PAPERS AND SHORT REPORTS

Effect of growth hormone on short normal children

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Abstract

The growth of 26 short normal prepubertal children (mean age 8·4, height velocity standard deviation score for chronological age between +0·4 and −0·8) was studied for two years. Sixteen children were treated with somatrem (methionyl growth hormone) during the second year, and the remaining 10 children served as controls. During one year of treatment the height velocity standard deviation score for chronological age increased from the pretreatment mean of −0·44 (SD 0·33) to +2·20 (1·03). These values represented a change in height velocity from a pretreatment mean of 5·3 cm/year (range 4·6-6·9) to 7·4 cm/year (range 5·7-9·9). In the control group the height velocity standard deviation score was unchanged. Bone age advanced by 0·75 (0·33) years in the treated group compared with 0·70 (0·18) years in the control group. There was a significant increase in the height standard deviation score for bone age (0·63 (0·55)) in the treated group.

Multiple regression analysis of predictive factors contributing to the change in height velocity standard deviation score over the first year of treatment showed that the dose of growth hormone and pretreatment height velocity standard deviation score were important, together yielding a regression correlation coefficient of 0·80. The only metabolic side effect of treatment was an increase in fasting insulin concentration, which may be an important mediator of the anabolic effects of growth hormone. Treatment had no effect on thyroid function, blood pressure, or glucose tolerance. At the end of the treatment year seven of the 16 treated children had developed antibodies to growth hormone, but they were present in low titre with low binding capacity and in no child was growth attenuated.

Biosynthetic growth hormone improved the height velocity of children growing along or parallel to the third height centile, but the effects on height prognosis need to be assessed over a longer period.

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Introduction

We have recently shown an asymptomatic relation between the height velocity of short prepubertal children and the amount of growth hormone secreted over 24 hours.[1] The implication of this relation was, firstly, that children growing poorly and secreting little growth hormone would respond best to growth hormone treatment, a hypothesis well tested and proved by experience with human growth hormone treatment[2,3]; and, secondly, short children growing with a normal growth velocity would also respond, albeit to a lesser extent.

The second hypothesis has not been tested to any extent owing to limited supplies of human growth hormone. Several groups have reported a beneficial effect of exogenous growth hormone in short "normal" children, but the definition of normality was based predominantly on the biochemical response to pharmacological testing with little account taken of the children's growth rate.[4-9] If children are not to gain or lose height compared with their peers then they must grow with a 50th centile height velocity.[10] In practice, as children growing along or parallel to the third height centile grow slightly slower and tall children slightly faster than the mean, height velocities that fall continuously between the 25th and 75th centiles are accepted as normal (height velocity standard deviation score +0·8 to −0·8). If height velocity is used to define normality only 12 of the 91 children reported on were normal.[4-9] The limitations of defining normality by pharmacological testing have been shown by Bercu *et al* with the identification of children with neurosecretory dysfunction.[11,12]

Further problems with previous studies included short treatment periods, lack of measurement of changes in skeletal maturation, and a failure to take into account the safety of treatment in terms of the formation of antibodies and other possible complications, which include hypertension and glucose intolerance.[4-9] We report the effect of treatment with somatrem (methionyl growth hormone) for one year on the growth of 16 short normal children and compare the results with those in 10 children who served as controls.

Patients and methods

We studied 26 children (16 boys, 10 girls; mean age 8·4 years) who presented to the growth disorder clinic over two years for an opinion about their growth. After discussion with the parents 16 children (10 boys, six girls) formed the treatment group in the second year and 10 children (six boys, four girls) served as controls. The children had to meet the following

criteria before entry into the study and have: (1) a growth velocity standard deviation score between 0 and −0·8 in the first year of the study; (2) skeletal age less than 10 years; (3) no signs of puberty; (4) a growth hormone response to hypoglycaemia induced by insulin of >15 mU/l; (5) a 24 hour growth hormone profile in which there were seven to nine pulses of growth hormone, of which at least two were greater than 20 mU/l; (6) normal pituitary function; (7) no clinical or biochemical evidence of organic disease, psychological problems, or malnutrition.

