PEDIATRICS®
OFFICIAL JOURNAL OF THE AMERICAN ACADEMY OF PEDIATRICS

Clinical Features Affecting Final Adult Height in Patients With Pediatric-Onset Crohn's Disease

Andrew Sawczenko, Anne B. Ballinger, Martin O. Savage and Ian R. Sanderson

Pediatrics 2006;118;124-129
DOI: 10.1542/peds.2005-2931

ARTICLE

Clinical Features Affecting Final Adult Height in Patients With Pediatric-Onset Crohn's Disease

Andrew Sawczenko, BM, BCh[a], Anne B. Ballinger, MD[a], Martin O. Savage, MD[b], Ian R. Sanderson, MD[a]

[a]Research Centre in Gastroenterology, Institute of Cell and Molecular Science, and [b]Department of Pediatric Endocrinology, Barts and The London, Queen Mary, University of London, London, United Kingdom

The authors have indicated they have no financial relationships relevant to this article to disclose.

ABSTRACT

BACKGROUND. Growth failure is a recognized complication of pediatric-onset Crohn's disease, but there are few data on final adult height.

OBJECTIVE. Our purpose with this work was to determine adult height and the clinical features that influence long-term growth impairment.

METHODS. We retrospectively studied 123 patients with Crohn's disease (65 male and 58 female) who had reached adult height. All of the case subjects were diagnosed before age 16.0 years. Heights were converted to SD scores and univariate analysis performed of factors postulated to influence final height, that is, interval from onset of symptoms to diagnosis, prepubertal onset of symptoms, gender, jejunal disease present at diagnosis, systemic steroid therapy, intestinal surgery, and midparental height SD scores. Significant univariate factors were additional analyzed in regression models.

RESULTS. Mean height deficit at diagnosis was −0.50 SD scores, which improved to −0.29 SD scores at final height. Mean final height compared with target height, calculated from parental height, was −2.4 cm (range: −20.0 to 9.0 cm). Nineteen percent of the case subjects achieved a final height >8.0 cm below target height. The length of the interval between symptom onset and diagnosis correlated negatively with height SD scores at diagnosis. Height SD scores at diagnosis were related to final height SD scores, independent of midparental height. The presence of jejunal disease was negatively related to final height.

CONCLUSIONS. Mean final adult height showed a modest deficit compared with target height, but in one fifth of patients, final height was significantly less than target height. Earlier diagnosis and improved treatment of jejunal disease would be likely to improve final height.

www.pediatrics.org/cgi/doi/10.1542/peds.2005-2931

doi:10.1542/peds.2005-2931

Key Words
adult outcomes, Crohn's disease, height

Abbreviations
SDS—SD score
MPH—midparental height
CI—confidence interval
OR—odds ratio

Accepted for publication Feb 15, 2006

Address correspondence to Ian. R. Sanderson, MD, Centre for Gastroenterology, Institute of Cell and Molecular Science, Barts and The London, Turner Street, London E1 2AD, United Kingdom. E-mail: i.r.sanderson@qmul.ac.uk

GROWTH IMPAIRMENT HAS been recognized as a complication of Crohn's disease[1,2] since the earliest descriptions of the disorder in children.[3,4] Short stature and concerns about adult height may cause considerable distress to patients and their parents, particularly during adolescence, the peak time of diagnosis.[5] Although numerous reports have described growth impairment at the time of diagnosis or impaired growth velocity in the first few years after diagnosis,[6–9] there are relatively few reports that have documented final adult height.[6,8,10,11] Most studies that exist have been relatively small, and only few factors that negatively impact on growth and, thus, potentially affect final height have been studied.

