The outcome of familial adenomatous polyposis in the absence of a polyposis registry

P. A. Goldberg, M. V. Madden, E. du Toit, S. Bailey, M. Torrington, W. H. Raynham

From 1964 to 1990, 70 patients with familial adenomatous polyposis were diagnosed at an institution without a polyposis registry. Those with symptoms at diagnosis were older (mean 34 v. 24 years) and more often had large-bowel cancer (7/30 v. 1/30, 23% v. 3%). The introduction of systematic screening significantly increased the number of cases diagnosed annually, from 2,3 to 5 per year, reduced the median age at diagnosis from 29 to 21 years and increased the proportion of cases diagnosed without symptoms from 52% to 90%. A colectomy with an ileorectal anastomosis achieved a low incidence of rectal cancer at 20 years (1/15, 7%) despite imperfect follow-up and annual sigmoidoscopy in only 40%. However, bowel cancer caused at least 35% of all deaths and 62% of deaths due to a known cause. A registry which maintained a screening programme should therefore prevent most large-bowel cancers and improve the life expectancy of patients with familial adenomatous polyposis who are managed at this institution. It might also refine the current method of screening by sigmoidoscopy alone, by facilitating the use of ophthalmoscopy and blood tests for DNA markers.

S Afr Med J 1995; **85:** 272-276.

Familial adenomatous polyposis (FAP) almost always leads to large-bowel cancer unless prophylactic surgery is performed. The results of treating large numbers of patients with FAP are usually reported from polyposis registries. Such registries have two main functions. Firstly they identify, among relatives of patients, those who have the disease and will benefit from surgery to prevent large-bowel cancer. Secondly, registries improve follow-up after surgery in order to reduce the risk of cancer of the rectum following colectomy and ileorectal anastomosis. Worldwide, however, it is likely that most patients with FAP have no contact with a registry. We have therefore studied the outcome of patients managed at a single institution, where screening programmes have been conducted sporadically by individual clinicians and no formal registry exists.

Surgical Gastro-enterology Unit and Department of Surgery, Groote Schuur Hospital and University of Cape Town

P. A. Goldberg, F.C.S. (S.A.)

M. V. Madden, F.C.S. (S.A.) F.R.C.S.

E. du Toit, S.R.N.

S. Bailey, S.R.N.

W. H. Raynham, F.R.C.S.

Medical Research Council of South Africa, Parowvallei, W. Cape

M. Torrington, PH.D.

Method

Patients with FAP were identified from hospital computer records of discharge diagnoses, the records of the Department of Pathology and the records of surgeons with an interest in the disease. All the patients managed at this hospital were included in the study. Many had previously been described in publications from the hospital.[1,2] Familial adenomatous polyposis was diagnosed if several adenomas were proven in patients with more than 100 polyps in the large bowel. The clinical details were obtained from the case notes and the patients were traced to establish their status. The first patient in the present series was identified in 1964. From 1964 to 1974 a research assistant and a surgeon traced members of some but not all families for screening and systematic follow-up. This system then lapsed until January 1988 after which screening was offered systematically to family members at risk for the disease.

The chi-squared test with Yates' correction was used to compare proportions for large samples and Fisher's exact test for small samples. Normally distributed data were compared by Student's *t*-test. Variables not normally distributed were compared with Wilcoxon's signed rank test.

Results

Over the 26 years, 70 patients with FAP were seen (35 men). Thirty-five were white and 35 of mixed race. None was black. Seven patients had no family history of polyposis and in 2 the family history was unknown. The remaining 61 patients were from 8 families. In 60 patients it was known if symptoms had been present at diagnosis, and the 30 patients with symptoms had a significantly higher prevalence of large-bowel cancer at diagnosis and were on average 10 years older than the asymptomatic patients (Table I).

Table I. Symptoms at presentation v. age

	No.	Mean age (yrs)	Large-bowel cancer at diagnosis
Symptomatic	30	34	7
Asymptomatic	30	24	1
Unknown	10	24	0
	70		

$P = 0{,}0005$ age, symptomatic v. asymptomatic.
$P = 0{,}02$ age, symptomatic v. unknown.
$P = 0{,}04$ proportion with cancer at diagnosis, symptomatic v. asymptomatic.