Studies were approved by the hospital ethical committee, and informed consent was obtained in writing from the parents in all cases.

Growth assessment—Standard assessment of growth was performed at intervals of three months.[13] Bone age was assessed at yearly intervals by the same observer, who did not know the state of the child.[14] At each clinic attendance pubertal staging was performed according to the method of Tanner.[15] All growth measurements were expressed as standard deviation scores for either chronological age or skeletal age.[16]

Blood pressure—Systolic and diastolic blood pressures were recorded as the mean of three readings at each clinic visit. To allow comparison during the treatment period blood pressure was expressed as the mean calculated from the formula[17] mean pressure=diastolic pressure+(systolic pressure−diastolic pressure)/3.

Biochemical evaluation—Blood was taken before the study from all patients and at each visit to the clinic during the treatment year for measurement of plasma urea and electrolyte and serum calcium concentrations, liver function tests, measurement of glycosylated haemoglobin and haemoglobin concentrations, and white cell and platelet counts. In addition, before entry to the study a screen of gastrointestinal function was performed, when the following markers were used: serum albumin, total protein, folate, iron, and vitamin B12 concentrations; total iron binding capacity; and red cell folate concentration. Glucose regulation was assessed at intervals of six months during the treatment year with an oral glucose tolerance test (1·75 g/kg body weight), during the course of which serum insulin concentrations were measured. Fasting triglyceride and cholesterol concentrations were measured when the oral glucose tolerance test was performed.

Hormonal evaluation and methods of assay—At 0, six, and 12 months blood was taken for measurement of serum cortisol, testosterone, oestrogen, and adrenal androgen concentrations. Serum thyroxine concentrations were measured at each visit to the clinic and a thyrotrophin releasing hormone test (200 μg intravenously) performed at 0, six, and 12 months. Serum concentrations of insulin like growth factor 1 were measured at each visit to the clinic by the method of Baxter and Turtle.[18] The 24 hour growth hormone profiles were performed as described previously.[1] On the day after the profile an insulin tolerance test (0·15 units insulin/kg body weight) was performed, combined with administration of exogenous gonadotrophin releasing hormone (100 μg). Samples for assay of growth hormone were centrifuged, separated, and stored at −20°C until measurement with a previously described technique (Tandem-R radioimmunometric assay; Hybritech, Europe).[19] Blood glucose concentrations were measured with a Yellow Springs glucose analyser (YSI 23AM, Ohio). Serum insulin concentrations were assayed by a modification of the double antibody method of Morgan and Lazarow.[20]

Treatment regimens—The treatment group received somatrem (Somatonorm; KaviVitrum) as a subcutaneous injection of two units on six nights out of seven. It was not thought ethical to give placebo injections to the control group.

Statistical methods—Non-parametric statistical methods of analysis were used to assess significance. The Mann-Whitney U test and Wilcoxon matched pairs signed rank test were used for between group and within group changes, respectively. Stepwise multiple regression analysis was used to investigate factors related to the growth response. The contribution of age, dose of growth hormone expressed in units/m²/week, pretreatment height velocity standard deviation score for chronological and skeletal age, and height standard deviation score for chronological age or bone age were studied. The area under the curve was used to measure the effect of somatrem on glucose tolerance, with a correction being made to take into account a rise in the baseline values. The resulting area was called the incremental area. The area under the curve is the sum of a series of trapezoids.

Results

GROWTH VARIABLES

Table I shows the growth variables in the two groups of children and the effect of treatment. The mean ages of the two groups were similar (8·38 (SD 1·94) years in the treated group, 7·29 (1·35) in the control group). Sex ratios were also similar (1·5M:1F), as were the peak growth hormone responses to an insulin tolerance test (27·9 (9·2) mU/l in the treated group, 28·2 (9·1) mU/l in the control group). Children in the control group were slightly taller, but height velocities were identical in the two groups.

