THE EFFECT OF CORTICOSTEROID THERAPY ON GROWTH IN BLACK SOUTH AFRICAN CHILDREN WITH NEPHROTIC SYNDROME

by

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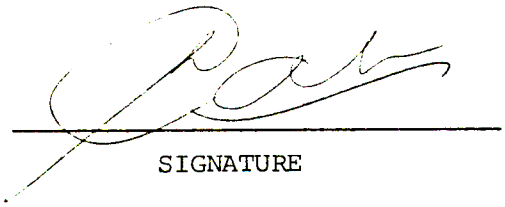
DECLARATION

I, NOEL EDWIN GEORGE MANIKKAM, hereby declare that this dissertation is my own work and has not been presented for any degree of another university.

The work reported in this dissertation was performed in the Department of Paediatrics and Child Health, University of Natal, Durban.



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DEDICATION

This is dedicated to all those children who, through sickness, suffering and even death, have contributed to our knowledge and understanding of disease processes.

SUMMARY

The most useful drugs in the management of nephrotic syndrome are the corticosteroids. These drugs are as well known for their adverse effects as they are for their therapeutic advantages. The two most common paediatric side effects are suppression of linear growth and posterior subcapsular cataracts. Both of these untoward effects are insiduous and therefore less easily perceived.

Although many workers have studied the growth inhibiting effects of the corticosteroids in the various diseases e.g. asthma, very little work was done to investigate these effects in patients with nephrotic syndrome. Furthermore, the Renal Clinic, King Edward VIII Hospital, Durban continues to use a daily regime of prednisone instead of the alternate day regime which is widely recommended to minimise growth retardation. This study was therefore undertaken to investigate the growth inhibiting effects of repeated courses of daily, high-dose prednisone in African and Indian children with nephrotic syndrome.

All children with nephrotic syndrome with relevant data in their records and with no other chronic illness were selected from the Renal Clinic. Of the 125 selected, 87 children had been treated with prednisone for an average of 35,9 weeks and 38 had been treated symptomatically. The heights of those that received prednisone were measured at an average of 77 weeks after completion of therapy. The mean height standard deviation score (SDS) of the treatment and control groups of Indian children were -1,06 and -0,92 respectively, both being between the 10th and 25th percentile, whilst the mean height SDS of the treatment and control groups of African children were -1,82 (just below the 5th percentile) and -1,77 (between the 5th and 10th percentile) respectively. From the results, it is evident that repeated courses of daily prednisone therapy, even when it exceeds 36 weeks, does not inhibit growth in both African and Indian children.

Although there was no significant difference between the races and sexes with respect to growth and corticosteroid therapy, this study does confirm earlier reports that most of the African children with nephrotic syndrome had obvious glomerular lesions whilst most of the Indians had minimal change nephrotic syndrome.

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ABBREVIATIONS

NCHS	-	National Center for Health Statistics
SDS	-	Standard deviation score
HPA	-	Hypothalamic - pituitary - adrenal
ACTH	-	Adrenocorticotropic hormone
DNA	-	Deoxyribonucleic acid

1. INTRODUCTION

1.1 The Corticosteroids

Certain steroid compounds produced by the adrenal cortex have anti-inflammatory properties and are referred to as glucocorticosteroids. These compounds are also known as glucocorticoids, corticosteroids, or for brevity as just "steroids". In the liver, they have anabolic effects, increasing production of protein, ribo-nucleic acid (RNA) and glucose. They also stimulate hepatic glycogenesis and gluconeogenesis. In peripheral tissues, however, they cause increased degradation and decreased synthesis of protein, fat, ribo-nucleic acid (RNA) and deoxyribo-nucleic acid (DNA); and decreased uptake of glucose and amino acids. Both the anabolic and catabolic action of these hormones increases total serum glucose concentration. In addition to these effects on carbohydrate metabolism, the glucocorticoids play an important role in the functions of all other body systems. Pharmacological doses of glucocorticoids retard or interrupt the growth of children[18]. This inhibition of growth is a rather widespread effect of the glucocorticoids. They, for example, inhibit cell division or DNA synthesis in thymocytes; fibroblasts; normal, developing or regenerating liver; gastric mucosa; developing brain; developing lung and epidermis[18]. Nevertheless, this growth inhibiting effect is selective; therefore the corticosteroids do not produce the bone marrow depression and other effects of antimitotic agents.

The only naturally occurring corticosteroids are hydrocortisone (cortisol) and corticosterone. Structurally, they resemble other steroids as they share the four-ring carbon skeleton which is common to these compounds. The structure of hydrocortisone is shown in Fig. 1. The introduction of a double bond between C_1 and C_2 converts hydrocortisone into a new compound - prednisone - with a consequent four-fold enhancement of anti-inflammatory activity.

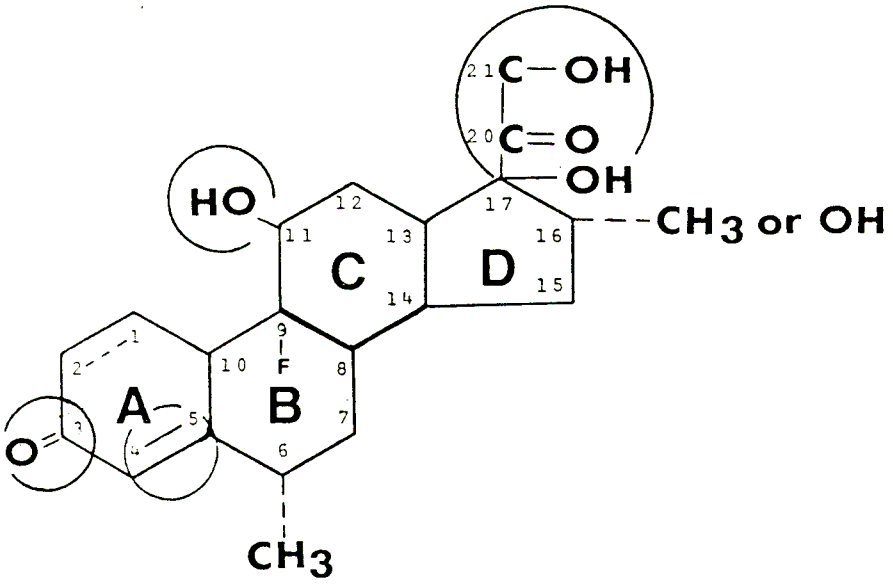

Figure 1. The Structure Of The Hydrocortisone Molecule. Those parts essential for glucocorticosteroid activity are encircled. Alterations that enhance the biologic activity of the molecule are shown with dotted lines.