In all, 99 operations were performed on 67 patients (1,5 operations per patient) (Fig. 1). The remaining 3 patients

refused both surgical treatment and follow-up; 2 were lost to follow-up, while the other died of colon cancer 6 years after diagnosis aged 55 years. The most common operation performed to prevent large-bowel cancer was a colectomy with an ileorectal anastomosis, in 58 patients. The mean age at this operation was 27 years (median 24 years, standard deviation 10). One patient had a prior colostomy for an obstructing carcinoma of the descending colon. Of these patients 15 (26%) subsequently had at least one other operation for FAP, excluding fulguration of rectal polyps, during a median follow-up period of 10 years. Two of these patients and 2 unoperated patients underwent ileo-anal pouch procedures. Two of these 4 patients later had their ileal pouch removed because of incontinence for which no organic cause could be found. Two of 58 patients (3%) had their colectomy and ileorectal anastomosis revised to a proctocolectomy with an ileostomy, 1 for rectal cancer after 12 years and the other for multiple large rectal polyps with severe dysplasia after 10 years.

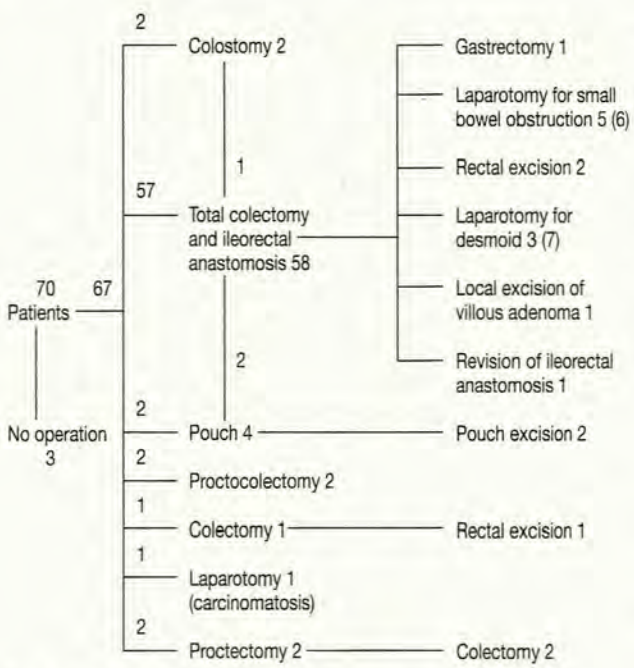

Fig. 1. Operations performed on all patients. (The number of operations is in brackets where patients had more than one procedure of the same type.)

Histological material from the first operation could be reviewed in 59 of the 67 operated patients. Fifty-one had adenomas and the remaining 8 (16%) had cancer (2 Dukes A, 4 Dukes C and 2 residual intra-abdominal disease); 4 of the latter were alive 5 years later. Because patients were followed up by several different surgeons after colectomy and ileorectal anastomosis, it was difficult to establish how often the retained rectum was examined. Consequently reliable data were available for 22 patients, of whom only 9 (40%) had undergone rigid sigmoidoscopy at least once a year. Of 15 patients who were followed up for 20 years after colectomy and ileorectal anastomosis, only 1 developed rectal cancer (7%, 95% confidence interval 0 - 33%) (Fig. 2).

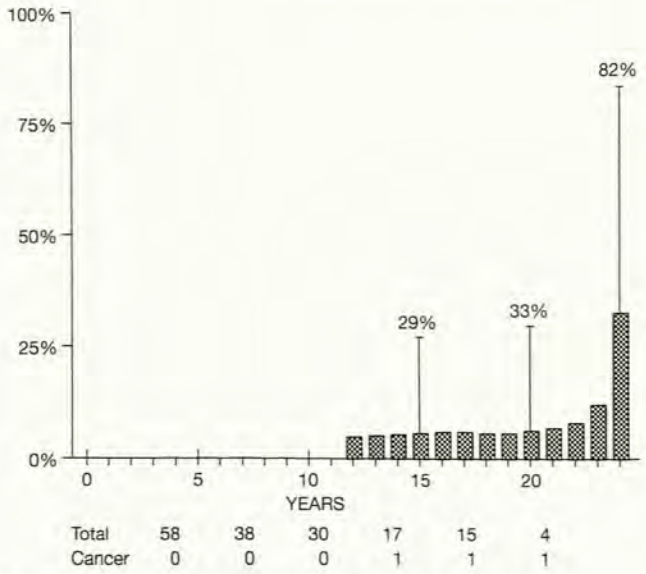

Fig. 2. Incidence of carcinoma of the rectal remnant after ileorectal anastomosis (with 95% confidence limits).