Potential clinical factors that affect final height include the interval from the onset of symptoms until time of diagnosis,[5,12] which may be interpreted as delay in diagnosis; the presence of jejunal disease at diagnosis[5,13]; prepubertal onset of symptoms[11]; gender[9]; and severity of illness.[9] It has also been suggested that parents of children with Crohn's disease may themselves have short stature, hence accounting for apparent growth impairment in their offspring,[11] although several reports have not noted this.[8,14,15] In addition, there are few data on the effect of therapy on final height.[11,16] Systemic corticosteroids are prescribed more cautiously in children with growth failure and intestinal resection undertaken on shorter children. The long-term impact on growth of such modern clinical practice is not well documented. The aims of the present study were, thus, first to analyze a sufficiently large cohort of patients with pediatric-onset Crohn's disease to accurately document possible final height deficit and, second, to determine factors that might adversely influence long-term growth.

METHODS

Source of Patients

Patients were identified from 2 clinics based at St Bartholomew's and the Royal London Hospitals (London, United Kingdom). The first group was prospectively identified from 1989 onward from a pediatric inflammatory bowel disease clinic. The second group was retrospectively identified to have childhood-onset disease but was subsequently transferred, between 1980 and 1995, to the adult gastroenterology department.

Diagnosis of Crohn's disease

All of the case subjects were diagnosed according to established criteria.[17] None had other conditions potentially affecting growth.

Patient Characteristics

A total of 123 patients, 65 male and 58 female, diagnosed before the age of 16.0 years was studied. Diagnosis was at a mean age of 12.2 years (±2.8 years SD) and a range of 4.2 to 16.0 years. Thirty cases were identified from the pediatric clinic and 93 from the adult clinic, with no overlap of patients from the 2 sources. All were born in the United Kingdom; 98 (80%) were of white origin, 16 (13%) of Indian subcontinent origin, 6 (5%) of African origin, and 3 (3%) from other ethnic groups.

At diagnosis, 27 (27%) of 99 case subjects had jejunal involvement. Different treatment regimens were used in the group as a whole, but 52 (58%) of 123 received ≥1 course of systemic steroids (defined as ≥1 mg/kg of prednisolone orally for a minimum of 2 weeks), and 21 of the 52 had ≥3 such courses. Fifty seven (46%) of 123 patients had had intestinal surgery, with the potential for affecting growth, such as a right-hemicolectomy or strictureplasty.

Auxology Observations

Height was assessed using standard anthropometric techniques.[18] Final height was available in all 123 of the patients, height at diagnosis (±3 months) in 112, and height at 16 years old (±1 month) in 91. Height data were converted to SD scores (SDS) using the 1990 United Kingdom standards.[19]

Final Height

Final height was defined as height when growth velocity was <1 cm per year over a minimum of 6 months. Height and growth velocity were obtained in 65 patients at a mean age of 18.2 years (±2.7 years SD) and in 58 patients from a single measurement at age >22 years (mean ± SD: 29.4 ± 5.4 years), when growth was considered to be complete.

Parental Heights

Heights were measured in 37 (33%) of 111 mothers and in 28 (25%) of 110 fathers. In all of the other cases, patients were asked to report parental height. Reporting of height by family members has been demonstrated to be accurate.[20]

Target Height

Target height was calculated as the mean of maternal and paternal height SDS values or as an absolute value in males using the formula: [paternal height + (maternal height + 13)]/2 cm, and in females by: [maternal height + (paternal height − 13)]/2 cm. These calculations produce target heights with 95% confidence intervals of ±8 cm. In practice, the midparental heights (MPHs) produced by these 2 methods are very similar.[21] Final height was also compared with target height to produce the difference in centimeters.

Prepubertal Onset of Symptoms

We used a chronological definition from a previous report of a prepubertal onset of symptoms as <13 years for males and <11 years for females.[11]

Statistical Analysis

The effects of variables on height SDS were examined at 3 time points: at diagnosis, at 16 years old, and at final height. Continuous variables analyzed were MPH SDS and interval from symptoms to diagnosis ("delay"); and dichotomous variables analyzed were gender, prepubertal onset of symptoms, presence of jejunal disease at diagnosis, intestinal surgery, and systemic steroid therapy. Significant univariate factors ($P < .10$, 2-tailed) were entered into regression models and nonsignificant factors removed stepwise to achieve the final models reported.