TABLE I—*Changes in growth variables (standard deviation scores; SDS) in the two groups of children over one year*

	At start of study (mean (SD))	At one year (mean (SD))	Significance of difference (p value)
Group given somatrem			
Height SDS for chronological age	−2·17 (0·58)	−1·70 (0·54)	<0·001
Height SDS for bone age	−0·87 (1·07)	−0·26 (1·07)	0·001
Height velocity SDS for chronological age	−0·44 (0·33)	+2·20 (1·03)	<0·001
Height velocity SDS for bone age	−0·69 (0·43)	+1·62 (0·84)	<0·001
Control group			
Height SDS for chronological age	−1·62 (0·55)	−1·64 (0·50)	NS
Height SDS for bone age	−0·42 (1·23)	−0·48 (0·90)	NS
Height velocity SDS for chronological age	−0·39 (0·38)	−0·37 (0·38)	NS
Height velocity SDS for bone age	−0·69 (0·39)	−0·60 (0·36)	NS

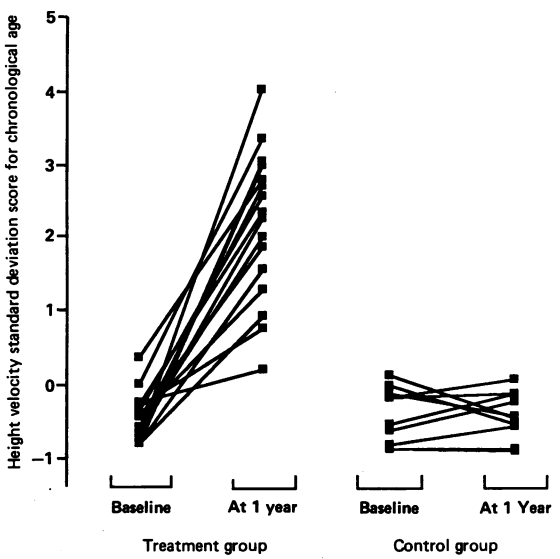

FIG 1—Changes in height velocity standard deviation score for chronological age in 16 children who received somatrem for one year compared with 10 controls.

Height velocity standard deviation score for chronological age increased from a pretreatment mean of −0·44 (0·33) to +2·20 (1·03); this rise was significant within the treatment group ($p<0·001$) and compared with the control group ($p<0·001$) (fig 1). This was reflected in the change in height standard deviation score for chronological age. The advance in bone age was 0·75 (0·33) years in the treatment group and 0·70 (0·18) years in the control group. Thus the improvement in height standard deviation score was not at the expense of an advance in skeletal maturity. This was confirmed by the significant increase in height standard deviation score for bone age in the treated group ($p=0·001$). All children remained prepubertal throughout the study.

Triceps and subscapular skinfold thickness standard deviation scores for chronological age at the start of treatment were +0·18 (0·56) and −0·46 (0·45), respectively, in the treated group and +0·26 (0·43) and −0·39 (0·47), respectively, in the control group. There was no significant change in either of the skinfold standard deviation scores after one year of treatment. There was, however, a significant decline in skinfold thickness in the treatment group over the first six months of observation and no change in controls.

There was no change in the mean blood pressure during the course of treatment (70·2 (10·7) mm Hg before treatment and 68·2 (7·4) mm Hg at the end of the year).

DOSE OF SOMATREM

The fixed dose regimen used produced a wide range of doses of somatrem when expressed in terms of body surface area (12·2-21·0 units/m² body surface area/week). The initial plot of change in height velocity standard deviation score for chronological age against somatrem dose suggested a

curvilinear relation, but a curvilinear plot did not significantly improve the description compared with a linear one (fig 2). There was a significant linear relation between the change in height velocity standard deviation score for chronological age (or bone age) and dose/m²/week (r=0·68).