There are many synthetic steroid preparations with differing degrees of potency available for use by the Paediatrician. These may be given orally, intramuscularly or intravenously. Oral absorption is generally good and this route of administration is preferred in most cases. The most common conditions for which steroid therapy may be indicated are those that are, or are thought to be immunologically mediated e.g. nephrotic syndrome, systemic lupus erythematosus and the allergic diseases e.g. asthma, allergic rhinitis and atopic dermatitis. Table I lists the conditions in which the corticosteroids have been used. While their proper use adds greatly to the quality of life, their misuse can have catastrophic consequences.

1.1.1 Growth Inhibition

The clinical complications of steroid therapy are as protean as the many therapeutic indications for which their use has been suggested. These complications have been listed in Table II. The most common adverse effects of corticosteroids are cushingoid features (obesity, moon facies, striae, acne and hirsutism) and growth suppression. The growth of children is of paramount importance to parents because they realise that poor growth may inicate disease and to be unusually short or tall may have social disadvantages. Most of the literature emphasizes that daily corticosteroid administration is associated with a reduction in linear growth. Growth failure in patients who receive daily prednisone may result from partial growth hormone deficiency and/or daily transient decrease in plasma somatomedin levels after prednisone administration[14, 28]. In addition steroids may suppress growth by direct action on cell metabolism and/or by effects on Calcium and Phosphorus metabolism. The two actions of steroids that appear to be most important in growth suppression are inhibition of sulphate incorporation into cartilage and inhibition of generation of somatomedin A[15]. Hence skeletal maturation is also retarded - see Table III.

Table 1. Paediatric Conditions In Which Glucocorticoids Have Been Used.

Physiologic dosage

Congenital adrenal hyperplasia
Adrenal insufficiency

Pharmacologic dosage (greater than 20 mg cortisol/M^2/day)

Haematologic

- Leukaemia
- Anaemia (autoimmune haemolytic and aplastic)
- Idiopathic thrombocytopenic purpura

Childhood nephrosis - minimal change
Systemic lupus erythematosus
Dermatomyositis
Polyarteritis
Rheumatoid arthritis
Rheumatic carditis
Ulcerative colitis
Ileitis
Allergic disorders

- Asthma
- Angioneurotic oedema
- Anaphylaxis
- Stevens-Johnson syndrome

Dermatologic disorders

- Contact dermatitis
- Atopic dermatitis
- Psoriasis

Infectious diseases

- Tuberculous meningitis
- Laryngotracheitis (croup)

Cerebral oedema
Infectious polyneuritis (Guillain-Barré)
Eye infections

- Uveitis, iritis

Diffuse pulmonary fibrosis
Idiopathic hypoglycemia
Chronic Aggressive Hepatitis (non Hepatitis B)

Massive dosage

Endotoxin shock
Renal transplant rejection

Table II. Complications of Steroid Therapy.

Renal

Sodium retention
- Oedema
- Hypertension

Potassium loss
- Muscle weakness
- Hypokalaemic alkalosis

Eyes

Posterior subcapsular cataracts

Muscular skeletal

Proximal Myopathy

Osteoporosis
- Vertebral collapse
- Pathologic fracture of long bones
- Aseptic necrosis of femoral head

Gastrointestinal

Ulceration and perforation
Abdominal distension (obesity)
Pancreatitis

Central nervous system

Personality changes

Increased intracranial pressure

Seizures
- Hypertensive
- Hyponatraemic (in nephrotic syndrome)
- Idiopathic

Haematopoietic system

Polymorphonuclear Leukocytosis

Ecchymoses

Susceptibility to infection

Endocrine

Steroid diabetes

Adrenal insufficiency

Growth failure

Cushingoid features

Table III. The Mechanisms By Which Corticosteroid Therapy May Cause Growth Suppression in Children.

1. Partial growth hormone deficiency.
2. Transient decreases in somatomedin levels.
3. Inhibition of cell division or DNA synthesis.
4. Interference with calcium and phosphorus metabolism.
5. Inhibition of sulphate incorporation into cartilage.
6. Excess protein catabolism.

Many workers have shown that the effect of corticosteroids on growth is not reversed when growth hormone is given[3]. Tanner et al (1971)[33] reported the use of human growth hormone in two children with rheumatoid arthritis who were receiving steroids. In the first case, there was no response, even to 60 i.u./week, while on a steroid dose equivalent to 50 mg cortisone daily. In the second case, a growth spurt occurred while the patient was still receiving prednisone 3 mg/day, but as she entered puberty at the same time the significance is obscure. Morris et al[26] reported that there was marked impairment of the action of growth hormone in eight steroid-treated children as compared to non-steroid-treated children. These observations are in good agreement with the experience of Preece[31].

1.1.2 Therapeutic Recommendations

To minimize the possibility of the undesirable sequelae while maintaining the therapeutic benefits of corticosteroid therapy, various recommendations have been made, as listed in Table IV. Of these, the most important is the frequency of dosage : specifically, on alternate-day rather than a daily regime. This approach has been used in all applications of systemic steroids for nearly twenty years, and its value has been widely proved[15]. The rationale for this regime is based upon the fact that many steroid side effects (especially growth inhibition) result from the drugs' interference with the normal function of the hypothalamic - pituitary - adrenal (HPA) axis. The tissue effects of the short-acting-steroids cease after about 36 hours, thus the HPA axis has a 12-hour interval to "recover" before being again subjected to the next dose of steroid. The two steroid actions that appear to be most important in growth suppression (vide supra) are lessened with use of an alternate-day regime. This supports the work of

Table IV. Recommendations For Corticosteroid Therapy.

1. Use only when no other treatment is effective.
2. Change to an alternate day regimen as soon as possible.
3. Give the drug in a single dose early in the morning.
4. Give as low a dose as possible.
5. Withdraw therapy as the activity of the disease diminishes.

Travis et al[34] who documented that in children with kidney disease, alternate-day therapy causes less growth suppression than does daily therapy; they also showed that in experimental animals and children with asthma alternate-day therapy has been associated with normal growth. Clark & Fitzgerald[8] have shown that an alternate-day regime has a positive effect on growth, presumably through control of the underlying disease.