The duration of follow-up of all 70 patients is shown in Fig. 3. Nine were lost to follow-up after 1, 1, 10, 10, 10, 12, 21, 23 and 24 years (mean 11 years) respectively, while of the remainder 14 have died. The cause of death is unknown in 5 patients, and 1 died of ischaemic heart disease. The remaining 8 patients (57%) died of FAP: 6 of carcinoma of the large bowel (present at diagnosis in 5), 1 patient of cancer of the duodenum and the other of a desmoid that caused perforation of the small bowel. Gastroscopy with an end-viewing instrument in 18 patients identified

Fig. 3. Duration of follow-up from diagnosis to last visit (all patients).

adenomatous polyps in 4, of whom 1 had an antrectomy. Five patients have had retention polyps. No duodenal polyps were found. A systematic screening programme for family members was resumed in 1988 and this was accompanied by three statistically significant changes. The median age at diagnosis fell, the number of new cases annually rose and the proportion without symptoms at diagnosis increased. Since the screening programme began no patients have developed cancer before diagnosis (Table II).

The outcome of all 70 patients is summarised in Table III.

Table II. Changes in number and age of patients diagnosed, and in proportions with symptoms or with cancer, after introduction of a screening programme

	Before screening programme (1964-87)	After screening programme (1988-89)	*P*
Total diagnosed	60	10	
Diagnosed per annum	2,3	5	<0,006
Median age at diagnosis (yrs)	29	21	<0,01
Without symptoms	31 (52%)	9 (90%)	<0,001
Cancer at diagnosis	8 (13%)	0	NS

Table III. Outcome in 70 patients with FAP

Refused surgery			3
died, large-bowel cancer	1		
lost after 0,5 yrs (age 39) & 24 yrs (age 54)	2		
Total colectomy and ileorectal anastomosis			58
Cancer at colectomy		2	
died, large-bowel cancer	1		
lost after 10 yrs (age 50)	1		
No cancer at colectomy		50	
died, duodenal cancer	1		
died, ischaemic heart disease	1		
died, desmoid perforation	1		
died, unknown cause	2		
lost after 1 yr (age 41), 2 yrs (age 19) & 23 yrs (age 56)	3		
well	42		
Histology of colectomy specimen not reviewed		6	
died, rectal cancer after 12 years	1		
lost after 10 yrs (age 35), 11 yrs (age 35), 12 yrs (age 30) & 21 yrs (age 42)	4		
well	1		
Other operations			9
died, large-bowel cancer	3		
died, unknown cause	3		
well	3		

Discussion

FAP is one of very few diseases in which diagnostic screening makes it possible to prevent cancer. In this series cancer was not present in any of the 10 patients identified through the recent screening programme, while there were 8 patients with cancer (13%) among the 60 cases diagnosed during an earlier period when screening was practised only intermittently (Table II). However, this small difference in cancer incidence underestimates the true value of diagnostic screening. More representative data from registries covering three geographically defined areas (Finland, The Netherlands and the northern region of the UK) have shown cancer in 32 - 62% of symptomatic patients compared with 0 - 9% of those screened.[3-5] The Finnish registry has also shown that if the disease was diagnosed by screening, a patient's probability of survival after the age of 30 years improved significantly, compared with patients not diagnosed by screening.

The traditional method of screening involves examination of the rectum for polyps with a rigid sigmoidoscope. Although a fibre-optic endoscope provides a clearer and more extensive view the examination is more complex and costly, so screening by colonoscopy is only important in the very rare families whose polyps develop above an unaffected rectum.[6] Endoscopy is now being complemented, but not replaced, by alternative methods of screening. The molecular genetic technique of testing DNA from blood samples holds most promise but other methods which have been used are examination of the optic fundi, and radiography of the jaw.