Ethical Approval

The study was approved by the North East London Local Research Ethics Committee and the London Multicenter Research Ethics Committee.

RESULTS

Age at Diagnosis, Interval From Symptom Onset to Diagnosis, and Prepubertal Symptoms

The mean (±SD) age at diagnosis was 12.2 (±2.8) years (range: 4.2 to 15.9 years) after a mean interval from symptom onset to diagnosis of 12.5 (±12.9) months (range: 1.0 to 60.0). Forty three (42%) of 102 patients had a prepubertal onset of symptoms.

Height at Diagnosis

The mean height SDS at diagnosis was −0.50 (95% confidence interval [CI]: −0.75 to −0.24; $n = 102$), with no gender difference. There was a negative relationship between the length of the interval between onset of symptoms and diagnosis with height SDS at diagnosis ($r = -0.22$; $P = .032$). When corrected for MPH, this correlation increased ($r = -0.29$; $P < .01$).

Final Height

After diagnosis, patients were followed-up for a mean (±SD) of 10.4 (±7.1) years (range: 1.2 to 25.4 years; $n = 123$). Mean final height SDS was −0.29 (95% CI: −0.51 to −0.07; range: −3.48 to 2.80), with no gender difference. Final height SDS was significantly greater than that at diagnosis ($P = .015$; Fig 1). There were no relationships between final height SDS and age at diagnosis, prepubertal onset of symptoms, systemic steroid therapy, or intestinal surgery. (However, children who had had intestinal surgery were significantly shorter at diagnosis). Children with prepubertal onset of symptoms who had received steroid therapy were not significantly shorter than other children at final height.

The mean height deficit compared with target height was −2.4 cm (95% CI: −3.6 to −1.2; Fig 2). Twenty (19%) of 108 children achieved final height <8.0 cm, that is, >95% CI, below target height. Males were more likely than females to have a final height deficit >8.0 cm below target height (odds ratio [OR]: 3.95; 95% CI: 1.20 to 13.76; $P = .01$). For males with prepubertal onset of symptoms, the risk of achieving a final height deficit of more than −8.0 cm was OR 3.70 (95% CI: 1.06 to 13.23; $P = .018$).

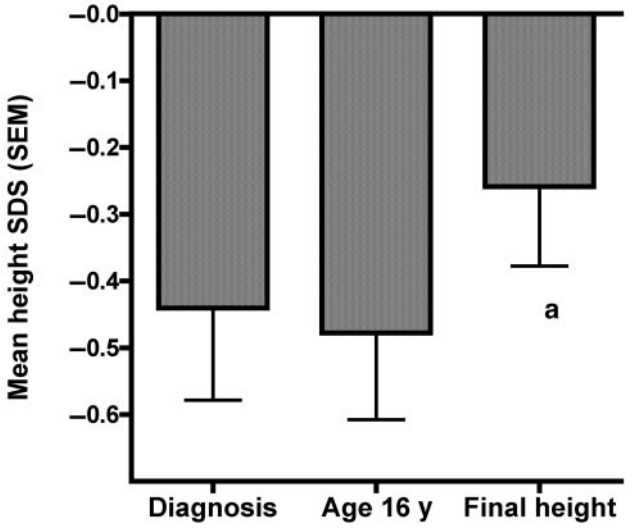

FIGURE 1
Final height is significantly greater than at diagnosis. Patients ($n = 91$) were included only if data were available at all 3 time points: diagnosis, age 16 years, and at final height. [a] $P <$ .05 for height SDS at diagnosis versus final height SDS.