Although catch-up growth may occur after cessation of daily steroid therapy this is not always the case especially when therapy has been prolonged for more than six months[20]. Another important recommendation is that the drugs should be administered early in the morning - 7 or 8 o'clock. This is because of the body's circadian rhythm governing the secretion of endogenous cortisol. Secretion begins in the early morning, triggered by the secretion of ACTH which starts about 1 or 2 am, peaks about 6 am and drops off during the afternoon and evening to low levels. By synchronizing the administration of exogenous steroids with the natural cycle, the tissues are exposed to these potent agents only at the 'normal' time of day. Also, small amounts of the drug given at night cause suppression, while the same dose given in the morning does not[32].

It is also necessary to emphasize that some of the basic underlying diseases being treated with corticosteroids e.g. asthma and nephrosis are themselves associated with growth retardation. Friedman[17] stated that the most important causes of growth failure in patients with chronic renal disease are osteodystrophy, protein - calorie malnutrition, and chronic glucocorticoid administration. He added that altered growth hormone production, metabolism or peripheral utilisation and acidosis may also be causally related to growth failure.

The growth suppressing effects of steroid therapy have already been examined in various diseases e.g. chronic aggressive hepatitis[8, 29], asthma[12, 25], juvenile chronic arthritis[6, 21] and in children who have had renal transplants[4] but little work has been done on the nephrotic syndrome which is a relatively common condition for which corticosteroid therapy is used. A recent study on height attainment in Caucasian children with steroid responsive nephrotic syndrome has been published[16]. No similar study has been undertaken among children in the third world. This project was therefore initiated to determine the effect of steroid therapy on linear growth in children with nephrotic syndrome.

1.2 The Nephrotic Syndrome

This is a clinical term and may be defined as massive proteinuria (more than 2 Gm/m^2/24 hrs); hypoalbuminaemia (<30 Gm/L), oedema and hyperlipaemia. It is merely a manifestation of a large number of morphologically distinct glomerular disorders which results from primary glomerular disease in approximately 90% of children. In the remaining 10%, the nephrotic syndrome is secondary to systemic disease. The causes of nephrotic syndrome in children are listed in Table V. The common factor in all these conditions is an abnormally raised permeability of the glomerular capillary for protein.

This condition was recognised as early as 1853 by Samuel Wilks. The term "Nephrosis" was first used by Friedrich Muller in 1905. It was observed that nephrotic syndrome may improve or disappear after an intercurrent infection e.g. measles or mumps (Vanucura, 1943), erysipelas (Schwartzer and Kreyher, 1941), typhoid fever and even appendicitis (Scheiner, 1929). It was therefore recommended that infection of these patients with measles (Blumberg and Cassady, 1947); malaria (Gairdner and Shute, 1955) or treatment with non-specific pyrogens such as typhoid vaccine (Schwartzer and Kreyher, 1941) would be useful. When it became known that the adrenocortical hormones decrease

Table V. Causes of Nephrotic Syndrome in Children.

1. Primary renal causes

Minimal change nephropathy

Mesangial proliferation

Focal glomerulosclerosis

Immune complex glomerulonephritis

- Membranoproliferative glomerulonephritis
- Acute poststreptococcal glomerulonephritis
- Membranous nephropathy

Congenital nephrosis

2. Systemic causes

Infections - syphilis, malaria, Hepatitis B virus infection

Toxins - mercurials, bismuth, gold, trimethadione, probenicid, renographic medium, penicillamine

Allergies - poison oak, bee sting, serum sickness, inhaled pollens, food allergy

Cardiovascular - sickle cell disease, renal vein thrombosis, passive congestive heart failure

Malignancies - Hodgkin's disease, leukaemia, carcinoma

Other - Amyloidosis, multiple myeloma, systemic lupus erythematosus, anaphylactoid purpura

capillary permeability, the idea of stimulating adrenal cortical activity with corticotrophin or of administering the adrenocorticoids themselves emerged. Many workers in the early 1950's demonstrated that in many of these patients the administration of corticotrophin induced remission. Thorn, Merrill and colleagues (1950) and Barnett, McNamara and colleagues (1950) found the same with cortisone. These results were soon confirmed by other workers. Presently treatment with prednisone is preferred. Although the alternate-day regime is widely recommended, Diethelm et al[11] have found that while this regime reduced the untoward side effects of corticosteroids in the recipients of renal allografts, the risk of precipitating allograft rejection became a significant threat. The subjective experience at the Renal Clinic, King Edward VIII Hospital (H.M. Coovadia, personal communication) is that alternate-day administration of prednisone did not produce the desired clinical response in Indian children with minimal change nephrotic syndrome. Prednisone was therefore administered on a daily basis. It is therefore imperative to establish the subsequent effect of steroid therapy on growth suppression - which is not only one of the more important but also an insiduous adverse effect and therefore less easily and quickly perceived.

2. PATIENTS AND METHODS

The patients were chosen if they:-

i. had nephrotic syndrome, the diagnostic criteria of which are oedema, hypoalbuminaemia (<30 Gm/l) and heavy proteinuria (>2 Gm/M^2/24 hrs or $\geqslant 3$ Gm/l on repeated random samples).

ii. had sufficient data with respect to therapy, clinical course and height measurements, and

iii. did not have any chronic illness other than nephrosis which might have affected their growth.

Thus only 125 of 478 patient records available at the Renal Clinic, King Edward VIII Hospital, Durban were suitable for this retrospective study.

Steroid therapy was administered once daily as follows : prednisone 2 mg/kg/24 hrs for four weeks, this dosage being gradually decreased over the following eight weeks. Most of the children i.e. 61 of 87 children received repeated courses of corticosteroids. The duration of therapy was obtained by calculating the number of weeks during which the patient was taking prednisone. Those children who did not receive steroids were treated symptomatically with diuretics (thiazides, spironolactone) or intravenous infusion of salt free albumin together with an intravenous injection of furosemide during severe relapses. The children were followed up from three months to fourteen years, the mean follow up period being 3,9 years.

