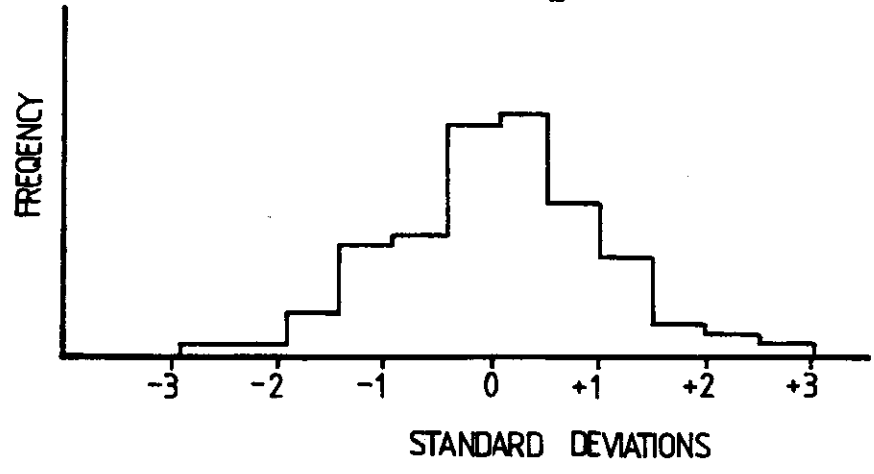


Fig.13.2

DISTRIBUTION OF LOG_{10} [Arm circumference]

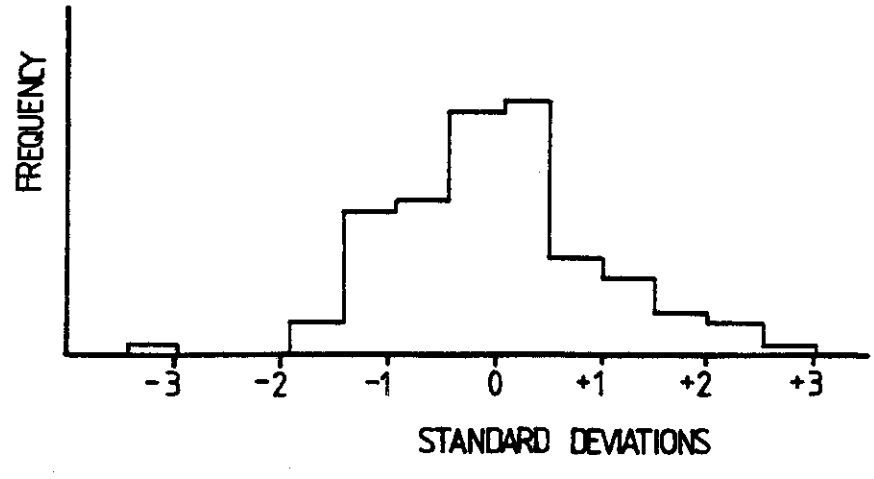


Fig. 13.3

(iii) Analysis of Variance : The means and standard deviations of the data were initially tabulated by age, sex and genotype groupings. Calculation of Student's t values to compare AA and SS children for each variable at each of the three ages, separately for boys and girls, produced inconsistent results and was an insensitive technique for assessing genotype differences as each t test was based on small sample sizes. Three way analysis of variance (107) was used for each variable to obtain an overall indication of the differences between AA and SS children, allowing pooling of information from the different age and sex groups. An example of the computation and the assumptions involved is shown below --

if Y = the height of a given child, then $Y = \mu + \varepsilon$, where μ = the mean height in a population of children of the same sex, genotype and age, and ε is an error term representing this child's deviation from the mean height. Initially there is a supposition that a separate μ is required for each of the twelve subgroups of children in the study, but the analysis is simplified if an additive model is assumed for the μ values

i.e. $\mu_{ijk} = \alpha + \beta_i + \gamma_j + \delta_k$

where μ_{ijk} = mean height of children in group ijk

β_i = genotype effect (i - 1 for AA, 2 for SS)

γ_j = sex effect (j = 1 for boys, 2 for girls)

δ_k = age effect (k = 1 for 4 yrs, 2 for 5 yrs, 3 for 6 yrs).

It can be assumed that $\beta_1 = \gamma_1 = \delta_1 = 0$ without loss of generality, i.e. the mean height of 4 year old AA boys is then defined simply as α. If the child were SS, add β_2; if female, add γ_2; if age 5 or 6 years, add δ_2 or δ_3. E.g. the mean height of 5 year old SS girls would be $= \alpha + \beta_2 + \gamma_2 + \delta_2$.

The model in use is therefore simplified involving only five

parameters (α, β_2, γ_2, δ_2, δ_3) instead of the original twelve (μ_{111},.....μ_{223}). The loss of the other seven parameters is permitted by the assumption that the genotype effect is the same regardless of sex and age, that is to say there are no interactions between sex, age and genotype. This hypothesis was tested for this data and in each case the interactions were found to be insignificant.

The model above, in which the effects of age, sex and genotype on each anthropometric variable were additive, was utilised to compute Student's t test values for differences attributable in turn to each of the three parameters (genotype, sex and age). As a further simplification, the effect of age was assumed to be linear and one t value was derived for its effect, rather than two, one for δ_2 and one for δ_3.