The first tests performed on DNA used markers for unique fragments of DNA which were known to lie near the gene. The gene itself has recently been located;[7-9] it seems to cause the disease by different mutations in different families. The diagnostic tests compare DNA from affected and unaffected family members, which means that the technique is useless in a family where the disease is due to a new mutation and only 1 affected subject is available. For the same reason it is seldom useful in families with few living members although DNA from the formalin-fixed tissue of dead relatives has been used.[10] At present DNA probes seem to be useful in about 50% of families.[11,12] They allow subjects to be divided into those at low or high risk of developing the disease. Definition of a subject's risk is helpful because it allows sigmoidoscopic screening to be done less often in some patients and more often in others. In addition to the use of DNA markers, the risk can also be estimated by examining the optic fundi for the lesion characteristic of FAP, congenital hypertrophy of the retinal pigment epithelium (CHRPE).[13] CHRPE is easily missed by conventional ophthalmoscopy and best identified by indirect retinoscopy; an interested ophthalmologist is therefore needed. The finding of four or more CHRPE lesions has been reported as identifying 54 (88%) of 66 affected individuals.[14]

There are therefore several ways of estimating the risk of FAP gene carriage in a subject who has not developed rectal polyps. Each test provides an independent estimate of the risk of carrying the gene and these estimates can be combined to calculate the overall risk very accurately. It is simplest, although not very accurate, to calculate the risk from the person's age at a sigmoidoscopy which shows no polyps, since these appear with increasing frequency as affected subjects grow older. For example, if polyps are still absent by the age of 24 years the risk of being affected is below 10%.[15] The findings on sigmoidoscopy and retinoscopy can be used together, or combined with the results of DNA analysis to give an overall estimate. Occult

radio-opaque jaw lesions are also common in FAP and the findings of jaw radiographs, although not widely used, further increase the value of the combined tests.[16]

In South Africa individual surgeons treat most patients with FAP and there is no polyposis registry. To what extent should the new diagnostic tests change their approach to patients and their families? It is now theoretically possible to estimate the risk for most family members quite accurately at an early age, but in practice this cannot be done without a clinical geneticist, an enthusiastic ophthalmologist and, ideally, a molecular genetics service. In any case, even precise risk estimates are likely to cause quite small changes in management. For example, the usual interval between sigmoidoscopic examinations is 2 years, starting from the early teens,[17] and it has been suggested that for low-risk persons (risk < 5%) this interval can be doubled.[12] In addition, if by the age of 40 years no polyps have been found, the overall risk will have fallen to about 0,1% and screening of these subjects can be stopped.[12] However, some surgeons stop screening before this age in any case.[15] Conversely, in those at high risk or whose category cannot be defined, the 2-year interval between examinations should probably be maintained, perhaps continuing every 5 years after 40 years of age.[12]

The main aim of treating patients with FAP is to prevent large-bowel cancer. How effectively was this achieved at our hospital? The usual prophylactic operation is a colectomy with an ileorectal anastomosis[18] and the major objection to it is that cancer may develop in the remaining rectum. The frequency of rectal cancer reported 20 years after the operation ranges widely, from 9% to 59%.[19-24] However, in this study only 1 of 15 patients (7%) developed rectal cancer after 20 years. This low incidence is curious because in most of our patients the rectal remnant was not examined regularly for polyps. The probable explanation is that the age of the rectum and not the age at colectomy determines the risk of rectal cancer. Twenty years after colectomy our patients (like those at St Mark's Hospital) had a mean age of 47 years and a very similar incidence of rectal cancer (7% compared to 9% respectively). Patients who underwent the same operation at the Mayo Clinic had a much higher incidence of cancer (38%) after 20 years[20] but had been, on average, 9 years older at colectomy.[25] Further support for the concept that the age of the rectum determines the risk of rectal cancer after an ileorectal anastomosis comes from the finding that the patients from St Mark's Hospital have experienced a substantial increase in the probability of rectal cancer after the age of 50 years.[26]

The alternative operation to a colectomy and ileorectal anastomosis involves a colectomy and the construction of an ileo-anal pouch. Only 4 (6%) of our patients had this done and 2 of these now have a permanent stoma. However, the functional outcome reported after ileo-anal pouch operations is generally satisfactory[27-29] although few surgeons consider it the operation of choice to prevent large-bowel cancer.[18]

Foregut cancer is likely to become a major cause of death in patients in whom surgery prevents colorectal cancer.[30-32] However, this occurred in only 1 of our patients who died of duodenal cancer which was diagnosed when liver metastases were present. It had not been diagnosed during an examination with an end-viewing duodenoscope 6 months previously. Furthermore, the apparent absence of duodenal adenomas in all 18 of our patients who were examined suggests that an end-viewing instrument may not be adequate for detecting them. A study of 102 cases with a side-viewing duodenoscope to take systematic biopsies and photographs identified duodenal adenomas in 94 of 102 duodenal biopsies (94%) and gastric adenomas in 6 of 73 gastric biopsies (8%).[29] The absolute risk of duodenal and ampullary cancer combined has been reported as 1/1 698 person-years of observation[31] so it seems reasonable to ignore most duodenal polyps. However, severe dysplasia in a duodenal polyp is difficult to manage since a prophylactic pancreaticoduodenectomy is dangerous and endoscopic destruction of adenomas may not prevent cancer. Screening endoscopy has been recommended[29,31] but seems illogical as long as there is no appropriate treatment for duodenal polyps.