Other factors important in predicting response to treatment were investigated in a multiple stepwise regression. The factors making a significant contribution to the prediction were pretreatment height velocity for either chronological age or bone age and dose of growth hormone. The final multiple regression was: change in height velocity standard deviation score for chronological age=−3·5−(1·2×pretreatment height velocity standard deviation score for chronological age)+0·34 (dose/m²/week). The multiple correlation coefficient was 0·80.

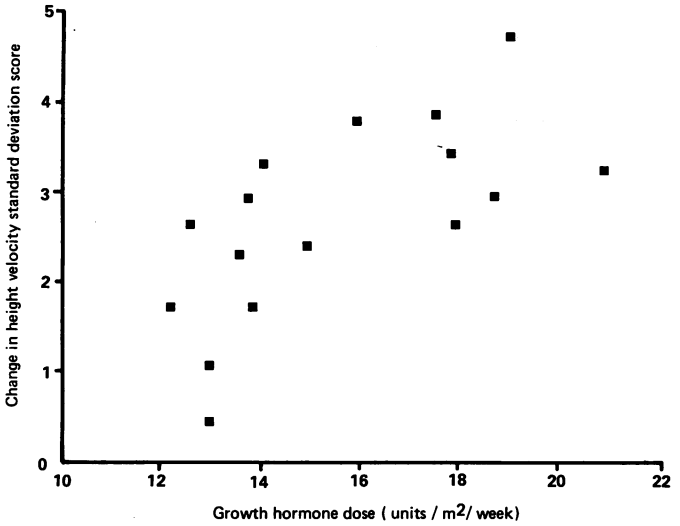

FIG 2—Relation between dose of growth hormone and change in height velocity standard deviation score over one year.

METABOLIC AND ENDOCRINE CHANGES

Glucose tolerance and lipid studies—Fasting glucose concentrations and the incremental area under the glucose curve were unchanged at six and 12 months of treatment. Similarly, haemoglobin A_1 concentration was unchanged at each clinic visit. The preservation of glucose homoeostasis was at the expense of an increase in the fasting serum insulin concentration from a pretreatment mean of 5·0 (3·7) mU/l to 15·7 (8·9) mU/l (p=0·003). This rise in the fasting concentration accounted for the change in the area under the insulin curve to glucose as the incremental area was unchanged during the treatment period. There seemed to be a direct association between the change in the fasting insulin concentration over the treatment period and the dose of growth hormone administered, but this did not achieve significance at the 5% level. No significant differences in fasting triglyceride and cholesterol concentrations were observed at six and 12 months compared with the pretreatment values.

Growth factors—All patients had serum insulin like growth factor 1 concentrations within the normal range for age (boys 0·25-4·40 U/ml, girls 0·36-1·40 U/ml). After a year of treatment serum insulin like growth factor 1 concentration had risen significantly from a pretreatment mean of 0·48 (0·18) U/ml to 1·11 (0·50) U/ml (p<0·001). There was no correlation between the change in height velocity for chronological age or bone age and the absolute or change in serum insulin like growth factor 1 concentration. There was no correlation between the height velocity/time and serum insulin like growth factor 1 concentration/time curves. The peak serum insulin like growth factor 1 concentration occurred in the second six month period, whereas the peak growth velocity was noted in the first six months, mainly in the first three months.

Thyroid state—Serum thyroxine concentration did not change during the treatment period. Basal serum thyroid stimulating hormone concentrations were also unchanged, as was the response of serum thyroid stimulating hormone to exogenous thyrotrophin releasing hormone.

Biochemical variables—There was no change in plasma urea and electrolyte and serum calcium concentrations, results of liver function tests, and haematological variables. In addition, there was no change in serum cortisol concentrations at 0800 during treatment or in serum testosterone, oestrogen, and adrenal androgen concentrations.