(iv) Analysis of Covariance : In order to study the genotype differences in various pairs of inter-related growth parameters (e.g. weight and height, sitting height and standing height) the statistical validity of expressing these inter-relationships as ratios (e.g. weight ÷ height) was studied. It seemed likely that there would be difficulties in their use. Only if the relationship between two variables was in direct proportion, i.e. it could be represented graphically as a straight line through the origin, would a ratio be a valid expression of their relationship in each individual child. Figure 13.4 illustrates the relationship between height and weight in AA boys, showing the distribution of individual children and the regression line. The intercept is not zero and the value of the ratio weight ÷ height varies from 0.14 at the lower end to 0.18 at the higher end. A ratio of 0.18 is recorded for two children, the first (A) is tall but has a normal weight for that height and the second (B) is shorter but is heavy for his size. The weight ÷ height

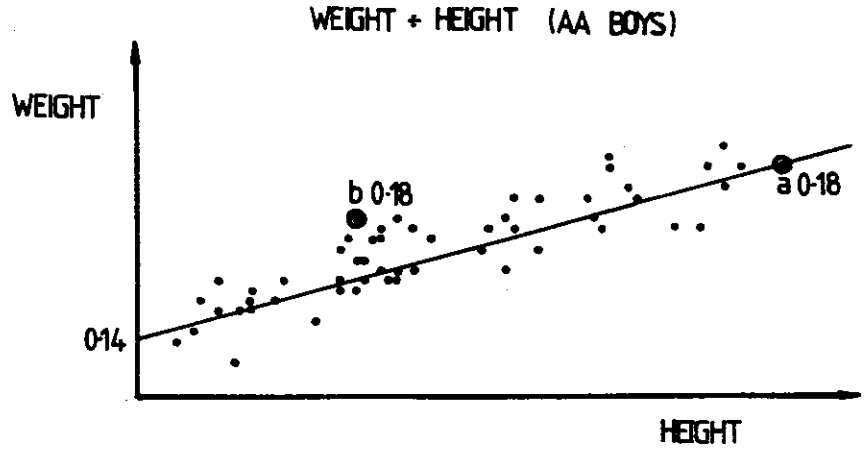


Fig. 13.4

ratio is clearly not a sensitive indicator of weight for height in these children. A more appropriate method of assessing the relationship is by analysis of covariance (107). This technique was applied to study the relationship of weight and height, sitting height and standing height, anteroposterior and lateral chest diameters, and interacromial and intercristal diameters. An example of the computation, for weight and height, is given below ---

The analysis attempts to answer whether the relationship between weight and height (which is likely to be strongly correlated) varies between the different sex and genotype groups. The effect of age is considered negligible and the data pooled over the three age groups on the grounds that this simplifies the analysis. The justification for this assumption is that, although the relationship between weight and height changes with age (108), the change over such a narrow age range is negligible. The data is then restricted to four sets of scatter plots, each relating weight to height for one of the sex/genotype combinations. In each case the relationships appeared linear and the data from these plots can be summarised by the equation :

$$y = \alpha_{ij} + \beta_{ij}x + \varepsilon$$

where y = weight, x = height, ε is an error term and α and β are calculated from the regression lines.

i = 1 for AA, 2 for SS

j = 1 for boys, 2 for girls

The slopes of each of the regression lines can be shown not to differ significantly from each other and a common slope β can be used for all four sets of data and the model becomes :

$$y = \alpha_{ij} + \beta x + \varepsilon$$

Any difference between the sexes and the genotypes are now reduced to differences in their four intercepts (α_{11}, α_{12}, α_{21}, α_{22}). Further analysis is similar to analysis of variance and an additive model for the intercepts, where $\alpha_{ij} = \mu + \gamma_i + \delta_j$ is assumed with $\gamma_1 = \delta_1 = 0$, i.e. that there is no significant genotype : sex interaction (γ_i = genotype effect, δ_j = sex effect). This assumption can be tested and shown to be correct and, from the final model, the intercepts in the four groups are given as : $\alpha_{11} = \mu$; $\alpha_{12} = \mu + \delta_2$; $\alpha_{21} = \mu + \gamma_2$: $\alpha_{22} = \mu + \gamma_2 + \delta_2$. The difference between the sexes is thus reduced to a single parameter δ_2 and that between the genotypes to γ_2.

Student's t values for these parameters predict the significance of the differences attributed to sex and genotype in the inter-relationship of the two measured variables.

Chapter 14

COMPARISON OF BODY SHAPE IN AA AND SS CHILDREN

1. INDIVIDUAL ANTHROPOMETRIC MEASUREMENTS

The means and standard deviations of the thirteen anthropometric measurements and the two derived values (arm and leg length) are tabulated by age, sex and genotype group in Tables 14.1 - 14.3. The data for arm circumference and skinfold thickness are presented in the transformed state. Using the technique of three way analysis of variance (Chapter 13.3(iii)) the Student's t test values for the differences individually attributable to the three parameters (age, sex and genotype) are shown in Table 14.4 for each anthropometric variable.

