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Original article

Effects of repeated courses of daily steroids and of persistent proteinuria on linear growth in children with nephrotic syndrome

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Abstract. The growth-inhibitory effects of courses of daily steroid therapy and of persistent proteinuria were assessed in 125 Indian and African children with nephrotic syndrome (NS) who were followed for an average of 3.9 years (range 0.25–14 years). Among the biopsied patients, 81% of Indians had minimal – change nephropathy and 49% of Africans had membranous nephropathy. The mean height standard deviation score (SDS) in 87 children who had received prednisone for an average of 36 weeks (range 4–250 weeks) was compared with that in 38 patients who had been managed symptomatically. Heights of untreated African children with persistent proteinuria were within the normal range for age, race and sex. The height SDS ± SD for 77 Indian children in the prednisone-treated group was -1.06 ± 1.44, which was not significantly different from -0.92 ± 0.96 observed among 6 children in the untreated group ($P = 0.75$). In Africans the height SDS in 10 prednisone-treated children was -1.82 ± 0.81 which was similar to that observed ($P = 0.74$) in 32 untreated patients -1.77 ± 1.61. No significant correlation was found between the duration of prednisone therapy and height SDS for individual children among the 87 treated patients using regression analysis. The findings remained unchanged when children who had received less than 12 weeks of prednisone were excluded, or when comparison were drawn between those treated for less than and longer than 36 weeks. We conclude that courses of daily steroids or persistent proteinuria do not inhibit linear growth in Indian and African children with NS.

Key words: Steroids – Proteinuria – Nephrotic syndrome

Introduction

The growth-suppressive effects of steroid therapy have been investigated in chronic aggressive hepatitis [1, 2], asthma [3, 4], juvenile arthritis [5, 6] and in children with renal transplants [7]. Some growth data have also been reported in the nephrotic syndrome (NS). Two recent studies on height attainment in Caucasian children with steroid-responsive [8] and steroid-dependent [9] NS, treated with short or long courses of alternate-day therapy, have been published. Alternate-day, rather than daily, steroid regimens have been recommended to minimise the effects of steroids on linear growth [10]. No similar studies have been undertaken among those treated with daily steroids and in children in the third world where average diets are protein and calorie restricted. In Durban, South Africa, 73% of Indian children have minimal-change NS while among African children hepatitis-B-positive membranous nephropathy is the commonest lesion [11–13]. The treatment we have used is daily steroids and not an alternate-day dosage regimen because we obtained inadequate control with the latter. Our aim in this project was to determine the effect of daily steroid therapy on linear growth in Indian and African children with NS. Comparisons were also made of the effect of persistent proteinuria on growth in African nephrotic children who had never received steroids.

Patients and methods

All patients had NS as defined by the presence of oedema, hypoalbuminaemia (<30 g/dl) and heavy proteinuria (>2 g/m^2 per 24 h or 3 g/l on repeated random samples). Patients were selected for the study if they had sufficient data with respect to therapy, clinical course and height measurements. Nephrotic patients with chronic renal failure or chronic illness which might affect their growth were excluded. Of 478 patient records available at the renal clinic, Kind Edward VIII Hospital, Durban, 125 were found suitable for this retrospective study; 83 were Indian and 42 African.

Indications for biopsy

When commencing this project little information was available on local patterns of disease so all Indian children were biopsied until it became clear that the clinicopathological features in these children were similar

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to those in Caucasian children. Thereafter Indian children were only biopsied if they did not respond to steroids or had clinical features incompatible with minimal-change nephropathy (MCN). Those who had a typical clinical history, response to steroids and on follow-up a course compatible with MCN, were regarded as having this diagnosis. All African nephrotic children continued to be biopsied.

Steroid regimen

Indian children. The steroid-treated children were given the drug as a single morning dose for each course as follows: prednisone 2 mg/kg per 24 h for 4 weeks, this dosage being gradually decreased over the next 8 weeks. Of 83 Indian children, 61 received repeated courses of steroids. The total duration of therapy was obtained by calculating the number of weeks during which the patient had been taking prednisone. Indian and African patients with membranous or proliferative glomerulonephritis were not given steroids. These patients were treated symptomatically with diuretics (thiazides, spironolactone) or occasionally during severe relapses with an i. v. infusion of salt-free 20% albumin together with i. v. furosemide.