ANTIBODY FORMATION AND EFFECTS OF TREATMENT

Seven of the 16 children receiving treatment developed antibodies to growth hormone. Table II shows the time course of appearances of the antibodies and the titres; both the titre and binding capacity were low. At 12 months only four of the seven children with antibodies to growth hormone had binding capacities above the lower limit of the assay. None of the children with antibodies to growth hormone developed growth attenuation; the development of antibody was not related to the dose of growth hormone used. There was also no relation with the dose used and the presence of antibodies to *Escherichia coli* protein: the titre of these antibodies during treatment was low and not significantly different from the pretreatment titre, although the number of children with the antibody did increase during the study (six at the start compared with 13 at 12 months).

TABLE II—*Antibody state of children receiving somatrem for one year*

	Time (months)		
	0	6	12
No positive for antibody to growth hormone	0/16	7/16	7/16
Mean (SD) log titre	0	1·96 (0·59)	2·47 (0·79)
Mean (SD) binding capacity (mg/l)	0	0·07 (0·02)	0·24 (0·25)
No positive for antibody to *E coli* protein	6/16	11/16	13/16
Mean (SD) titre of antibody to *E coli* protein	0·25 (0·21)	0·28 (0·21)	0·26 (0·17)

The presence of antibody to *E coli* protein fluctuated during the course of treatment.

The treatment was well tolerated by all patients, and there were no untoward systemic effects.

Discussion

Children growing along or parallel to the third height centile grow with a height velocity standard deviation score between 0 and −0·8, and hence the height centiles widen with age. Our studies of physiological growth hormone secretion in short prepubertal children predicted that such children could be made to grow faster by being given exogenous growth hormone.[1] This hypothesis was tested in this study, and the increase in height standard deviation score for bone age seen was attributable to somatrem as all patients remained prepubertal; there was no change in serum cortisol, testosterone, oestrogen, adrenal androgen, or thyroxine concentrations; and growth variables did not change in the controls.

For ethical reasons we did not include a placebo treatment. This, however, does not detract from the findings because the main reason for a control group in studies such as this is not so much to exclude the placebo effect but to provide a group against which subtle but important changes in height velocity and absolute stature can be compared. The placebo effect was not observed in the trial by the health services human growth hormone committee of human growth hormone in short, slowly growing children or children with Turner's syndrome[21] or in studies of the effect of oxandrolone, an anabolic steroid, in constitutional delay of puberty (R Stanhope *et al*, paper presented at meeting of the British Society for Paediatric Endocrinology, 1986).

Analysis of the individual responses to exogenous growth hormone (fig 1) showed a heterogeneous pattern, and the data were therefore subjected to multiple regression analysis to discern variables important in the response. The dominant factor was dose of growth hormone (expressed as units/m²/body surface area/week), but pretreatment height velocity for chronological age (and also for bone age) was also important. The contribution of pretreatment height velocity standard deviation score was less than expected[2 3 22] and is explained by the small variation in this variable in this group of short normal children. Together the two factors produced a correlation coefficient of 0·80.

Dose response relations for growth hormone have been shown,[23-25] but little attempt has been made to tailor the dose of growth hormone to body size in the United Kingdom.[26] Physiological studies of growth hormone secretion have shown a clear rise with

age, which makes the use of fixed dose regimens all the more inappropriate.[27-29] In treating short normal children these effects need to be considered and may explain the poor response to treatment of such children in the past.[2,3] Our regimen, given to children with a wide range of ages, enabled us to obtain a wide range of doses and an equally wide range of responses (fig 2).