(i) Genotype Effect : On average, weight, height, sitting height, limb lengths, interacromial and intercristal distances were all significantly lower in SS children. Average skinfold thickness was also lower in SS children although the difference in triceps skinfold thickness failed to achieve significance. Anteroposterior chest diameter was significantly greater in the SS children while lateral diameter showed no difference, and although the resulting chest circumference was greater in the SS group, it did not achieve significance. Head circumference was not different in the two groups. The most significant effects of genotype were those on height, sitting height, arm span, pelvic and shoulder girdle dimensions and arm circumference. The overall pattern of the differences implied effects on skeletal growth and soft tissue thickness.

(ii) Sex Effect : While standing height was no different between boys and girls, sitting height was significantly less in girls. The relatively good growth performance of Jamaican girls, who show less difference from boys by the age of five than girls in other ethnic groups, has been noted previously (109). As expected, leg length in girls was greater than in boys but the effect did not reach significance. Weight was less in

TABLE 14.1 (4 Years)

MEASUREMENT	BOYS						GIRLS					
	AA			SS			AA			SS		
	n	Mean	SD	n	Mean	SD	n	Mean	SD	n	Mean	SD
Weight (Kg)	25	15.7	1.6	12	14.6	1.0	29	14.9	1.9	10	14.5	1.5
Height (cm)	25	102.1	3.2	12	99.0	2.2	29	101.6	4.3	10	101.2	2.8
Sitting height (cm)	24	56.5	2.1	12	55.0	1.2	29	55.5	2.3	10	55.3	1.1
Leg length (cm)	24	45.6	2.1	12	44.0	1.5	29	46.0	2.5	10	45.9	2.3
Arm length (cm)	23	39.9	2.0	11	38.7	1.8	26	39.0	2.3	8	39.9	1.3
Interacromial distance (cm)	25	22.4	1.1	12	21.3	1.1	29	21.8	1.3	10	21.4	1.2
Arm span (cm)	23	102.3	4.6	11	98.8	3.9	26	99.6	5.3	8	98.6	3.1
Intercristal distance (cm)	25	14.8	0.6	12	14.2	0.4	29	14.6	1.0	10	14.2	0.5
Chest circumference	25	51.5	1.9	12	51.7	1.5	29	49.8	2.1	10	49.9	2.6
Chest AP diameter (cm)	24	10.5	0.8	12	10.6	1.0	29	10.0	0.8	10	10.4	0.8
Chest lateral diameter (cm)	25	16.3	0.8	12	16.3	0.6	29	16.0	0.7	10	15.6	0.7
Log_{10} arm circumference	25	2.21	0.03	12	2.18	0.04	29	2.19	0.03	10	2.18	0.03
100 log_{10} (triceps SF - 18)	25	170.9	12.0	11	163.3	13.3	28	176.4	10.4	10	173.9	12.4
100 log_{10} (Subscap SF - 18)	25	154.9	11.2	11	152.3	10.8	28	157.5	12.3	10	152.1	12.3
Head circumference	25	50.2	1.7	12	50.9	2.0	29	49.5	1.4	10	49.4	1.3

TABLE 14.2 (5 years)

MEASUREMENT	BOYS						GIRLS					
	AA			SS			AA			SS		
	n	Mean	SD	n	Mean	SD	n	Mean	SD	n	Mean	SD
Weight (Kg)	22	17.1	1.9	8	16.1	1.8	25	16.6	2.3	15	16.0	1.8
Height (cm)	22	108.3	5.2	8	106.8	3.0	25	108.1	3.7	15	105.8	5.6
Sitting height (cm)	22	58.7	2.0	8	57.6	1.8	25	57.8	1.8	15	56.2	2.8
Leg length (cm)	22	49.7	3.9	8	49.2	1.6	25	50.3	2.7	15	49.7	3.0
Arm length (cm)	22	42.3	2.3	8	42.3	2.3	25	42.0	2.1	15	41.4	2.7
Interacromial distance (cm)	22	23.5	1.1	8	22.4	0.8	25	23.3	1.2	15	22.6	0.8
Arm span (cm)	22	108.1	5.3	8	107.1	5.0	25	107.3	5.0	15	105.4	5.7
Intercristal distance (cm)	22	15.3	0.9	8	15.3	1.0	25	15.4	1.0	15	14.8	0.7
Chest circumference (cm)	22	52.4	2.4	8	52.9	1.6	25	51.3	2.7	15	52.2	1.7
Chest AP diameter (cm)	22	10.5	0.9	8	10.9	0.7	25	10.6	0.6	15	11.1	0.8
Chest lateral diameter (cm)	22	16.7	0.9	8	16.8	0.8	25	16.6	1.0	15	16.9	0.5
Log_{10} arm circumference	22	2.21	0.03	8	2.17	0.01	25	2.20	0.04	15	2.18	0.03
100 log_{10} (triceps SF - 18)	22	170.2	14.4	8	164.2	10.4	25	171.4	13.9	14	170.7	14.4
100 log_{10} (subscap 18)	22	151.9	12.4	8	140.7	13.4	25	152.0	15.4	14	150.7	14.3
Head circumference (cm)	22	50.4	1.5	8	50.4	1.0	25	50.6	1.3	15	49.7	1.7

TABLE 14.3 (6 years)