We observed when using alternate-day therapy that patients experienced earlier relapses than those on daily steroids (M. Adhikari, N. E. G. Manikkam, H. M. Coovadia, unpublished data) and over a period of 10–15 years we found the complication rate of daily steroids was no different from that with alternate-day therapy.

African children. Steroids have been largely unsuccessful in the management of African children with nephrosis. In 10 African children, the duration of each course of steroids was often less than 12 weeks because of the lack of response or severe side effects (hypertension and fluid retention). Indeed, African children with MCN on renal biopsy are no longer given steroids as paradoxically they do not respond to such therapy [14]. Of 32 African children treated with steroids, 30 did not respond, 3 had severe side effects and 2 died. The few African children given prednisone were treated in the earlier years, until further work indicated their poor response. Parents or the referring doctor were fully informed of the reasons for withholding steroids in any child.

Steroid toxicity

The overall experience of steroid toxicity relates to a larger study [11] and was as follows: about 40% of Indian children developed cushingoid features, 3 required cyclophosphamide for gross toxicity and 1 child had aseptic necrosis of the femoral head.

Follow-up period

Overall the children were followed for a mean of 3.9 years (range 0.25–14 years) – African children were followed for a mean period of 32 months (range 3–138 months) and Indian children 53 months (range 5–168 months). When those followed for less than 1 year were excluded, the mean duration of follow-up for the remaining 28 African children was 47 months, and for 72 Indian children 60.5 months.

Height measurements

Data for the last recorded height taken at an average of 77.1 weeks after completion of steroid therapy (range 1 week to 364 weeks) were analysed. Heights were measured by H.M.C. or M.A. with the child standing barefoot against a vertical wall and with both the heels and occiput touching the wall. A square rule was used to maintain the vertex at right angles to the wall to determine the height, which was read off a measuring scale attached to the wall. Heights were recorded to the nearest quarter centimetre; variability was not measured. Heights of boys and girls at different ages were compared by calculating the height standard deviation score (SDS) according to the following equation:

$$\text{SDS} = \frac{x - \bar{x}}{s_x}$$

where x ist the measured height, $\bar{x}$ the mean height and s_x the SD. The figures for $\bar{x}$ and s_x were taken from tables compiled by the National Centre for Health Statistics (NCHS) [15].

The mean height percentile was determined from calculated mean SDS values 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. The results according to direct measurements are shown on the NCHS growth curves.

After exclusion of those who had been treated with prednisone for less than 12 months, an analysis of the height differences between the patients and normal children in their respective communities, and between the two races and sexes, was performed. Regression analysis of the duration of prednisone treatment against SDS for individual children was also carried out.

Renal biopsy classification

The histological classification and other details of these patients have been reported previously [12].

Statistics

The Mann-Whitney U test was used to access the significance of group differences, and linear regression of the slopes was performed by comparing SDS and duration of prednisone therapy for individual children.

Results

A total of 83 Indians (51 males) and 42 Africans (25 males) were studied. Their ages ranged from 1 to 12 years; mean age of the Indian children was 4.8 years whilst that of the African children was 7 years. Of the biopsied patients, 18 (49%) of 37 African children had membranous nephropathy so were not given steroids, while 57 (81%) of the 70

Table 1. Clinical details of patients

	Indians	Africans
n	83	42
Males	51	25
Mean age (years)	4.8	7
Mean follow-up (months)	32	53
Mean duration of total steroid therapy (weeks)	54	18
Histological types		
Minimal-change nephrotic syndrome	57 (57)[a]	7 (3)
Membranous	0	18 (2)[b]
Focal sclerosis	3 (2)	0
Focal proliferative	4 (4)	2 (1)
Other	6 (1)	10 (3)
Not biopsied	13 (13)	5