Serum insulin like growth factor 1 concentrations have been regarded by some as having predictive value in assessing response to growth hormone treatment,[4] although it is generally accepted that the correlation is poor[7,9,30]; our findings confirm this last observation. This poor relation probably reflects the fact that insulin like growth factor 1 is predominantly a paracrine hormone, so that serum concentrations need not necessarily reflect important changes in tissue concentrations.[31-33]

Administration of human growth hormone has been associated with alterations in thyroid function, reduced thyroxine and triiodothyronine concentrations,[34] and blunted thyroid stimulating hormone responses to thyrotrophin releasing hormone.[34-36] Increased somatostatin secretion has been postulated as the mechanism.[35] Several of the patients reported on, however, had borderline thyroid function; growth hormone treatment may have unmasked hypothyroidism or it may have arisen in the context of an evolving endocrinopathy.[36] None of the children in our study developed low serum thyroxine concentrations, nor was the response of serum thyroid stimulating hormone to exogenous thyrotrophin releasing hormone blunted. This last observation is complemented by animal work, which shows that growth hormone autofeedback is mediated by reduced secretion of growth hormone releasing hormone rather than enhanced release of somatostatin.[37] Growth hormone also directly feeds back on the pituitary.[38-40]

Acromegaly is characterised by excessive growth hormone secretion, and concern has been expressed that short normal children given growth hormone may develop a similar condition in association with hypertension and diabetes mellitus.[41] None of our children developed hypertension or glucose intolerance as measured by oral glucose loading and glycosylated haemoglobin concentrations.

The unchanged glucose tolerance was obtained at the expense of a rise in fasting insulin concentrations, but the insulin response to glucose loading (indicated by the incremental area under the insulin curve) was unchanged. This suggests that the predominant effect of growth hormone is to produce insulin resistance as previously reported.[42] This effect may be interpreted either as an undesirable side effect of treatment, which might lead to carbohydrate intolerance, or as an inevitable consequence of treatment and a necessity for the full expression of growth hormone anabolic activity: evidence for the last suggestion comes from animal work showing that growth hormone does not affect serum insulin like growth factor 1 concentrations in the absence of insulin.[43] Growth hormone and insulin act synergistically in generating insulin like growth factor 1.[44] Indirectly, during puberty an increase in serum insulin concentrations occurs during the growth spurt,[29] and the postoperative growth of children deficient in growth hormone with craniopharyngiomas can be explained by increased insulin secretion.[45] Diabetic children need an increased insulin dose during the growth spurt in puberty.

Roughly 44% of the children developed antibodies to somatrem; experience with patients with hypopituitarism produced similar results[46,47]; this suggests that the development of antibodies to growth hormone cannot be ascribed simply to patients being immunologically naive to growth hormone. It cannot be ascribed to the development of antibodies to *E coli* protein either as in this study there was no relation between the development of antibodies to somatrem and antibodies to *E coli* proteins. There was also no relation in this study between the dose of growth hormone administered and the development of antibodies. The binding capacity of these antibodies was low, and no growth retardation was observed. Experience with antibodies to pituitary human growth hormone has shown that a binding capacity >5 mg/l leads to inhibition of growth.[48] Antibody development is perhaps advantageous to patients as growth hormone activity has been shown to be enhanced by antibody formation.[49]

Previous studies have defined normality on the basis of pharmacological tests of growth hormone secretion.[4-9] Analysis of the growth records of these children has shown that most were not growing normally and could conceivably have had growth hormone "neurosecretory dysfunction"[11] or yielded false positive results to tests. Further problems in interpreting some of the studies arose as puberty supervened in several of the children. We defined normality by growth velocity as well as by pharmacological tests and 24 hour growth hormone profiles. The normal growth velocity makes the possibility of our patients producing bioinactive growth hormone extremely unlikely.

This study has shown that giving growth hormone to children growing along or parallel to the third height centile leads to an increase in growth velocity without an untoward advance in bone age so that actual height is improved. Apart from an increase in the fasting insulin concentration there was no other untoward effect of treatment, and the increase in fasting concentrations of insulin may be an important requirement for the full expression of the anabolic effect of growth hormone. The extent to which the stature of these children will be improved in the long term remains to be seen.