	BOYS						GIRLS					
	AA			SS			AA			SS		
	n	Mean	SD	n	Mean	SD	n	Mean	SD	n	Mean	SD
Weight (Kg)	15	19.6	1.7	13	18.3	2.3	7	18.5	1.7	6	16.9	2.0
Height (cm)	15	115.8	3.8	13	113.1	5.2	7	116.2	5.0	6	109.2	5.7
Sitting height (cm)	15	62.1	2.1	13	60.7	3.0	7	61.3	2.1	6	58.2	2.8
Leg length (cm)	15	53.8	2.5	13	52.4	2.5	7	54.9	3.3	6	51.0	3.4
Arm length (cm)	14	45.1	1.4	13	43.3	1.8	7	45.9	2.5	6	42.6	3.2
Interacromial distance (cm)	15	25.1	0.9	13	24.0	0.4	7	24.8	1.0	6	23.4	1.3
Arm span (cm)	14	115.2	3.3	13	110.7	4.7	7	116.6	5.7	6	108.7	7.4
Intercristal distance (cm)	15	16.1	0.7	13	15.9	1.0	7	15.9	0.7	6	15.1	0.7
Chest circumference (cm)	15	53.7	1.8	13	54.5	2.9	7	52.2	2.2	6	53.1	2.5
Chest AP diameter (cm)	14	11.2	0.5	13	11.3	0.8	7	10.8	0.5	6	11.2	0.7
Chest lateral diameter (cm)	15	17.4	0.7	13	17.4	0.9	7	17.2	0.9	6	17.0	0.8
Log_{10} arm circumference	15	2.11	0.03	13	2.20	0.03	7	2.20	0.01	6	2.20	0.02
100 log_{10} (triceps SF - 18)	15	159.4	14.1	13	156.5	15.5	7	163.3	4.7	6	164.6	11.5
100 log_{10} (subscap SF - 18)	15	142.8	9.7	13	136.9	12.7	7	147.4	7.2	6	144.6	8.3
Head circumference (cm)	15	51.8	1.6	13	51.8	1.7	7	50.9	1.2	6	51.4	1.3

TABLE 14.4

ANTHROPOMETRIC VARIABLE	STUDENT'S t STATISTICS		
	GENOTYPE EFFECT(1)	SEX EFFECT(2)	AGE EFFECT(3)
Height	-3.68***	-0.63	16.01***
Sitting height	-4.05***	-3.32***	12.17***
Leg length	-2.59**	1.62	15.29***
Weight	-3.20**	-2.43*	9.95***
Arm span	-3.60***	-1.52	13.33***
Interacromial distance	-4.97***	-1.87	12.62***
Arm length	-2.79**	-1.16	12.11***
Intercristal distance	-3.24***	-1.53	8.38***
Chest circumference	1.67	4.21***	6.20***
Chest AP diameter	2.73**	-1.70	4.88***
Chest lateral diameter	0.07	-2.29*	7.57***
Log_{10} arm circumference	-4.29***	-1.48	1.87
100 log_{10} (triceps SF - 18)	-1.74	2.98**	-4.00***
100 log_{10} (subscap SF - 18)	-2.40*	1.79	-4.79***
Head circumference	0.08	-2.90**	5.04***

(1) negative t = SS<AA

(2) negative t = girls<boys

(3) negative t = decrease with age

* p <0.05

** p <0.01

*** p <0.001

girls and skinfold thicknesses were greater although arm circumference was less. Chest dimensions and head size were greater in boys.

(iii) Age Effect : As expected, all variables showed a highly significant increase with age, except arm circumference, which is known to be relatively age independent in pre-school children (110), and skinfold thickness which decreases after the first year of life until age eight or nine years in all ethnic groups (105, 111, 112).

2. INTER-RELATED GROWTH PARAMETERS :

The relationships in four pairs of measurements were investigated using analysis of covariance (Chapter 13.3 (iv)) : weight and height; sitting height and standing height; interacromial and intercristal diameters; anteroposterior and lateral chest diameters. The Student's t values for the differences attributable to genotype and sex are shown in Table 14.5

1. Genotype Effect : The only relationship to achieve a significant difference attributable to genotype was that between the chest diameters. The result implied that, for a given lateral diameter, SS children's chests had larger anteroposterior dimensions. The relationship between height and weight suggested that, although both weight and height were significantly reduced in SS children, the weight for height relationship was similar in the two genotypes. A similar conclusion to the pelvic and pectoral girdle widths which were both reduced in SS children, and to standing and sitting height -- an index of leg : trunk length ratio .

2. Sex Effect : Two effects emerged -- first that for a given height girls tended to be lighter than boys, and second, sitting height was a proportionately smaller fraction of standing height in girls than in boys.