[a] On steroids

[b] Hepatitis B surface antigen (HBsAg) status – of 14 tested, 13 were positive

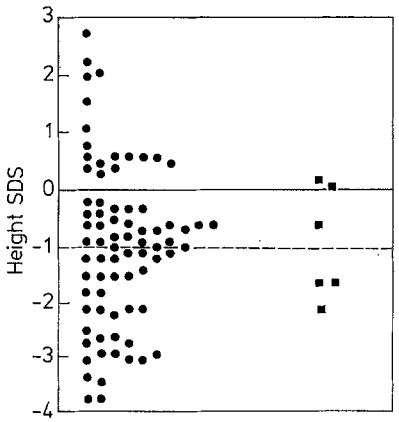

Fig. 1. Distribution of height standard deviation score (*SDS*) of treated (●) and untreated (■) Indian children

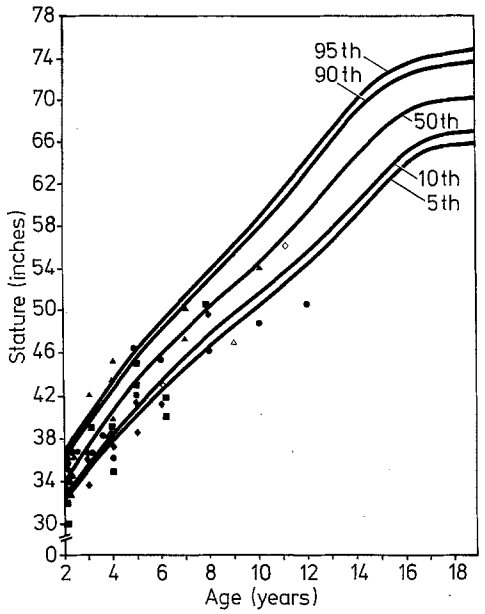

Fig. 2. Stature and duration of steroid for consistency treatment in Indian (*closed symbols*) and African (*open symbols*) boys (aged 2–18 years) on National Center for Health Statistics (NHCS) growth curves. *Diamond*, 1–12 weeks prednisone; *triangle*, 13–24 weeks prednisone; *circle*, 25–36 weeks prednisone; *square*, >36 weeks prednisone. One Indian male aged 1 year height 68.5 cm, 5th percentile not represented above

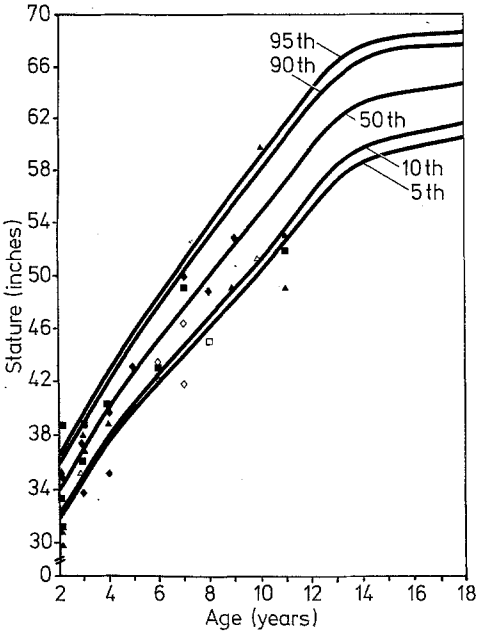

Fig. 3. Stature and duration of steroid treatment in Indian (*closed symbols*) and African (*open symbols*) girls (aged 2–18 years) treated with steroids on NHCS growth curves. *Diamond*, 1–12 weeks prednisone; *triangle*, 13–24 weeks prednisone; *circle*, 25–36 weeks prednisone; *square*, >36 weeks prednisone

Indian children had MCN and were treated with steroids. Of the unbiopsied patients, 1 of 5 Africans and 12 of 13 Indians were steroid sensitive (Table 1). The proportions of these histological types reflect the overall picture of NS among African and Indian children in Durban, South Africa [12, 13].

Eighty-seven children received prednisone for an average of 36 weeks (range 4–250 weeks) and 38 patients were treated symptomatically. There was no significant differences in height SDS between the races and sexes. Of the 83 Indians, 77 (93%) were treated with prednisone for an average of 54 weeks (range 4–250 weeks). The mean (+ SD) height SDS of the steroid-treated (77) and untreated (6) groups were –1.06+1.44 and –0.92+0.96, respectively (both values lie between the 10th and 25th NCHS percentiles) (Fig. 1, Table 2). There was no significant difference in height between the two groups ($P = 0.75$). The actual heights of treated and untreated Indian children plotted on NCHS percentiles are shown in Figs. 2–5. The growth of both groups falls within the range of locally established percentiles for Indian children (data not shown) [16].