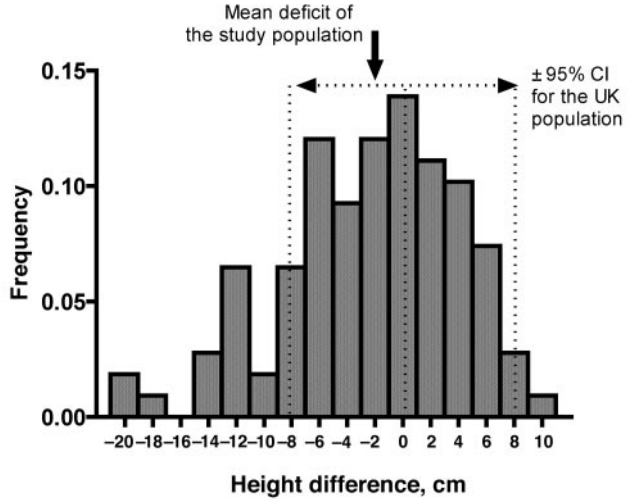

FIGURE 2
Mean final height is 2.4 cm below target height. Final height was compared with target height for all patients in whom both parental heights were recorded ($n = 108$). See text for methods. 95% of British children should lie within ±8.0 cm of the abscissa. Although the height of the study population is normally distributed, there is a left shift, with the mean height deficit being −2.4 cm (vertical arrow), and a tail of 19% of patients that achieved a final height less than −8.0 cm below target height.

Jejunal Disease at Diagnosis

At final height, patients with jejunal disease at diagnosis were shorter than those without jejunal disease (mean height: SDS −0.70 vs −0.15; $P = .034$).

Parental Height

The mean MPH and paternal and maternal heights were the same as in the general population: −0.03 SDS (SD: 0.88), −0.03 SDS (SD: 0.98), and −0.04 SDS (SD: 1.13), respectively, suggesting that growth retardation was not related to parental height. MPH correlated with height SDS at diagnosis, at 16 years old, and at final height (r = 0.58; r = 0.67; and r = 0.60, respectively; all $P < .0001$), similar to that of the reference United Kingdom population.[22]

Change in Height SDS

Sixty four (57%) of 112 children had an increase and 48 (43%) a decrease in height SDS from diagnosis to final height. The correlation between height SDS at diagnosis and final height SDS was r at 0.75 (r^2 = 0.56; $P < .001$). There was a negative relationship between height SDS at diagnosis and the change in SDS at final height (r = 0.49; $P < .001$), indicating that shorter children were more likely to have a gain in height. Those who had heights more than −1.0 SDS below the mean at diagnosis were more likely to have a positive increment in height (OR: 4.01; 95% CI: 1.44 to 11.55; P = .003).

Multivariate Analysis

At diagnosis, MPH SDS was positively related and interval between symptom onset and diagnosis was negatively related to height SDS (Table 1). At 16 years old, MPH SDS and height SDS at diagnosis were positively related to height SDS. Jejunal disease and intestinal surgery were negatively related to height at 16 years. At final height, MPH SDS and height SDS at diagnosis were positively related to height SDS, whereas the presence of jejunal disease was negatively related. The SDS increment (final height SDS minus diagnosis height SDS) was negatively correlated with the difference from midparental SDS (ie, midparental SDS minus diagnosis SDS; $P < .001$) and the presence of jejunal disease (P = .078; r^2 = 0.39).

DISCUSSION

This population of Crohn's patients, with presenting characteristics representative of current United Kingdom cases,[5] constitutes the largest series to be followed until final height. It is sufficiently large for the analyses we have performed to provide clinical conclusions about several factors influencing final height. Importantly, our findings suggest a relatively favorable final height prognosis for the majority of patients, albeit when cared for in a specialist unit in which the primary therapy is enteral feeding. The finding that the mean final height deficit was relatively modest at −0.29 SDS is reassuring. We observed, however, that growth impairment was not a universal finding, but that there was a subset of approximately one fifth of patients who were especially at risk (Fig 2). This is a key group to which future attention needs to be addressed.