Heights were measured with the child standing barefooted against a vertical wall; with both the heels and occiput touching the wall. A square rule was used to maintain the vertex at right angles to the wall and thereby accurately localising the upper limit of height which was read off a measuring scale attached to the wall. The last recorded height was chosen, which was an average of 77,1 weeks after completion of steroid therapy (range:from 1 week of being put onto prednisone to 364 weeks of having completed therapy). Height of boys and girls at different ages were compared by calculating the height standard deviation score (SDS) according to the following equation:

$$SDS = \frac{x - \bar{x}}{S_x}$$

where x is the measured height, $\bar{x}$ the mean height and S_x the standard deviation. The figures for $\bar{x}$ and S_x were taken from tables compiled by the National Center for Health Statistics (NCHS)[27].

Once the mean height SDS was known, the mean height percentile was determined as follows: S_x and $\bar{x}$ were obtained from the respective NCHS tables and height x was obtained by substitution of these values in the equation. This height was then plotted on the respective NCHS Growth Curves and the percentile extrapolated (See Addendum, p. 36).

The histological classification of nephrotic syndrome adopted by the clinic was based on the one suggested by Morel-Maroger (1976)[24] - see Table VI.

In addition to comparing the height of all the children who received steroid therapy (treatment group) with the heights of those who did not receive this treatment (control group), an analysis of the height differences between the two races and the sexes, on treatment, was also done. Analysis was undertaken using a non-parametric statiscal, The Mann-Whitney U Test. A significance level of 5% was used. No comparison was made between the histological subtypes of nephrotic syndrome, because other than minimal change nephrotic syndrome, the numbers were too small.

3. RESULTS

3.1 Race, Age, Sex, Histology

There was a total of 83 Indian patients (51 males) and 42 African patients (25 males). Their ages ranged from 1 to 12 years, the mean age of the Indian children was 4,8 years, whilst that of the African children was 7 years. One hundred and seven children had renal biopsies performed on them. The subsequent histological classification was done according to the system suggested by Morel-Maroger (1976)[24]. The distribution of the different histological sub-types of nephrotic system in both African and Indian children is shown in Table VII. Eighteen of the 37 African children who had undergone renal biopsies i.e. 49% had membranous glomerulo-nephropathy while 57 of the 70 Indian children, i.e. 81% who

Table VI. Histological Classification of Nephrotic Syndrome.

No Obvious Lesions

Minimal Change

Obvious Glomerular Lesions

1. Extramembranous
2. Proliferative
    a) Mesangial
    b) Exudative
    c) Endocapillary
    d) Membrano proliferative
    e) Focal
3. Focal Glomerulosclerosis
4. Tropical Extramembranous
5. Tropical Nephropathy
6. Unclassified

Table VII. The Incidence Of The Histological Sub-types Of Nephrotic Syndrome In The Different Races and Sexes.

The Sub-type	Africans			Indians		
	M	F	T	M	F	T
Minimal Change	3	4	7	35	22	57
Membranous Glomerulonephropathy	14	4	18	0	0	0
Proliferative Glomerulonephritis	4	5	9	2	2	4
Membrano-proliferative Glomerulonephritis	1	0	1	1	1	2
Focal proliferative Glomerulonephritis	0	2	2	2	2	4
Focal Glomerulosclerosis	0	0	0	2	1	3
Not Biopsied	3	2	5	9	4	13
TOTAL	25	17	42	51	32	83

M = male

F = female

T = total

had undergone renal biopsies had minimal change nephrotic syndrome. Of the 5 African children who were not biopsied one was steroid sensitive, and 12 of the 13 Indian children who were not biopsied were steroid sensitive. These proportions reflect the overall picture of nephrotic syndrome among African and Indian children in Natal, South Africa (Coovadia et al)[9]. They reported that the majority of African children (86%) had obvious structural glomerular lesions which were associated with unresponsiveness to steroid therapy, while 75% of the Indian children had minimal change nephrotic syndrome which was steroid responsive.

3.2 Height Attainment in Indian Children

Fifty-seven of the 83 Indian patients had received repeated courses of prednisone while 20 received one course. The distribution of the height SDS's of both the treatment and the control groups is shown in Figures 2(a) and 2(b). The mean height SDS's of the treatment and control groups are -1,06 (between the 10th and 25th percentile) and -0,92 (between the 10th and 25th percentile) respectively. On the basis of the Mann-Whitney U Test, there was no significant difference in height between the two groups ($p = 0,75$). These results together with their standard deviations are shown in Table VIII.

3.3 Height Attainment in African Children

Four of the 42 African children received repeated courses of prednisone while 6 received one course. The distribution of the height SDS's of both the treatment and the control groups is shown in Figure 3(a) and 3(b). The mean height SDS's of the treatment and control groups are -1,82 (just below the 5th percentile) and -1,77 (between the 5th and 10th percentile) respectively. On the basis of the Mann-Whitney U Test, there was no significant difference in height between the two groups ($p = 0,74$). These results, together with their standard deviations are shown in Table IX (See Addendum, p. 38).