While FAP has been reported in South African blacks,[33, 34] no cases have been diagnosed at our hospital. One reason may be the founder effect that causes a high incidence in white immigrants, as the first affected individual in one of our families is thought to have arrived from Holland in about 1685. Another reason is that until recently the hospital has served a population of predominantly mixed or Caucasian descent.

We conclude that in our setting family screening has reduced the incidence of cancer when FAP was diagnosed, and a colectomy with an ileorectal anastomosis has been surprisingly effective in preventing large-bowel cancer. Therefore a registry which facilitates early diagnosis and prophylactic surgery may well prove cost-effective. It should help surgeons manage members of polyposis families more appropriately, as collaboration with clinical and molecular geneticists is becoming increasingly important.

We thank the National Cancer Association for financial support and are grateful to the following colleagues for their help: Professors D. R. de Villiers, D. M. Dent, K. C. Household, E. J. Immelman, the late J. H. Louw, A. E. Retief and J. Terblanche, Doctors K. Brice, P. J. Cant, A. H. Girdwood, D. J. de Villiers, M. S. Elliot, the late A. Katz, J. Klompje, S. K. Price, I. Sacks and D. Stein and Sister P. J. d'E. Stevens.

REFERENCES

1. Raynham WH, Louw JH. Familial polyposis of the colon. *S Afr Med J* 1966;**40:** 857-865.
2. Aitken RJ, Elliot MS, Torrington M, Louw JH. Twenty year experience with polyposis coli in Cape Town. *Br J Surg* 1986; **73:** 210-213.
3. Jarvinen HJ. Epidemiology of familial adenomatous polyposis in Finland: impact of family screening on colorectal cancer rate and survival. *Gut* 1992; **33:** 357-360.
4. Vasen HFA, Griffioen G, Offerhaus GJA, *et al.* The value of screening and central registration of families with familial adenomatous polyposis. A study of 82 families in The Netherlands. *Dis Colon Rectum* 1990; **33:** 227-230.
5. Rhodes M, Chapman PD, Burn J, Gunn A. Role of a regional register for familial adenomatous polyposis: experience in the Northern Region. *Br J Surg* 1991; **78:** 451-452.
6. Rhodes M, Bradburn DM. Overview of screening and management of familial adenomatous polyposis. *Gut* 1992; **33:** 125-131.
7. Kinzler K, Nilbert M, *et al.* Identification of FAP locus genes from chromosome 5q21. *Science* 1991; **253:** 661-665.
8. Nishisho I, Nakamura Y, Miyoshi Y, *et al.* Mutations of chromosome 5q21 genes in FAP and colorectal cancer patients. *Science* 1991; **253:** 665-669.
9. Groden J, Thliveris A, Samowitz W, *et al.* Identification and characterisation of the familial adenomatous polyposis coli gene. *Cell* 1991; **66:** 589-600.
10. Morton DG, MacDonald F, Cachon-Gonzales MB, *et al.* The use of DNA from paraffin wax preserved tissue for predictive diagnosis in familial adenomatous polyposis. *J Med Genet* 1992; **29:** 571-573.
11. MacDonald F, Morton DG, Rindl PM, *et al.* Predictive diagnosis of familial adenomatous polyposis with linked DNA markers: population based study. *BMJ* 1992; **304:** 869-872.