Growth velocity has been reported to be abnormally decreased in approximately one half of Crohn's cases before diagnosis.[10,14,15,23,24] Recently, we have shown that the −174 G/C interleukin-6 polymorphism determines poor growth at diagnosis,[25] although DNA from the majority of the current cohort is not available. Our current findings show that when height deficit was present at diagnosis, because of subnormal growth after the onset of symptoms, normal growth potential may be compromised. A similar observation has been noted in other growth-impairing conditions, such as celiac disease and malnutrition.[26,27]

Therefore, prevention of abnormal growth by earlier

TABLE 1 **Effect of Clinical Variables on Height SDS at Diagnosis, Age 16 Years, and Final Height**

Variables Used in Model	Unstandardized Coefficients		Standardized Coefficients		*P*
	β	SE	β	*t*	
Model A: height SDS at diagnosis					
Constant	−.20	0.17		−1.22	.23
MPH SDS	1.03	0.14	.64	7.58	<.001
Length of symptoms before diagnosis, mo	−.02	0.01	−.23	−2.72	<.001
Model B: height SDS at 16 y					
Constant	.08	0.11		0.73	.47
Jejunal disease present at diagnosis: (1) yes (0) no	−.37	0.17	−.12	−2.18	.03
Intestinal surgery: (1) yes (0) no	−.32	0.15	−.12	−2.11	.04
MPH SDS	.2	0.1	.14	1.93	.06
Height SDS at diagnosis	.71	0.07	.75	10.22	<.001
Model C: height final SDS					
Constant	.05	0.1		0.56	.58
MPH SDS	.45	0.11	.33	4.14	<.001
Height SDS at diagnosis	.49	0.07	.55	6.86	<.001
Jejunal disease present at diagnosis: (1) yes (0) no	−.33	0.18	−.12	−1.85	.07

Coefficient of multiple determination for model A is R^2 = 0.46; for model B, R^2 = 0.80; for model C, R^2 = 0.67. All *P* values are 2-tailed. See text for methods.

diagnosis, thus reducing the duration of symptoms before treatment, is an important goal. However, many children present with nonspecific symptoms, which may not immediately be recognized to be associated with Crohn's disease.[5] Increased awareness by primary care doctors and pediatricians of the possibility of Crohn's disease, with wider use of screening investigations, such as erythrocyte sedimentation rate, C-reactive protein, serum albumin, and platelet count, may help in earlier diagnosis.[28]

Although it has been suggested previously that jejunal disease at diagnosis might be linked to impaired growth,[9] a statistical association has only been demonstrated recently.[5] The present study expands this association to show that jejunal disease affects final height. Extensive small bowel disease presents a particular challenge for management, but it is clear that, from the growth perspective, particular attention should be focused on this group.

The size of the current study has enabled us to show a statistically significant gain in height SDS from diagnosis to final height. It is likely that this occurred because of the active treatment received. It has been reported that approximately half of patients with Crohn's disease improved their height SDS during treatment.[9,29] We also observed this and also that the shortest children had the greatest increment in height. This latter observation will be useful in counseling patients. Although there were no overall effects of prepubertal symptom onset or gender on final height, males with prepubertal onset of symptoms were at the greatest risk of failing to attain final height within their genetic potential. It has been reported previously that girls experienced better catch-up growth than boys.[9]

In much of North America, corticosteroids are often used as initial treatment for Crohn's disease. In contrast, in the United Kingdom, enteral feeding has been the favored therapy for inducing remission for ~20 years because of concerns about the potential of systemic steroids to lead to growth impairment.[30] This has limited corticosteroids to children who have failed dietary therapy and who may, therefore, have more intractable disease. Despite this policy, in practice many of our patients did receive ≥1 course of systemic steroids. However, we did not observe a long-term effect on height, which is in agreement with other reports.[9,31] Given that, in the United Kingdom, pediatric inflammatory bowel disease clinics were, in part, specifically established to limit the use of corticosteroids (especially among children identified as being short), this finding is reassuring. These data do not argue in favor of the use of systemic steroids based on disease activity alone, but patients can be informed that there is no evidence that judicious use of systemic corticosteroids in the setting of a specialist clinic will cause significant long-term growth sequelae.