TABLE 14.5

VARIABLES		STUDENT'S t STATISTICS	
y	x	GENOTYPE EFFECT(1)	SEX EFFECT(2)
Weight	Height	-1.69	-2.73 **
Height	Sitting height	1.38	-3.79 ***
Interacromial	Intercristal	-1.46	-1.37
Chest A-P	Chest lateral	3.07 ***	-1.40

(1) negative t = SS<AA

(2) negative t = girls<boys

** p<0.01
*** p<0.001

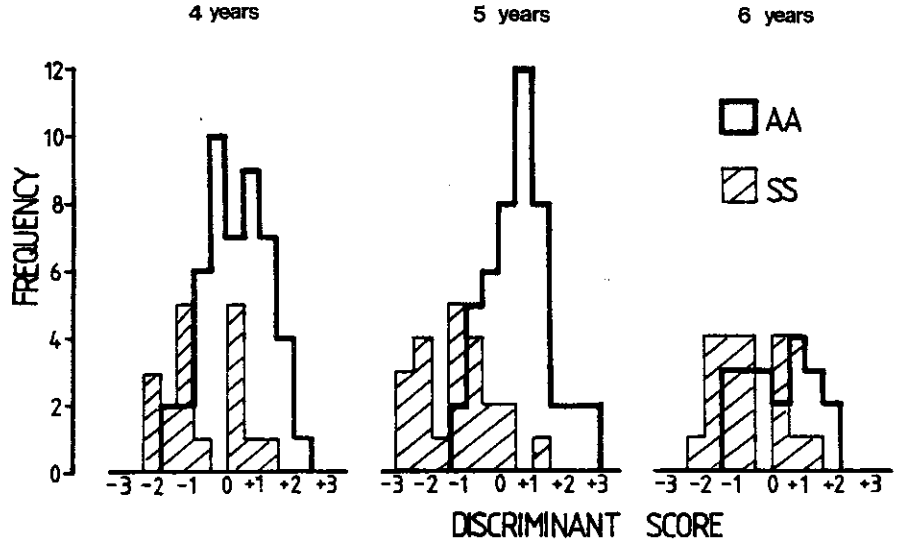
BODY SHAPE : CORRELATIONS WITH CLINICAL AND HAEMATOLOGICAL DISEASE SEVERITY

1. DISCRIMINANT ANALYSIS :

SS children were significantly different from AA children in most indices of body shape. It was not possible to select a single anthropometric measure which best represented the overall growth performance of SS children and an attempt was made to look for a weighted sum of factors which would optimise the differences observed between the genotypes and provide a criterion for assessing the "severity" of growth changes amongst SS children. Forward stepwise discriminant analysis utilising all the anthropometric variables and bone age scores was applied to the data from the five year old children in the study. This group served as a model for the analysis to ensure that bone age estimation was included in the derivation of a weighted score. A limit was set on the selection of those three variables which together best separated the AA and SS children. Sitting height, chest circumference and arm circumference were selected and the analysis provided standardised discriminant function coefficients for each of these variables which were applied to the measurements obtained for every child in the anthropometry study, producing a numerical discriminant factor. A negative factor characterised these children with the most SS-like growth data and vice versa for the AA children. The distribution of discriminant factors between the genotypes at each age level is shown in Fig 15.1.

2. CLINICAL RELATIONSHIPS :

The same criteria for the assessment of clinical disease severity were used as in the analysis of the longitudinal growth data (Chapter 11). The frequencies of episodes of major illness and minor illness and of sick visits were calculated for each child at the time of the study and expressed as the mean number of episodes per year to permit pooling of data from each of the three age groups. Linear correlation was performed between the discriminant factor and the frequency of these events in each child. No significance emerged with correlation coefficients of -0.10, -0.13, -0.13 for the frequencies of major illness, minor illness and sick



Distribution of discriminant scores between AA and SS children

Fig. 15.1

visits respectively. The occurrence of early splenomegaly was also assessed and observed in 14/34 children with discriminant factors less than the mean (i.e. children with the most SS-like characteristics) and 8/25 in those with factors greater than, or equal to, the mean. The difference was not significant (Chi square = 3.71, $p>0.05$).

3. HAEMATOLOGICAL RELATIONSHIPS :

The haematological factors selected for analysis were as outlined in Chapter 12 (total haemoglobin, foetal haemoglobin, mean cell volume, percent reticulocytes, serum iron and serum folate). No significant variation in these factors was known to occur between sexes or with age over the range of this study (62, 113). Linear correlations were calculated between the discriminant factor and individual haematological measurements for each SS child in the study. The data was pooled for both sexes and all ages. There was no significant correlation with any of the haematological indices (Table 15.1).

TABLE 15.1

HAEMATOLOGICAL FACTOR	n	r	p
Hb F (Betke)	43	0.20	>0.10
Total Hb	44	0.25	>0.05
MCV	44	0.15	>0.10
% Retics	43	0.01	>0.10
Serum iron	41	0.20	>0.10
Serum folate	35	-0.01	>0.10

Chapter 16

SKELETAL MATURATION

1. METHODS :

i) Population : The children seen at age 5 years for detailed anthropometric measurement were selected for bone age assessment. Previous studies (69, 91) had suggested that significant differences in skeletal maturity were unlikely before this age and the number of older children available for assessment was limited by the age of the cohort study at that time. Sixty two children (41 AA, 21 SS) were x-rayed but films of poor quality from two AA boys were excluded (Table 16.1). The number of SS boys in this group was particularly small but all those available were x-rayed successfully.

ii) Radiographic technique : Films were obtained using a Phillips Superpractix portable x-ray machine with Agfa Curix Rpl non-screen film. All x-rays were taken by myself. The child, mother if present and myself wore protective aprons of standard design with 0.33 mm lead protection. Particular care was taken to ensure complete screening of the gonads whilst the child sat adjacent to the x-ray table. The left hand was used in all cases, positioned on a lead sheet with the x-ray tube centred as near as possible above the third metacarpal at a distance of 76 cm (114). Exposure was for one second at 85 kV and the films were developed in a Kodak RPX-omat processor.