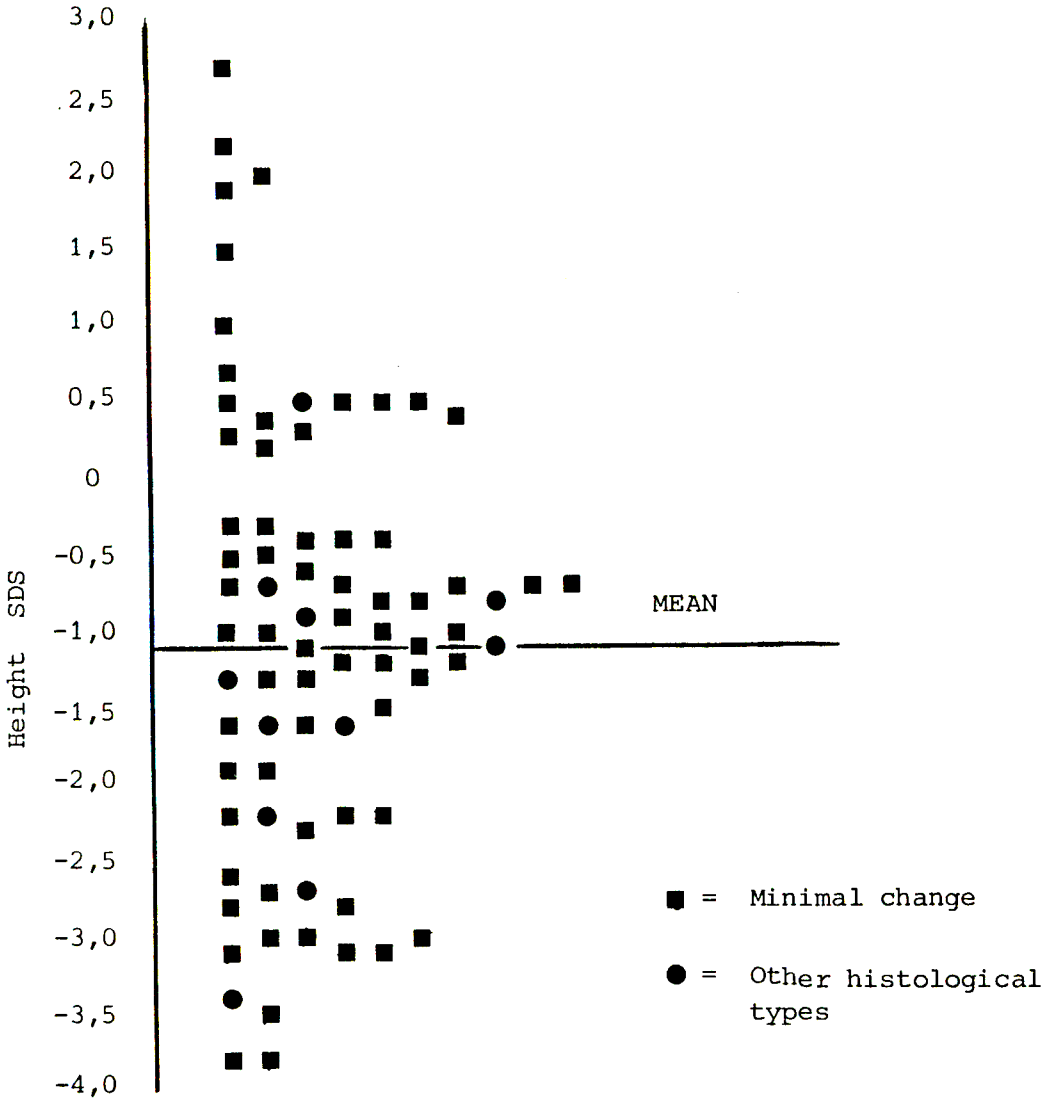

Fig. 2(a). Distribution of Height SDS of Indian Children - Treatment Group.

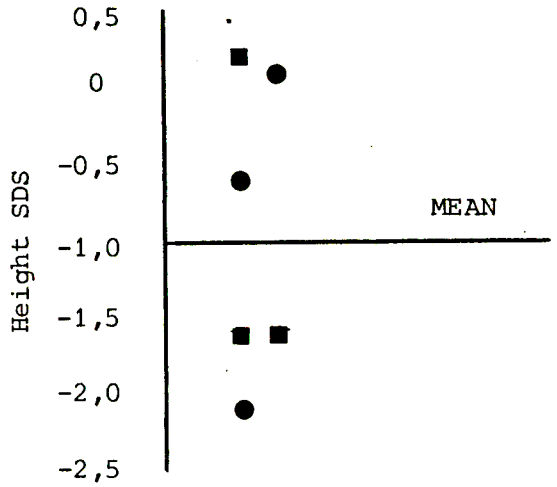

Fig. 2(b). Distribution of Height SDS of Indian Children - Control Group.

Table VIII. Height Analysis Of The Indian Children.

Group	No. of Patients	Mean Height SDS	Standard Deviation	p value
Treatment	77	-1,06	1,44	0,75
Control	6	-0,92	0,96	

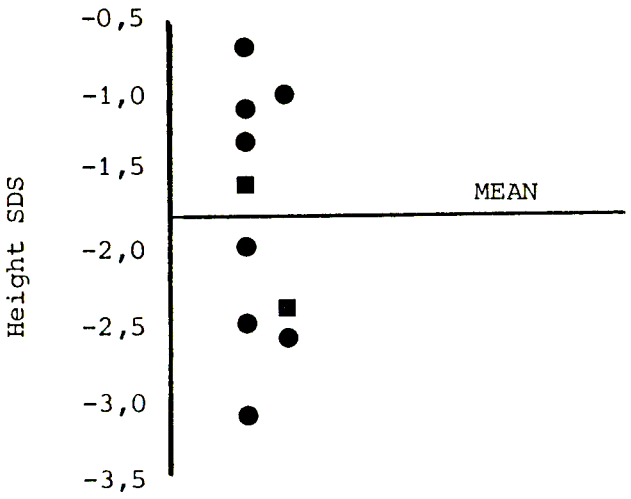

Fig. 3(a). Distribution of Height SDS of African Children - Treatment Group.