We also found no effect of intestinal surgery on final height, concurring with a previous report.[6] The targeted use of surgery as an intervention for poor growth explains this apparent contradiction. Parents can be advised that, in selected cases, as well as impressive short-term postoperative catch-up growth,[16] a positive effect on final height is a likely outcome.

CONCLUSIONS

Decreasing the length of delay in diagnosis would be likely to improve final adult height in pediatric Crohn's disease patients. Children with jejunal disease are at increased risk of growth retardation, and prepubertal males should be observed carefully in this regard. Although the growth prognosis for most children is relatively good, there is a subgroup who are more at risk of long-term height deficit and, thus, may require more intensive surveillance and management.

ACKNOWLEDGMENTS

Dr Sawczenko was supported by the Crohn's in Childhood Research Association.

We are grateful to Dr Tim Cole, Dr Peter Fairclough, Prof David Rampton, and Shivai Misra for their help in the preparation of this article.

REFERENCES

1. Dalziel TK. Chronic intestinal enteritis. *BMJ.* 1913;2:1068–1070
2. Crohn BB, Ginsburg L, Oppenheimer GD. Regional ileitis: a pathologic and clinical entity. *JAMA.* 1932;99:1323–1329
3. Snapper J, Gruen J, Foyer A. Observations sur l'ileite regionale. In: *Proceedings of the Second International Congress of Gastroenterology*. Brussels, Belgium: Societé of Internationale Gastroenterologie; 1937:935–937
4. Logan AH, Brown PW. Intestinal infantilism as a result of regional enteritis. *Proc Mayo Clin.* 1938;13:335–336
5. Sawczenko A, Sandhu B. Presenting features of inflammatory bowel disease in Great Britain and Ireland. *Arch Dis Child.* 2003;88:995–1000
6. Castile RG, Telander RL, Cooney DR, et al. Crohn's disease in children: assessment of the progression of disease, growth, and prognosis. *J Pediatr Surg.* 1980;15:462–469
7. Kirschner BS. Growth and development in chronic inflammatory bowel disease. *Acta Paediatr Scand.* 1990;366:S98–S104
8. Markowitz J, Grancher K, Rosa J, Aiges H, Daum F. Growth failure in pediatric inflammatory bowel disease. *J Pediatr Gastroenterol Nutr.* 1993;16:373–380
9. Griffiths AM, Nguyen P, Smith C, MacMillan JH, Sherman PM. Growth and clinical course of children with Crohn's disease. *Gut.* 1993;34:939–943
10. Hildebrand H, Karlberg J, Kristiansson B. Longitudinal growth in children and adolescents with inflammatory bowel disease. *J Pediatr Gastroenterol Nutr.* 1994;18:165–173
11. Alemzadeh N, Rekers-Mombarg LT, Mearin ML, Wit JM, Lamers CB, van Hogezand RA. Adult height in patients with early onset of Crohn's disease. *Gut.* 2002;51:26–29
12. Spray C, Debelle GD, Murphy MS. Current diagnosis, management and morbidity in paediatric inflammatory bowel disease. *Acta Paediatr.* 2001;90:400–405
13. Motil KJ, Grand RJ, Davis-Kraft L, Ferlic LL, Smith EO. Growth