iii) Scoring : The TW_2 method of assessing skeletal maturity was used (114) This method provides a scoring system for clearly defined stages in the radiological appearance of 20 bones in the hand and wrist (radius, ulna, the seven bones of the carpus and the metacarpals and phalanges of the first, third and fifth digits). The stages seen during bone maturation are the same in all populations and for both sexes, although the length of each stage is variable. Although the progress of many of the bones in the hand and wrist appear to give the same information about maturity, it is possible that there is some variability. Three separate scoring systems are used, one concerns only the carpal bomes, the second only the radius, ulna and short bones of the fingers (RUS) and the third combines

TABLE 16.1

	AA		SS	
Nos.	Boys	Girls	Boys	Girls
Attended	22	25	8	15
x-rayed	20	21	8	13
Scored	18	21	8	13

the two (20 bone). The scores allocated to each bone on the different system incorporate a factor designed to equalise the relative importance of each bone scored. Bones mature earlier in girls and separate scores are used for the same stages in the two sexes.

All scoring was done by myself using the x-rays labelled blindly with a code number and processed in random order. Each of the twenty bones was examined and staged according to the defined criteria. From these stages overall maturity scores were obtained which were summed appropriately to give the three individual scores - carpal, twenty bone and RUS. These scores were transcribed using tables derived from the corresponding centile charts to give bone age.

iv) Statistics : The data were available in each of the four small groups defined by genotype and sex. In order to pool data and study inter-genotype differences, further analysis was handled using analysis of variance as described in Chapter 13.3 (iii).

2. RISKS AND ETHICS :

The apparatus was checked and the extent of radiation scatter assessed by the radiation safety officer at the University Hospital of the West Indies No faults were detected and scatter outside the immediate field was negligible. Standard safety precautions were taken with the use of lead aprons and no mother was permitted to stay in the room if there was any possibility of pregnancy. The author used a radiation safety badge, monitored monthly by the Department of Radiology without detection of excess exposure.

Particular attention was paid to an explanation of the procedure when permission was sought for these studies. It was emphasised that the x-ray was of no direct clinical relevance to the management of an individual child and no child was x-rayed (or measured) without parental consent.

The ethics of wrist x-ray in normal children have been a source of some debate. It is accepted that the dose of irradiation received is very small

(4-10 millirads measured at the skin) and the risks are over exaggerated (114,115). Nevertheless there has been editorial comment about ethical and legal considerations (116). It is interesting that accidental environmental radiation exposure has occurred on a much larger scale without attracting concern (117). In attempting to detect changes in bone maturation, control data, matched for age and sex were essential for this study.

3. INTERGENOTYPE COMPARISON OF SKELETAL AGE

i) Bone Age : The maturity scores and corresponding values for bone age are given for each genotype group in Tables 16.2 (boys) and 16.3 (girls) The values for SS children are less than those for AA children in both sexes for all scores, although the differences achieved significance only for the RUS score in girls. One SS girl had a particularly low bone age with values of 1.8, 1.9 and 1.5 years for the 20 bone, RUS and carpal methods. Nevertheless the mean RUS bone age for SS girls remained significantly less than for AA girls when this child was omitted from the analysis. In all groups bone age calculated from the carpal score was less than by the other two methods and the distribution of carpal scores was wider, as seen by their larger standard deviation. In each sex and genotype group there was a highly significant positive correlation between the individual scores, except for the RUS : carpal correlation in SS boys (Table 16.4). This exception might be explained on the basis of the small numbers involved.

ii) Analysis of variance : The results of the calculated Student's t values representing the individual effects of genotype and sex are shown in Table 16.5. SS children had a significantly lower RUS bone age than AA children.

It has been suggested that differences between RUS and carpal bone ages may be of differential diagnostic significance in certain circumstances and there is some information available about the effects of different hormones on the relative maturity of the carpal and RUS bones (114). The importance of the observation that only RUS bone age was significantly reduced in SS children

TABLE 16.2

Score / Method	AA (n=18) Mean	AA (n=18) SD	SS (n=8) Mean	SS (n=8) SD
20 bone :				
Score	268	58	250	43
Bone age (yrs)	4.5	10	4.1	0.8
R.U.S. :				
Score	161	29	145	25
Bone age (yrs)	5.0	1.0	4.4	0.8
Carpal :				
Score	245	69	237	48
Bone age (yrs)	4.1	1.3	4.0	1.1

TABLE 16.3

Score	AA (n=21)		SS (n=13)	
Method	Mean	SD	Mean	SD
20 Bone :				
Score	351	62	321	68
Bone age (yrs)	4.4	1.0	3.9	1.1
R.U.S. :				
Score	239	28	209	34
Bone age (yrs)	4.7	1.0	3.8	0.9**
Carpal :				
Score	328	100	309	85
Bone age (yrs)	4.3	1.2	4.0	1.3