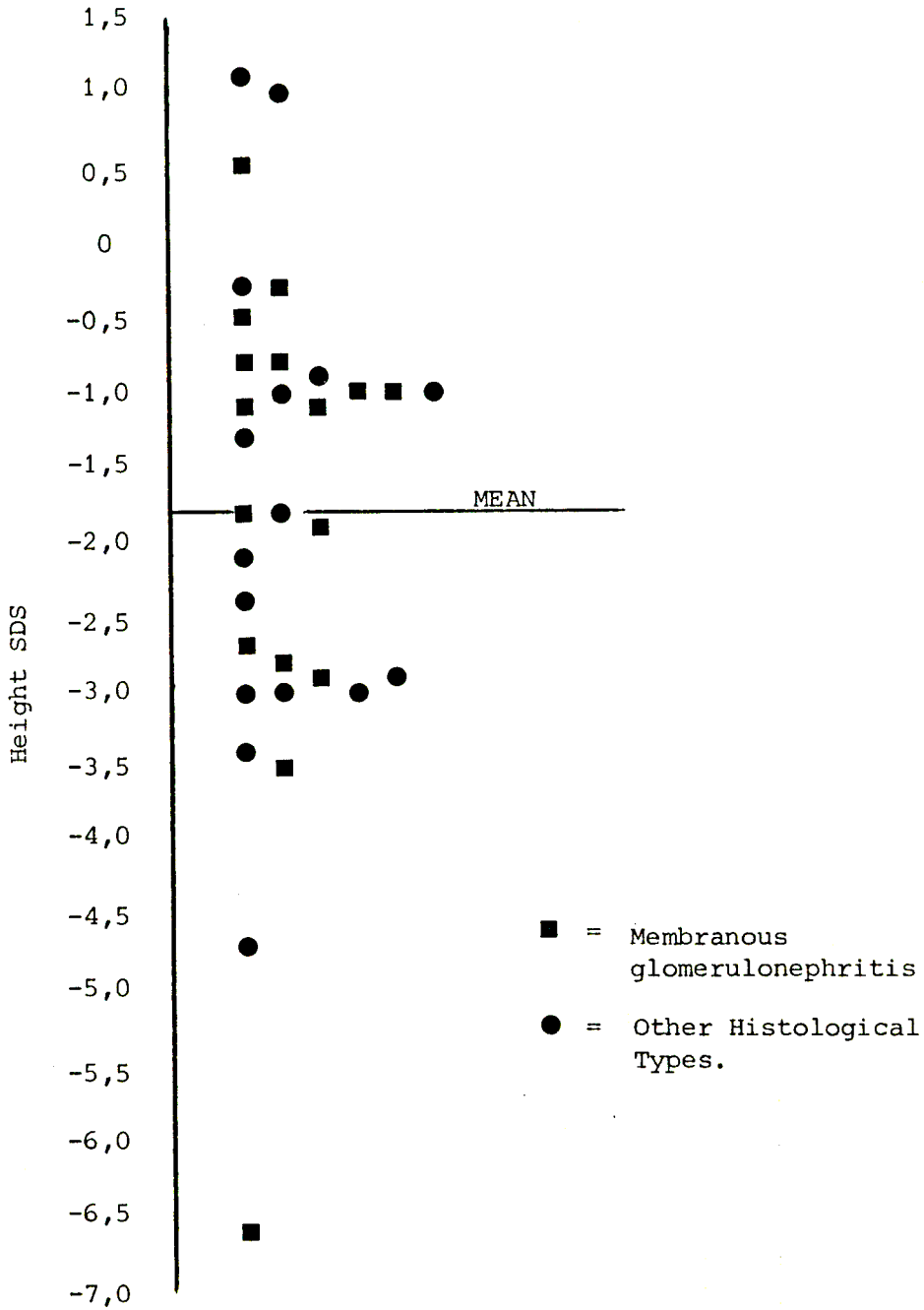

Fig. 3(b): Distribution of Height SDS of African Children - Control Group.

Table IX. Height Analysis Of The African Children.

Group	No. of Patients	Mean Height SDS	Standard Deviation	p value
Treatment	10	-1,82	0,81	0,74
Control	32	-1,77	1,61	

3.4 Race

Since African nephrotic children differ from Indian nephrotic children with respect to histological type, response to treatment, etc., the results were further analysed to determine if prednisone affected their heights differently. The results are shown in Table X. Mean height SDS of Indian children was -1,06 (between 10th and 25th percentile) whilst that of the African children was -1,82 (just below the 5th percentile). There is no significant difference in height between Indian and African children treated with steroids ($p = 0,08$).

Since the effects of corticosteroid therapy on linear growth is similar for both races, the following analyses were made irrespective of race.

3.5 Sex

Males on treatment were compared with females on treatment to determine whether prednisone affected the height of one sex more than the other. The 52 males on prednisone had a mean height SDS of -1,24, equivalent to a height between the 5th and 10th percentile, whilst the 35 females had a mean height SDS of -1,53 equivalent to the 5th NCHS percentile (Table XI). There is no significant difference in height between the sexes.

3.6 Duration of Steroid Therapy

Sixty-four of the 87 children who received prednisone, received the drug for less than 36 weeks, whilst 23 were on treatment for more than 36 weeks. This period of 36 weeks was chosen as it was the mean duration of steroid therapy. In addition, Lam[20] states that the chances of catch up growth decreases when children receive prednisone therapy for longer than 6 months. The statistical analysis of these two groups is shown in Table XII. No significant difference in height between the two groups is evident ($p = 0,68$).

Table X. Height Comparison Between Group A : Indian Children on Steroids Versus Group B : African Children on Steroids.

Group	No. of Patients	Mean Height SDS	Standard Deviation	p value
A	77	-1,06	1,44	0,08
B	10	-1,82	0,81	

Table XI. Height Comparison Between Group A : Males On Steroids Versus Group B : Females On Steroids.

Group	No. of Patients	Mean Height SDS	Standard Deviation	p value
A	52	-1,24	1,21	0,98
B	35	-1,53	1,06	

Table XII. Height Analysis. Group A : Children Who Received Steroids For Less Than 36 Weeks. Group B : Children Who Received Steroids For More Than 36 Weeks

Group	No. of Patients	Mean Height SDS	Standard Deviation	p value
A	64	-1,09	1,41	0,68
B	23	-1,23	1,48	

4. DISCUSSION

It is evident from this study that both Indian and African children with nephrotic syndrome on repeated courses of daily, high-dose prednisone continue to grow normally. Growth suppression is documented as one of the most common adverse effect of corticosteroid therapy with children who receive repeated courses of high-dose steroids or prolonged maintenance therapy being at the greatest risk[20]. The most important recommendation to reduce the adverse effects of corticosteroid therapy is alternate-day therapy rather than a daily regime. However, children at the Renal Clinic were put onto daily treatment because of the experience that alternate-day treatment was not accompanied by a good clinical response of the disease in Indian children. Despite this regime no growth retarding effects were noted.

The NCHS reference population, which is representative of healthy American children was used to compare the linear growth of these children. It is appropriate to use these NCHS standards for comparison because, as Graitcer and Gentry, 1981 found, child growth is mainly influenced by socio-economic status and not by race or by ethnicity[19]. Also, as has been shown by Coovadia et al, 1978 the length measurements of Negro children less than 2 years of age in the Durban area are similar to the Harvard standards, whereas older children are considerably shorter, their mean height lying between the 5th and 10th Harvard percentiles[10]. This decrease in height (and weight) probably reflects the damaging effects of an impoverished socio-economic environment on growth.

The findings of Cherian et al[7], in their study of children in Zaria, Nigeria, are very similar. Furthermore, studies of Indian children[2] confirms that they grow similarly to the NCHS standards. Moosa[23] in his study on growth of middle and upper class Indian school children in Durban confirms that their growth parallels that of American children and therefore one is justified in using the NCHS standards for the local population.