Table 2. Height standard deviation scores (SDS) in steroid-treated and untreated Indian and African children with nephrotic syndrome

	Indians		Africans		Duration of steroid treatment, both races (weeks)	
	Untreated group	Steroid group	Untreated group	Steroid group	<36	>36
n	6	77	32	10	64	23
SDS mean ± SD	–0.92±0.96	–1.06±1.44	–1.77±1.61	–1.82±0.81	–1.09±1.41	–1.23±1.48
P	0.75		0.74		0.68	

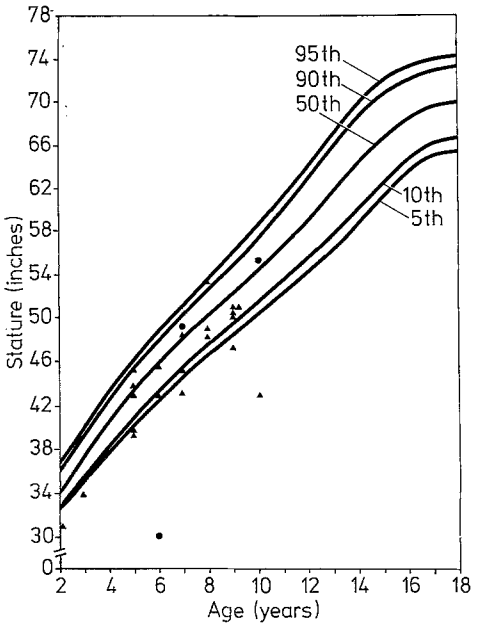

Fig. 4. Stature of untreated (controls) Indian (●) and African (▲) boys on NHCS growth curves

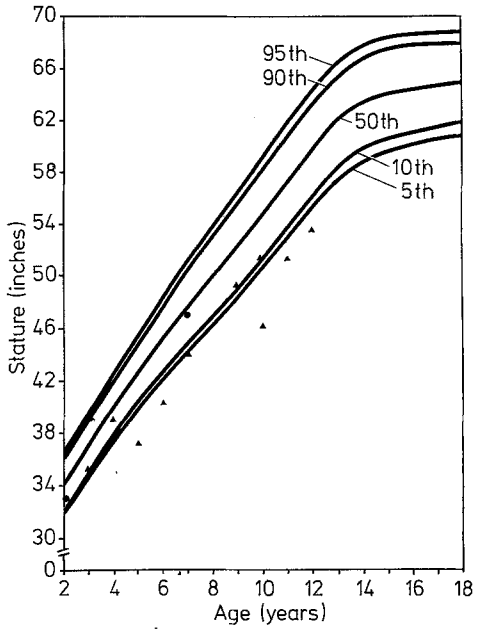

Fig. 5. Stature of control (untreated) Indian (●) and African (▲) girls on NHCS growth curves

Of the 42 African children, 10 (24%) received prednisone therapy for an average of 18 weeks (range 6–70 weeks). The mean (+ SD) height SDS of the steroid-treated (10) and untreated (32) groups were -1.82 ± 0.81 (<5th NCHS percentile) and -1.77 ± 1.61 (between 5th and 10th NCHS percentiles). The untreated group had persistent proteinuria. Growth of these patients was within the normal range according to both NCHS (Figs. 2–5) and locally established percentiles (data not shown) [17]. There was no statistical difference between the two groups (Mann-Whitney U Test $P = 0.74$, Fig. 6 and Table 2).