** $p < 0.01$

TABLE 16.4

	AA boys		AA girls		SS boys		SS girls	
CORRELATION	r	p	r	p	r	p	r	p
20 bone vs. R.U.S.	0.93	<0.001	0.83	<0.001	0.87	<0.01	0.87	<0.001
20 bone vs. Carpal	0.95	<0.001	0.95	<0.001	0.92	<0.01	0.93	<0.001
R.U.S. vs Carpal	0.79	<0.001	0.61	<0.01	0.61	N.S.	0.69	<0.01

TABLE 16.5

BONE AGE	STUDENT'S t STATISTIC	
	GENOTYPE EFFECT[1]	SEX EFFECT[2]
20 Bone	-1.50	-0.37
R.U.S.	-3.03**	-1.74
Carpal	-0.67	0.51

** $P<0.01$

1. negative t test = SS<AA
2. negative t test = Girls< Boys

must remain speculative in the absence of further observations, particularly as the population studied was small. It could be assumed that changes in the maturity of the RUS bones were therefore a more sensitive indicator of the effect of the disease on skeletal growth. This supposition was tested by looking at the correlation between RUS and carpal bone ages with anthropometric data, using the discriminant factor (calculated as described in Chapter 15) as an index of overall physical development. The correlation coefficients (for both sexes together) were $r = 0.14$, $p = N.S.$ for RUS bone age and $r = 0.47$, $p < 0.05$ for carpal bone age. This suggested the converse, that carpal rather than RUS bone age might be a better reflection of growth status. Both bone age scores were therefore used for comparison with indices of disease severity.

4. CLINICAL RELATIONSHIPS:

The criteria used for an assessment of clinical disease severity were the same as used previously. Standard linear correlations were calculated between the bone ages and the frequencies of illness or sick visits (Table 16.6). None of these relationships achieved significance.

5. HAEMATOLOGICAL RELATIONSHIPS :

The haematological indices selected for comparison were the same as those selected previously (Chapter 15). Data from both sexes were combined for analysis. Standard linear correlations were calculated between each haematological factor and the carpal and RUS bone ages for each child. The results are shown in Table 16.7. None of these correlations achieved significance although the inverse nature of the correlation with the reticulocyte count seemed appropriate. HbF had been shown to have a significant relationship with delay in skeletal maturity in Jamaican adolescents with SS disease (89) but correlations in another population of prepubertal Jamaican children were inconsistent (91). In the absence of substantial retardation in average bone maturity in the SS children, it was unlikely that there would be sufficient inter-individual variation to demonstrate relationships with individual haematological factors. In addition, the population studied was small.

TABLE 16.6

Clinical Variable	Carpal Bone Age n	r	RUS Bone Age n	r
Major Illness	21	-0.27	21	0.18
Minor Illness	21	-0.02	21	0.05
Sick Visits	22	0.09	21	0.18

TABLE 16.7

Haematological Variable	Carpal Bone Age n	r	RUS Bone Age n	r
HbF	19	0.12	19	0.20
Total Hb	20	0.22	20	0.34
MCV	20	0.05	20	0.01
Retics	20	-0.21	20	-0.33
Se iron	19	-0.06	19	-0.13
Se folate	15	-0.15	15	0.26

Chapter 17.

CONCLUSIONS

The appearance of a socially disadvantaged, physically immature adolescent with sickle cell disease contrasts strangely with the tall, slender build of an affected adult. The paradox of these observations, applicable to only some affected individuals, can be answered by careful examination of the growth pattern seen in SS patients from childhood to adult life. The earliest descriptions of the adult habitus have been confirmed in Jamaica and the peculiarities of adolescent growth were defined in the same population. A diagramatic representation of a growth pattern which explains progression from short stature in early adolescence to normal,or above normal, adult height is shown in Figure 17.1. Delayed entry into puberty, with delay in its associated growth spurt and delay in epiphyseal fusion, provides conditions for prolonged growth of long bones and recovery of height lost in early childhood. Height, representing the most characteristic change in the growth pattern from childhood to adult life, can be explained by these characteristics of adolescent growth, but other features of the adult habitus cannot. The findings of low weight, slender skinfolds and characteristic chest dimensions may have their origin in early childhood. Abnormal pre-adolescent growth will have a profound effect on final adult size and may influence the timing of puberty itself.

The analysis of the longitudinal data collected from birth to five years demonstrated a significant deficit in weight by the age of one year, and in height by two years. Size at birth did not account for any early differences. Analysis of the progression of these changes was complicated by the diminishing numbers in the study at the older ages. Weight deficit was greater than height deficit, girls doing rather less well than boys compared to their controls. Height deficit was proportionately less in the