failure in children with inflammatory bowel disease: a prospective study. *Gastroenterology.* 1993;105:681–691
14. Kirschner BS, Voinchet O, Rosenberg IH. Growth retardation in inflammatory bowel disease. *Gastroenterology.* 1978;75:504–511
15. Kanof ME, Lake AM, Bayless TM. Decreased height velocity in children and adolescents before the diagnosis of Crohn's disease. *Gastroenterology.* 1988;95:1523–1527
16. Lipson AB, Savage MO, Davies PS, Bassett K, Shand WS, Walker-Smith JA. Acceleration of linear growth following intestinal resection for Crohn disease. *Eur J Pediatr.* 1990;149:687–690
17. Chong S, Bartram CI, Campbell C, Williams C, Blackshaw A, Walker-Smith J. Chronic inflammatory bowel disease in childhood. *Br Med J (Clin Res Ed).* 1982;284:101–103
18. Cameron N. The methods of auxological anthropometry. In: Falkner F, Tanner JM, eds. *Human Growth*. New York, NY: Plenum; 1978:35–87
19. Freeman JV, Cole TJ, Chinn S, Jones PRM, White EM, Preece MA. Cross-sectional stature and weight reference curves for the UK: 1990. *Arch Dis Child.* 1995;73:17–24
20. Reed DR, Price RA. Estimates of the heights and weights of family members: accuracy of informant reports. *Int J Obes Relat Metab Disord.* 1998;22:827–835
21. Cole TJ. Galton's midparent height revisited. *Ann Hum Biol.* 2000;27:401–405
22. Alberman E, Filakti H, Williams S, Evans SJ, Emanuel I. Early influences on the secular change in adult height between the parents and children of the 1958 birth cohort. *Ann Hum Biol.* 1991;18:127–136
23. Gryboski JD, Spiro HM. Prognosis in children with Crohn's Disease. *Gastroenterology.* 1978;74:807–817
24. Saha MT, Ruuska T, Laippala P, Lenko HL. Growth of prepubertal children with inflammatory bowel disease. *J Pediatr Gastroenterol Nutr.* 1998;26:310–314
25. Sawczenko A, Azooz O, Paraszczuk J, et al. Intestinal inflammation-induced growth retardation acts through IL-6 in rats and depends on the −174 IL-6 G/C polymorphism in children. *Proc Natl Acad Sci USA.* 2005;102:13260–13265
26. Alvear J, Artaza C, Vial M, Guerrero S, Muzzo S. Physical growth and bone age of survivors of protein energy malnutrition. *Arch Dis Child.* 1986;61:257–262
27. Cacciari E, Corazza GR, Salardi S, et al. What will be the adult height of coeliac patients? *Eur J Pediatr.* 1991;150:407–409
28. Beattie RM, Walker-Smith JA, Murch SM. Indications for investigation of chronic gastrointestinal symptoms. *Arch Dis Child.* 1995;73:345–355
29. Hildebrand H. *Inflammatory Bowel Disease in Children With Special Respect to Epidemiology and Growth*. Goteborg, Sweden: University of Goteborg; 1993
30. Sanderson IR, Udeen S, Davies PS, Savage MO, Walker-Smith JA. Remission induced by an elemental diet in small bowel Crohn's disease. *Arch Dis Child.* 1987;62:123–127
31. Ferguson A, Sedgwick DM. Juvenile onset inflammatory bowel disease: height and body mass index in adult life. *BMJ.* 1994;308:1259–1263

TV VS WEB

"These days, people are spending as much time in front of a computer as a television—in some cases, even more. Adults spend about 14 hours a week watching TV and 14 online, compared with 11 watching TV and 10 online two years ago, according to JupiterResearch. Young adults, ages 18 to 24, spend about 10 hours a week online, two hours more than they spend watching TV. Many don't even own TVs but have laptops."

McBride S. *Wall Street Journal*. May 15, 2006
Noted by JFL, MD

Clinical Features Affecting Final Adult Height in Patients With Pediatric-Onset Crohn's Disease

Andrew Sawczenko, Anne B. Ballinger, Martin O. Savage and Ian R. Sanderson

Pediatrics 2006;118;124-129
DOI: 10.1542/peds.2005-2931