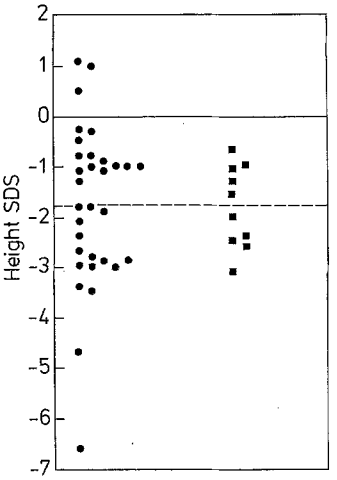

Fig. 6. Distribution of height SDS of treated (■) and untreated (●) African children

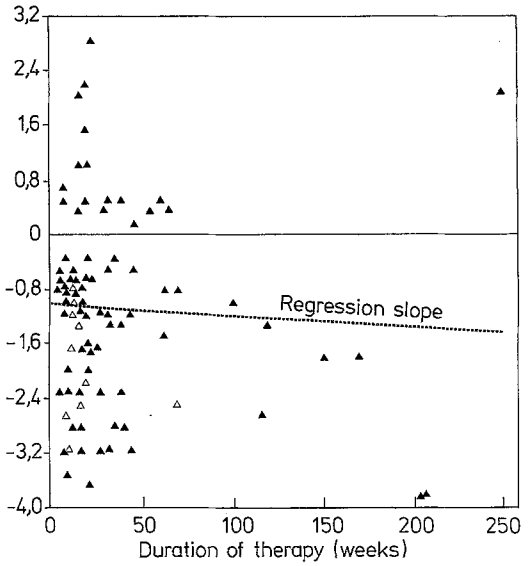

Fig. 7. Height SDS versus duration of prednisone therapy. ▲, Indian children; △, African children

We evaluated the effect of the duration of steroid therapy on growth in both individual children and in subgroups stratified for the length of steroid treatment. A period of 12 weeks was chosen as a criterion for exclusion, as therapy for less than this is unlikely to produce lasting effects on height. Figure 7 shows all the data for the height SDS and the duration of prednisone therapy for individual patients. Regression analysis of the data revealed no significant effects of steroids in the 87 prednisone-treated patients ($T = 0.69$, slope = -0.002 ± 0.003, Y intercept = -1.04 ± 0.15, $r = -0.075$). Exclusion of those children who had had less than 12 weeks of prednisone resulted in the remaining 60 Indian patients having an SDS of -0.98 ± 1.48 and 7 Africans -1.69 ± 0.61. These results were not significantly different ($P = 0.87$ and 0.88, respectively) when compared with their appropriate controls (SDS values given above).

Sixty-four children (55 Indians, 9 Africans) who received prednisone for less than 36 weeks had an SDS of -1.09 ± 1.41, whilst 23 (21 Indians, 2 Africans) who had received this therapy for more than 36 weeks had an SDS of -1.23 ± 1.48 ($P = 0.68$). Thirty-six weeks duration of therapy was chosen as it is likely to be associated with growth inhibition.

Discussion

This study shows that both Indian and African children with NS on repeated courses of daily steroids continue to grow normally over an average observation period of almost 4 years. The mean total duration of repeated courses of steroids amounted to 54 weeks for Indians and 18 weeks for Africans. The findings remain consistent when only those patients who had received a prolonged period (>12 weeks or >36 weeks) of steroids were analysed by regression analysis for any correlation between the duration of therapy and height attainment score in individual children. Our results support the findings of two recent studies on the effect of alternate-day steroids [8, 9] which showed that statural growth remained unaffected.

Growth suppression is an adverse effect of steroid therapy in children who received repeated courses, with those who are on prolonged maintenance therapy (>6 months) being at greatest risk [18]. Alternate-day rather than daily regimens have been recommended to reduce the growth-inhibitory effects. We have shown that steroids given on a daily basis for NS in patients living under disadvantageous circumstances do not prevent the attainment of height levels similar to those prevailing among normal children in the community. The possibility that we failed to detect clinically important effects on growth because of the small size of the untreated Indian and steroid-treated African groups must however be considered.

Catch-up growth, which usually occurs after cessation of daily steroids may fail when therapy has been prolonged for longer than 6 months [18]. We therefore compared children who had received prednisone for less than 36 weeks with those who had received treatment for longer than 36 weeks; no significant difference in height beetween these groups was observed (Table 2). This supports the finding of Foote et al. [8] of a lack of correlation between total prednisone dose and ultimate height attainment.