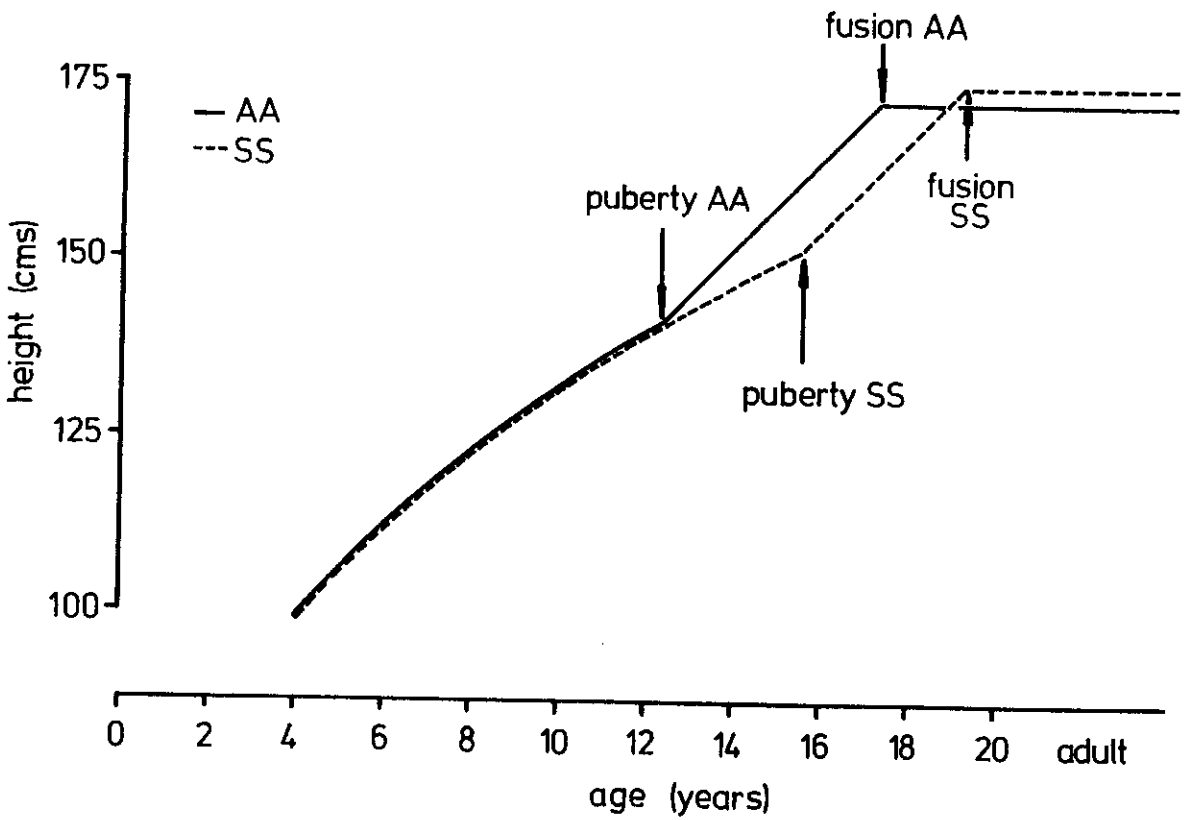


Fig. 17.1 : Suggested pattern of growth in SS disease

SS boys, explaining the increased deviation of weight against height seen in older boys. Generally the differences observed between the sexes were slight and interpretation of their significance was restricted by the statistical difficulties of the small numbers of children at older ages. Nevertheless, a consistent early deficit in height and weight was recognised in the SS children, weight being low for age and for height.

The detailed studies performed on the 4-6 year old children confirmed that the anthropometric abnormalities documented in adults were already established in early childhood. Reduced body fat, narrower pelvic and pectoral girdles and smaller limb circumference already gave an impression of slender build. The chest showed a significantly increased antero-posterior to lateral diameter and the relationship of weight to height was reduced.

The sub-population used for assessment of skeletal maturity was small and not evenly divided by sex, however, bone age was less in the SS children although the difference did not consistently achieve significance. It seemed likely, from previous studies, that retardation in bone age was more a feature of adolescent growth in sickle cell disease and that evidence for delayed bone age would become more apparent in later childhood.

The prospective nature of the cohort study afforded an unique opportunity to assess the evolving contribution of the clinical and haematological features of the disease. It would be difficult to claim that all other factors contributing to individual variation in growth pattern, seen in any population, could be excluded in this study. The control population was, however, matched for age and sex, and the socioeconomic background was the same for cases and controls. Many of the possible sources of bias in the collection and analysis of the data have been discussed and excluded. It must be concluded that the differences observed were real.

Many of the factors relating to the abnormal features of growth in sickle cell disease must be operative in early childhood. There is also considerable variation in growth performance amongst SS children. The demonstration of a general relationship between growth and the clinical and haematological features of the disease was not possible. It could be predicted that any effect imposed by these factors would be modified by other variables, notably environment and inheritance. No relationship between growth performance and several indices of clinical illness was found, nor was it possible to identify consistent relationships between height and weight and individual haematological factors. Using analysis of variance, a model was constructed which demonstrated a significant relationship with HbF and MCV. This suggested that the children who grew best were likely to have a higher HbF and lower MCV - both factors which have themselves been linked to other indices of disease severity (104(a)). The relationship of haematological variables to the anthropometric abnormalities was made more complex by the need to compute a discriminant score which best represented the severity of the overall growth disturbance. No relationship with individual haematological variables could be ascertained. It seemed unlikely that the growth of these children with more severe disease would be unaffected: a larger study of the same population at an older age might be necessary to explore this further.

The clinical significance of the growth changes identified in this study seems slight, at this age. The mean differences from the control population, although significant, were small and would only be sufficient to cause concern about growth performance in a few individuals. However, abnormalities of adult shape may be severe and the social impact of a significant retardation in pubertal development should not be under-estimated. It is in these areas that prospects for clinical intervention may be realised. It is clear that the factors responsible for these changes are active in early childhood.

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