FAMILIAL ADENOMATOUS POLYPOSIS: THE OUTCOME AT AN ACADEMIC HOSPITAL IN THE ABSENCE OF A POLYPOSIS REGISTRY.

Paul Adrian Goldberg

MB. ChB. 1978 FCS(SA) 1988

A Dissertation in fulfillment of part three of the M.MED.SURG

Submitted to the University of Cape Town

- 1991 -

Contents

Acknowledgements:

I thank Doctor MV Madden for his tireless help and advice in performing this study.

I am appreciative of the assistance given by Sisters S Bailey and E du Toit with data collection and Doctors M Torrington and WH Raynham for their advice.

I thank the National Cancer Association for financial support and I am grateful to the following colleagues for their help: Professors DR de Villiers, DM Dent, KC Househam, EJ Immelman, JH Louw, AE Retief and J Terblanche, Doctors K Brice, PJ Cant, AH Girdwood, DJ de Villiers, MS Elliot, A Katz, J Klompje, SK Price, I Sacks and D Stein and Sister PJd'E Stevens.

Summary

This study presents a retrospective review of the outcome of familial adenomatous polyposis treated at an academic hospital, but in the absence of a formal Polyposis Registry.

Familial adenomatous polyposis is a disease which is inherited in an autosomal dominant pattern. It causes large bowel adenomas at a mean age of 16 years, symptoms at a mean of 24 years and death from large bowel cancer at, on average 42 years. Its easily recognisable mode of inheritance, and the possibility of preventing colon cancer by colectomy, have led to the early diagnosis of family members, to prophylactic surgery, and to the establishment of Polyposis Registries to facilitate this.

Introduction

The St Mark's Polyposis Registry was the first Polyposis Registry to be established. It originated from three families identified and studied by Lockhart-Mummery in 1925[1]. From then the St. Marks Polyposis Registry has grown to be the largest register of intestinal polyps in the world and more than 200 families were registered by 1975.[2]

Registries have been established in many countries including Denmark[3], Japan[4], The Netherlands[5], United Kingdom[2] and Western Australia[6]. It has generally been assumed that these Registries have been effective in reducing deaths from colorectal cancer in familial adenomatous polyposis. This question however has never been studied systematically.

In 1964 the first patient with familial adenomatous polyposis was identified at Groote Schuur Hospital and investigation of this family[7] became the subject of the first South African publication on this condition.

A polyposis registry is designed to identify family members of patients at risk of developing the disease and arrange their screening. In addition it ensures optimum follow up of patients proven to have familial adenomatous polyposis. Registries also provide most of the available data concerning familial adenomatous polyposis. It is likely, however, that the majority of patients world wide with familial adenomatous polyposis are managed without access to such a registry.

A registry is expensive. In order to justify its cost it must provide major benefits. The majority of patients who develop large bowel cancer in association with familial adenomatous polyposis do so at an age when they are economically active. The registry may justify its existence economically if it reduces the incidence of cancer of the large bowel at diagnosis and increases the longevity of these patients.

There is no polyposis registry in South Africa. The patients seen at Groote Schuur Hospital thus illustrate the course of the disease in patients who do not have access to a registry. Their outcome may perhaps merit comparison with that of patients managed through a registry, although no data which allow a valid comparison have been published to date. Hence this study does not try to answer the question of whether a Polyposis Registry is cost effective, but merely documents the outcome of the disease in our patients. This study is unusual in providing data on a relatively large number of cases treated in the absence of a formal registry.

Historical Review

The first report of multiple polyps of the colon is usually ascribed to Menzel[8] who in 1721 probably described inflammatory polyposis. Adenomatous polyposis may have been recorded by Corvisart[9] in 1847 and 12 years later Chargelaigue[10] probably gave the first account of the disease in a 16 year old girl and a 21 year old man. Woodward[11] differentiated adenomatous polyps which he called primary from inflammatory or secondary polyps. The development of microscopy and with it histology allowed the differentiation of polyps and the separation of hyperplastic and neoplastic from inflammatory ones. Cripps[12] first recorded the familial nature of adenomatous polyps in a brother and a sister. By 1900 the familial nature was well established.[13-15] The association between cancer and familial polyps was probably mentioned first by Handford[16].

With the passage of time, familial polyps have become increasing defined. Peutz[17] in 1921 and Jeghers[18] in 1949 separated hamartomatous polyps from the familial adenomatous grouping. Though early reports of this condition associated it with a high incidence of cancer, it was later shown that this was not correct and was probably due to mistaken interpretation of the pathology.[19-21]

In 1966 Veale[22] recognised that adenomatous polyps rarely occurred in patients under 10 years. The condition of multiple juvenile polyps (mucous retention polyps) was identified. This stressed the importance of histological confirmation in all cases of polyposis.