The height SDS's of the treatment and control groups are representative of all the nephrotic patients seen at King Edward VIII Hospital,

and not just a selected group with an altered sensitivity to steroid therapy. The mean height SDS of all the children was -1,38 equivalent to a height on the 5th percentile (NCHS).

Seventy-seven of the 83 Indian nephrotic children i.e. 92,8% received steroid therapy whereas only 10 of the 42 Africans i.e. 23,8% received steroids. The mean height SDS of the treatment group of Indian children was -1,06 equivalent to the 10th percentile (NCHS) and that of the control group was -0,92, equivalent to a height between the 10th and 25th percentile. There is no significant difference in height between these two groups (p = 0,75). Similarly, no significant difference was found when comparing the treatment and control groups of African children (p = 0,74). The mean height SDS of those who had been on prednisone was -1,82 (just below the 5th percentile) whilst the mean height SDS of those who had not been on steroids was -1,77 (between the 5th and 10th percentiles). These are close to the observed heights of average urban Negro children in Durban[10]. Thus corticosteroid therapy in children with nephrotic syndrome does not affect their height.

The data compiled were further analysed to determine whether prednisone might have had any growth inhibiting effects which were variable with race. When comparing the 6 Indian children from the control group with the 32 African children from the same group, no significant difference in height (p = 0,20) is evident (see Table XIII). This is not unexpected since, as has been mentioned above, child growth is not affected by race. Also, the height of these children are normally distributed (Fig. 2 and 3) implying a similar socio-economic status. Similarly a comparison between the 77 Indian children and the 10 African children within the treatment group reveals no significant difference in height (p = 0,08) — Table X. Since there is no significant difference in height between the Indian and African nephrotic children from both the control and treatment group, it can be concluded that the effects of prednisone on height do not vary with race.

Foote et al[16] showed in their study of 80 patients with steroid responsive nephrotic syndrome that growth was suppressed during

Table XIII. Height Analysis Between Group A : Indian Children Not On Steroids Versus Group B : African Children Not On Steroids.

Group	No. of Patients	Mean Height SDS	Standard Deviation	p value
A	6	-0,92	0,95	0,20
B	32	-1,77	1,60	

corticosteroid therapy, but their ultimate height attainment was not significantly affected. However, they do also indicate that their patients were a "selected group whose nephrotic syndrome was, on average, much more severe than would be encountered in a non-specialist unit. Thus, most received large doses and long courses of prednisone ...".

Travis et al[34] stated that "In children treated with steroids for glomerulonephritis or nephrotic syndrome and especially in children with renal transplantation, factors other than steroid therapy may contribute to growth retardation". The specific disorders in kidney disease which have been associated with growth failure[30] are:

i. acidosis
ii. impaired conservation of water
iii. osteodystrophy
iv. endocrine factors: the role of endocrine in the growth retardation of renal disease is unclear. Growth hormone levels are normal or increased in children with renal failure. Somatomedin has been reported to be low in growth retarded children with renal insufficiency.
v. abnormalities of protein metabolism and decreased food intake.

One can therefore argue that in the study by Foote et al that the stunting of growth which occurred during steroid therapy might have been the result of the severity of the disease, or of a combination of both these factors.

Although Indian and African children behave similarly with respect to growth and prednisone therapy, this study does confirm the contrasting clinicopathological patterns of nephrotic syndrome in these two South African races. Coovadia et al[9] showed that 86% of African children with nephrotic syndrome had obvious structural glomerular lesions which were associated with unresponsiveness to steroid therapy in contrast with the 75% of the Indians who had minimal change nephrotic syndrome which was steroid responsive. Extramembranous and proliferative lesions accounted for most of the

histological types of nephrotic syndrome in African children. In the present study 30 of the 37 African children, i.e. 81%, whose histology was confirmed had obvious structural glomerular lesions (membranous glomerulonephropathy—49%) whilst 57 of the 70 Indian children i.e. 81% had minimal change nephrotic syndrome. Of the 5 African children who were not biopsied, only 1 was steroid responsive, whilst 12 of the 13 Indian children who were not biopsied were steroid responsive.

It has been reported that catch-up growth may occur after cessation of daily steroid therapy but that this was not always the case especially when therapy had been prolonged for more than 6 months[20]. An investigation was therefore done to ascertain whether the height of children was affected by duration of prednisone therapy. The children in this study received steroids for a period of 4 to 250 weeks, the mean period being 35,9 weeks. When comparing children who received prednisone for less than 36 weeks with those who received treatment for longer than 36 weeks one finds no significant difference ($p = 0,68$) in height (Table XII). The mean height SDS of these groups were -1,09 and -1,23 respectively, both being between the 10th and 25th percentile (NCHS). Thus there was no correlation between duration of prednisone therapy and height. This confirms the findings of Foote et al[16] that there was no correlation between total prednisone dose and ultimate height attainment (See Addendum, p. 38).

The 52 males on prednisone had a mean height SDS of -1,24, equivalent to a height between the 5th and 10th percentile whilst the 35 females had a mean height SDS of -1,53, equivalent to the 5th NCHS percentile (Table XI). Using the Mann-Whitney U Test, no significant difference in height between males and females on steroids is evident ($p = 0,98$). Thus the effects of prednisone were not altered by the sex of the individual.

Other than the minimal change nephrotic syndrome, the numbers of each of the other histological types of nephrotic syndrome were too small for any further statistical analysis.

5. CONCLUSION

Although it is widely accepted that prolonged corticosteroid therapy adversely affects the growth of young children, this study of 125 nephrotic children clearly demonstrates that prednisone therapy did not inhibit linear growth. Furthermore, neither the duration of treatment, nor the race and sex of patients determined the effects of prednisone on growth.

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ADDENDUM

1. Determination of mean height percentile if mean height SDS is known (Refer to p. 14):-

   i. Given:

   Mean height SDS = -1,06

   ii. Select S and $\bar{x}$ from NCHS tables for any age and sex:-

   For a 7,5 yr. old male

   $S = 5,2$ cm

   $\bar{x} = 124,5$ cm

   iii. Substitute these values in equation (Refer to p. 13):-

   $$SDS = \frac{x - \bar{x}}{S_x}$$

   $x = 119$ cm

   iv. Read off the percentiles from the respective percentile charts.