We considered it appropriate to use the NCHS standards for comparison. Coovadia et al. [17] demonstrated that the length measurements of African children under 2 years of age in Durban were similar to Harvard standards, and Moosa [16], in his study on growth of middle- and upper-income Indian schoolchildren in Durban, showed that their growth parallels NCHS values. Older African children were considerably shorter, their mean height lying betwen the 5th and 10th Harvard percentiles. This decrease in height (and weight) of older children probably reflects the damaging effects on growth of an impoverished socio-economic environment. The majority of our patients of both race groups were poor and therefore it is not surprising that both steroid-treated and untreated children had height attainment scores below zero (i.e. 50th percentile), but still within the normal range for community controls.

African children generally have steroid-unresponsive nephrosis with severe persistent proteinuria [11, 12]. Furthermore, such children come from socially disadvantaged communities and their diets are often inadequate in protein and calories [19]. Normal height attainment by these nephrotic African children who were not given steroids, suggests a good prognosis for growth despite these nutritional deficiencies.

Although it is widely accepted that prolonged steroid therapy adversely affects the growth of young children [3], this study of 125 nephrotic children, either considered individually or as a group, clearly demonstrates that prednisone therapy given in repeated courses on a daily basis for brief or prolonged periods did not inhibit their linear growth. Furthermore, persistent proteinuria in those nephrotic children who were not prescribed steroids was also not associated with growth retardation.

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Ask the expert*

A girl with an "isolated" neurogenic bladder due to partial sacral agenesis and severe bilateral vesico-ureteral reflux, goes into end-stage renal failure at the age of 8 years. What are the special measures to be taken prior to and after renal transplantation?

Key word: Neurogenic bladder

The usual combination of problems in neurogenic bladder dysfunction leading to end-stage renal failure comprises high pressure bladder outflow obstruction, bilateral vesico-ureteral reflux and recurrent urinary tract infections. Of these, it is the high pressure bladder outflow obstruction that is the main problem, as without this, reflux alone or in combination with recurrent urinary infection does not commonly lead to end-stage renal failure, whereas high pressure bladder outflow obstruction alone commonly does. The crucial factor in management therefore is to identify and treat high pressure bladder outflow obstruction.

High pressure bladder outflow obstruction involves three main factors. Firstly, constantly elevated intra-vesical pressures due to a poorly compliant bladder, secondly, hyper-reflexic detrusor contractions that superimpose waves of bladder pressure on the already elevated baseline pressure, and thirdly, outflow obstruction at the level of the urethral sphincter mechanism, because this fails to relax as it should at the onset of voiding and indeed may actively contract instead. These features are all recognised by a video urodynamic study, so this is the crucial investigation in making the diagnosis and thus in determining management.

Although some such bladders respond to treatment with anticholinergic medication and specifically oxybutynin 5 mg four times a day, terodiline 25 mg twice a day or imipramine 25 mg three times a day, most patients with severe neuropathic dysfunction require augmentation ("clam") entero-cystoplasty, preferably using the ileum. Augmentation cystoplasty is extremely effective at reducing intra-vesical pressure and abolishing hyper-reflexic contractions, but in so doing reduces voiding efficiency and makes any existing voiding inefficiency worse. It therefore commonly needs to be combined with clean intermittent self-catheterisation (CISC) to produce adequate bladder emptying thereafter. In those who persist with recurrent urinary infections, prophylactic antibiotics should be used. However, most patients on CISC do not suffer recurrent urinary infections and therefore do not require prophylactic antibiotics.

If there is still a useful degree of renal function the ureters should be reimplanted at the same time, if there is not and a bilateral nephro-ureterectomy is proposed at some stage then reimplantation is unnecessary.

It is critically important that urine continues to "wash through" a cystoplasty to prevent mucus retention. If transplantation without an intervening period of dialysis is planned, then the cystoplasty can be performed before transplantation. Otherwise the cystoplasty should be performed after transplantation when renal function has stabilised, immunosuppression has been reduced and continuing urine production can be (as far as possible) guaranteed.

There are theoretical risks with entero-cystoplasty from the inevitable metabolic acidosis that occurs, and this particularly concerns growth which should be carefully monitored. Bicarbonate should be given as necessary and could reasonably be given routinely and prophylactically. The other potential risk in the long run is of an adenocarcinoma developing at the bowel/bladder interface. At the moment this is a theoretical risk, as seen in the past in patients with uretero-sigmoidostomy. Whether or not it will turn out to be relevant to augmentation cystoplasty has yet to be seen.

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* The editors imite questions for this section