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SHORT REPORTS

Severe sexual dysfunction in women with the irritable bowel syndrome: comparison with inflammatory bowel disease and duodenal ulceration

Good evidence now exists that the irritable bowel syndrome is a much more diffuse gut disorder than was originally appreciated,[1] and we reported recently that among other symptoms women with the syndrome commonly suffer from dyspareunia.[2] Relatively little attention has been paid to the problem of sexual dysfunction in patients with gastrointestinal disorders except in relation to pelvic or abdominal surgery. We undertook a more detailed evaluation of sexual function in women with the irritable bowel syndrome, using groups of women with colonic inflammatory bowel disease and duodenal ulceration as controls.

Patients, methods, and results

Fifty consecutive women outpatients with the irritable bowel syndrome (abdominal pain, abdominal distension, and an abnormal bowel habit) were studied, with no refusals. Patients with painless diarrhoea were excluded. The control group consisted of 30 patients with active duodenal ulceration and 30 with active inflammatory bowel disease affecting the colon with no history of surgery. Five patients with inflammatory bowel disease and six with duodenal ulceration had symptoms suggesting coexisting irritable bowel syndrome and were not included in the control group because we would not have been able to ascertain which disorder was contributing to any sexual problem reported.

Forty two, 27, and 25 of the patients with, respectively, the irritable bowel syndrome, inflammatory bowel disease, and duodenal ulceration were sexually active. The distribution of social class in the groups was similar, but the mean age of the patients with duodenal ulcers was higher by nine years. Subjects were interviewed by a woman doctor (a trained psychiatrist) in their own homes. As part of a wider assessment of psychosocial state patients completed a self report questionnaire about sexual function in relation to their bowel disorder; only those with a score indicating severe or very severe disturbance (4 or 5 on a five point scale) were considered positive for the purposes of this analysis. Psychiatric state was measured with the psychiatric assessment schedule, a score of 11 or more indicating possible psychiatric illness.[3] Results were analysed with contingency tables (χ^2).

The table shows that the irritable bowel syndrome was associated with a profound impairment of sexual function, with 83% of patients reporting problems compared with 30% of women with inflammatory bowel disease and 16% of those with duodenal ulcers. When patients with psychiatric disorder were excluded from the analysis the same significant trend emerged, with 77%, 29%, and 14%, respectively, of women showing sexual dysfunction.

Comment

This study showed that sexual dysfunction is common in women with the irritable bowel syndrome. The presence of abdominal symptoms cannot be the sole explanation as the controls were specifically chosen because they had abdominal disease. In addition, the explanation cannot simply be the presence of psychopathology[4] because when women with psychiatric

Number (%) of sexually active women with the irritable bowel syndrome, inflammatory bowel disease, and duodenal ulceration with sexual dysfunction, and its relative significance

	Irritable bowel syndrome	Inflammatory bowel disease	Duodenal ulceration	Irritable bowel syndrome *v* inflammatory bowel disease *v* duodenal ulceration		Inflammatory bowel disease *v* duodenal ulceration		Irritable bowel syndrome *v* inflammatory bowel disease and duodenal ulceration	
				χ^2	p	χ^2	p	χ^2	p
Sexual function affected by bowel disorder									
All	35/42 (83)	8/27 (30)	4/25 (16)	34·7	<0·001	0·96	0·33	33·7	<0·001
Without psychiatric disorder	17/22 (77)	6/21 (29)	2/14 (14)						
Abdominal pain on sexual intercourse									
All	29/42 (69)	2/27 (7)	0/25	45·0	<0·001	0·32	0·57	44·7	<0·001
Without psychiatric disorder	13/22 (59)								
Vaginal pain on sexual intercourse									
All	7/42 (17)	2/27 (7)	3/25 (12)	1·28	0·26	0·24	0·62	1·04	0·31
Without psychiatric disorder	3/22 (14)	1/21 (5)	1/14 (7)						