   Height SDS of -1,06 = a height between the 10th and 25th percentile.

2. Two additional analyses were performed:-

   i. Patients that received less than twelve weeks of Prednisone were excluded from the study since it is unlikely that short courses of steroids inhibit growth; and the inclusion of these patients might have prejudiced the results. Seventeen Indians and three Africans were subsequently excluded and the results are shown in Table XIV.

Table XIV. Height analysis after exclusion of children who received less than 12 weeks of Prednisone.

Race	Group	No. of patients	Mean Height SDS	Standard Deviation	p value
Indian	Treatment	60	-0,98	1,48	0,87
	Control	6	-0,92	0,95	
African	Treatment	7	-1,69	0,61	0,88
	Control	32	-1,77	1,60	

There is no significant difference in height between the treatment and control groups in both Indian and African patients ($p = 0,87$ and $0,88$ respectively).

ii. A regression analysis - as illustrated in Figure 4 - was done to determine whether duration of prednisone therapy affected growth.

Although there appears to be a tendency towards growth inhibition with increasing duration of prednisone therapy, using Pearson's Correlation Coefficient, one finds no significant correlation.

The results are:-

Correlation	=	-0,075	
T	=	0,6916	
Regression Slope	=	-0,0023	$\pm$ 0,0033
Y - intercept	=	-1,04	$\pm$ 0,15
P	>	0,05	

Thus, duration of prednisone therapy did not affect growth.

3. i. The small sizes of the Indian control and African treatment groups were unavoidable since it would be unethical to alter treatment for the purposes of this study. The non-parametric Mann-Whitney U Test was therefore chosen as it allows for comparisons between groups with distribution of samples free of any specific pattern.

ii. Two African children in the control group (SDS = -4,7 and -6,7) were short at the onset of their disease (SDS = -4,6 and -6,6 respectively). Their short stature is due to chronic malnutrition.

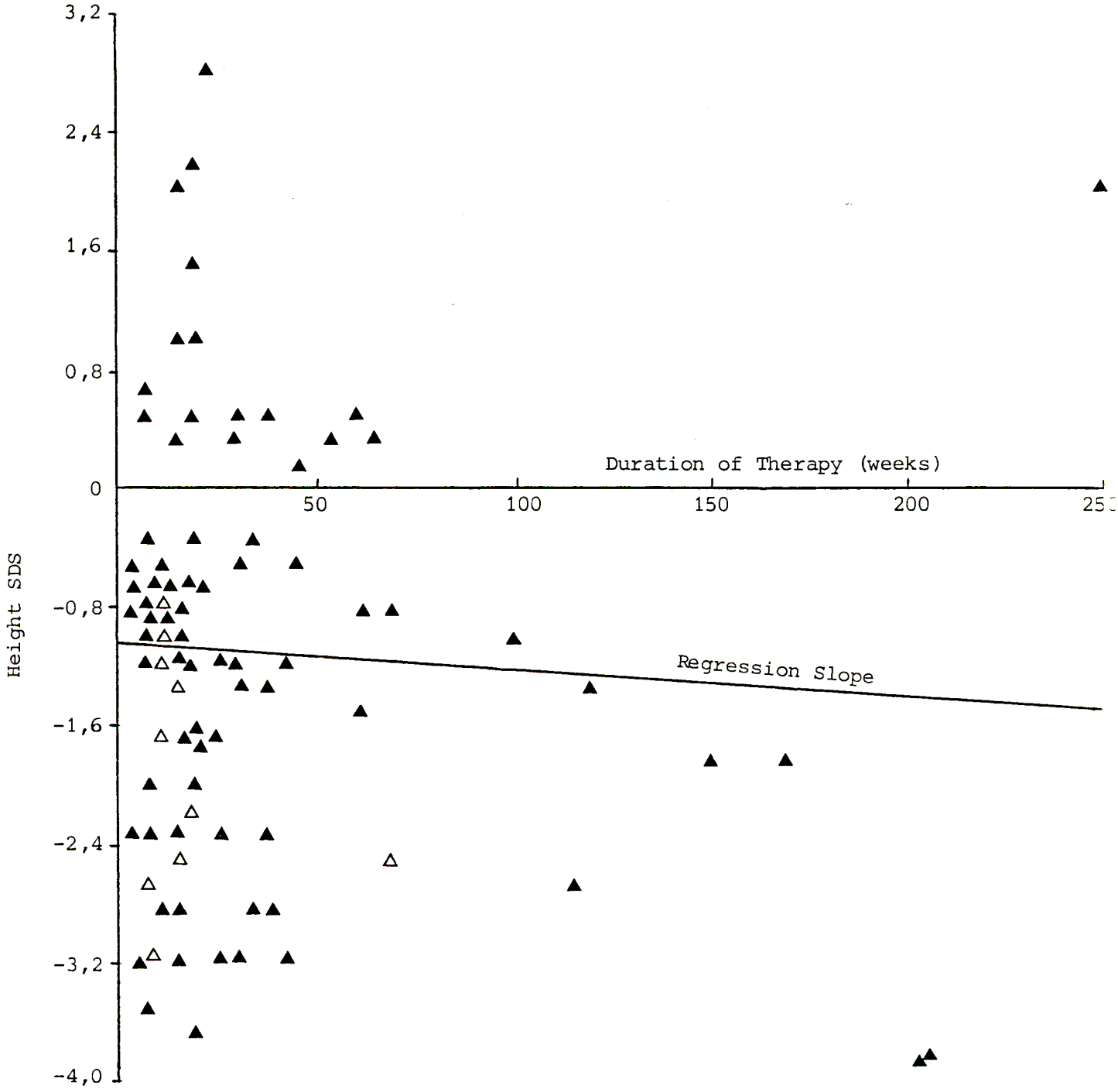

Figure 4. Height SDS versus Duration of Prednisone Therapy.

▲ : Indian Children

△ : African Children

iii. Growth charts for average Indian children in Durban are unavailable. However, the majority of these children are malnourished, (pers. comm. Professor H.M. Coovadia, Department of Paediatrics and Child Health, University of Natal) and it is therefore not surprising that they are shorter than Moosa's select study group of upper and middle class children.

iv. The conclusions of this study are applicable to the groups as a whole and not necessarily to individuals. Growth inhibition could have occurred in a few children but because the Indian control and African treatment groups were so small, the effects could have been masked.