12. Koorey DJ, McCaughan GW, Trent RJ. Gallagher ND. Risk estimation in familial adenomatous polyposis using DNA probes linked to the familial adenomatous polyposis gene. *Gut* 1992; **33:** 530-534.
13. Traboulsi EI, Krush AJ, Gardner EJ, *et al.* Prevalence and importance of pigmented ocular fundus lesions in Gardner's Syndrome. *N Engl J Med* 1987; **316:** 661-667.
14. Burn J, Chapman P, Delhanty J, *et al.* The UK Northern Region genetic register for familial adenomatous polyposis coli: use of age of onset, congenital hypertrophy of the retinal pigment epithelium, and DNA markers in risk calculations. *J Med Genet* 1991; **28:** 289-296.
15. Northover JMA, Murday V. Familial colorectal cancer and familial adenomatous polyposis. *Ballieres Clin Gastroenterol* 1989; **3:** 593-613.
16. Giardiello FM, Offerhaus GJA, Graybeal JC, *et al.* Value of combined phenotypic markers in identifying inheritance of familial adenomatous polyposis. *Gut* 1991; **32:** 1170-1174.
17. Bülow S. The Danish Polyposis Register: Description of methods of detection and evaluation of completeness. *Dis Colon Rectum* 1984; **27:** 351-355.
18. Symposium (Dozois RR, moderator). Surgical aspects of familial adenomatous polyposis. *Int J Colorectal Dis* 1988; **3:** 1-16.
19. Moertel CG, Hill JR, Adson MA. Surgical management of multiple polyposis. The problem of cancer in the retained bowel segment. *Arch Surg* 1970; **100:** 521-526.
20. Bess MA, Adson MA, Elveback LR, Moertel CG. Rectal cancer following colectomy for polyposis. *Arch Surg* 1980; **115:** 460-466.
21. Bussey HJR, Eyers AA, Ritchie SM, Thompson JPS. The rectum in adenomatous polyposis: the St Mark's policy. *Br J Surg* 1985; **72:** S29-S31.
22. Sarre RG, Jagelman DG, Beck GJ, *et al.* Colectomy with ileorectal anastomosis for familial adenomatous polyposis: The risk of rectal cancer. *Surgery* 1987; **101:** 20-26.
23. Gingold BS, Jagelman D, Turnbull RB. Surgical management of familial polyposis and Gardner's syndrome. *Am J Surg* 1979; **137:** 54-56.
24. Schaupp WC, Volpe PA. Management of diffuse colonic polyposis. *Am J Surg* 1972; **124:** 218-220.
25. Beart RW jun. Familial polyposis, *Br J Surg* 1985; **72:** S31-S32.
26. Nugent KP, Phillips RKS. Rectal cancer risk in older patients with familial adenomatous polyposis and an ileo-rectal anastomosis: a cause for concern. *Br J Surg* 1992; **79:** 1204-1206.
27. Madden MV, Neale KF, Nicholls RJ, Landgrebe JC, Thomson JPS, Bussey HJR. Morbidity and bowel function after restorative proctocolectomy or ileo-rectal anastomosis for familial adenomatous polyposis. *Br J Surg* 1991; **78:** 789-792.
28. Everett WG, Forty J. The functional result of pelvic ileal reservoir in 10 patients with familial adenomatous polyposis. *Ann R Coll Surg Engl* 1989; **71**(1): 28-30.
29. Ambroze WL, Dozois RR, Pemberton JH, Beart RW, Ilstrup DM. Familial adenomatous polyposis: results following ileal pouch-anal anastomosis and ileorectostomy. *Dis Colon Rectum* 1992; **35:** 12-15.
30. Spigelman AD, Williams CB, Talbot IC, Domizio P, Phillips RKS. Upper gastrointestinal cancer in patients with familial adenomatous polyposis. *Lancet* 1989; **2:** 783-785.
31. Arvanitis ML, Jagelman DG, Fazio VW, Lavery IC, McGannon E. Mortality in patients with familial adenomatous polyposis. *Dis Colon Rectum* 1990; **33:** 639-642.
32. Offerhaus GJ, Giardiello FM, Krush AJ, *et al.* The risk of upper gastrointestinal cancer in familial adenomatous polyposis. *Gastroenterology* 1992; **102:** 1980-1982.
33. Bremner CG. Ano-rectal disease in the South African Bantu — III. Carcinoma of the rectum. *S Afr J Surg* 1965; **3:** 35-40.
34. McQuaide JR, Stewart AW. Familial polyposis of the colon in the Bantu. *S Afr Med J* 1972; **46:** 1241-1246.

Accepted 3 Aug 1993.

Dokter en digter

yin-yang

ek is 'n trassiemens
tegelyk vervulling wens
in die bloed
ek en jy
segment vir segment
bevrugte emosies

G. J. H. Sauermann