Existing registries

The first Registry to be established was that at St Mark's hospital in 1925 around three families reported by JP Lockhart-Mummery[1]. All forms of polyposis of the gastrointestinal tract were included.[2] This registry remains a loco-regional one and is not a national registry but by 1989 it maintained records of nearly 1000 patients.[23] It is estimated that this registry contains information on only between one tenth to one third of all British polyposis families.[2]

A number of other local registries exist within the United Kingdom[23] and Australia.[6]

National registries have been completed in Denmark[3] and Sweden[24] and are being developed in Norway and Japan. The Danish register is probably complete as between 1977 and 1979 only two new families were identified and between 1979 and 1984 there were no new families diagnosed.[3]

Pathological abnormalities in familial adenomatous polyposis

The condition was originally labeled familial polyposis coli because it was thought to be limited to the colon and rectum. It has however become evident that virtually all patients develop upper gastrointestinal adenomas and the generally accepted name for the condition has thus changed to familial adenomatous polyposis. In the early 1950's Gardner and his colleagues described a condition associated with familial adenomatous polyposis involving all three germ layers.[25-28] Some lesions are associated with morbidity and mortality while others are markers of patients who have yet to express the phenotype.[29]

A) Abnormalities of endodermal origin

1. Colorectal polyps

Though the mean age of development of polyps is 16 years[30] the range is at least from eighteen months to 34 years of age. Affected individuals usually have at least 1000 adenomas but this may depend on the age of the patient at the time of removal of the colon. There are reports of rectal sparing and sigmoidoscopic examination alone will miss these individuals.[31]

2. Gastric polyps

Fundic polyps are usually mucous retention hamartomas with little malignant potential.[32] 10% of patients have gastric adenomas[33] and a few cases of gastric carcinoma have been reported.[34-36]

3. Duodenal / periampullary polyps

Duodenal polyps may be found in up to 94% of patients with familial adenomatous polyposis.[37] They are most numerous in the second and third parts of the duodenum especially in the periampullary region. Duodenal and periampullary carcinoma appears to be more common than originally thought, and may be the

most common cause of death in patients who survive colorectal malignancy.[38,39] Bile may be a co-carcinogen in this condition.[40]

4. Small bowel polyps

Adenomas may occur both in the jejunum and ileum. The risk of malignancy appears small.[41,42]

5. Gall bladder, Bile duct, pancreas and pancreatic duct

There appears to be an increased frequency of hepato-billary and pancreatic adenomas and carcinomas.[43,44]

6. Thyroid carcinoma

Females under 35 years have a 160X greater incidence of papillary carcinoma if they have familial adenomatous polyposis.[45]

7. Other endocrine tumours

Adrenal carcinomas, multiple endocrine neoplasia type 2b, pituitary adenomas and pancreatic islet tumours have all been reported.[46-50]

B) Abnormalities mesoderm origin

1. Skeletal abnormalities

Occult osteomata may occur in up to 90% of patients with familial adenomatous polyposis.[51]

2. Dental Abnormalities

These form part of the original description of Gardner's syndrome [26,27] and include early caries with tooth loss, supernumerary teeth, odontomas, dentigerous cysts and impacted permanent teeth.

3. Hepatoblastoma

There is a higher than expected incidence of hepatoblastomas in the offspring of patients with familial adenomatous polyposis.[52]

4. Desmoids

Two types of desmoids occur in about 10% of familial adenomatous polyposis patients.[2] The intra-abdominal type are either mesenteric of retroperitoneal vascular tumours, whereas the muscular-aponeurotic type are more fibrotic and tend to occur in scars. Growth rate is variable and may possibly be stimulated by pregnancy or surgery.[53] The intra-abdominal variety is difficult to remove totally, has a high recurrence rate and may bleed uncontrollably during surgery.[54] There appears to be a high incidence of post operative intestinal obstruction which may be related to a disorder of fibrous tissue formation.[55]

C) Abnormalities of ectodermal origin

1. Cutaneous lesions

Epidermoid and sebaceous cysts form part of the original description by Gardner.[25-27]

2. Central nervous system tumours

Astrocytoma and medulloblastoma occur in Turcot's syndrome[56]

3. Congenital hypertrophy of the retinal pigment epithelium.(CHRPE)

These discrete pigmented lesions are multiple and bilateral in patients with familial adenomatous polyposis but they may be absent. They serve as a marker of the gene when present.(see below)

The present study

Method

Between 1964 and 1974, at Groote Schuur Hospital, a social worker and a part-time consultant surgeon followed up patients with familial adenomatous polyposis and screened their families. This service lapsed between 1974 and 1988, when a systematic screening service was again instituted. In January 1988, a research nurse was employed to trace all patients with familial adenomatous polyposis treated at Groote Schuur Hospital to establish their outcome.

During 1988 the hospital records were searched for all patients who had been seen at Groote Schuur Hospital and a diagnosis of familial adenomatous polyposis made. These records were reviewed as were those of the Department of Pathology. The private records of a number of surgeons were compared with the list of names obtained from the above sources. Additional patient names were identified from the raw data collected for the article by Aitken et al.[57]

Once the names of all patients treated at Groote Schuur Hospital had been collected their hospital folders were searched and the information about the course of the disease in the individual patients collected on a pro-forma (appendix).

The genealogical records of Dr Marie Torrington (the social worker mentioned above) who had traced patients at Groote Schuur Hospital from 1964 to 1974, of the Medical Research Council were reviewed to identify family members of patients seen at Groote Schuur Hospital who were at risk of developing the disease. Attempts were made to trace these family members. Those that could be contacted were called up for screening.

Familial adenomatous polyposis was diagnosed if several adenomas were proven in patients with more than 100 polyps in the large bowel. More than one polyp was always biopsied for proof of adenoma.

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 using Wilcoxon's signed rank test.

Results

During the 26 years 70 patients with familial adenomatous polyposis were seen. The number of patients diagnosed per year is demonstrated graphically in figure I, with the age at diagnosis in figure II. Figure III shows the race and sex distribution.

Symptoms vs stage of disease

Two patients had no family history of familial adenomatous polyposis and in seven the family history was unknown. The remaining 61 patients were from 8 families (Figure IV). In patients for whom information on symptoms at presentation was available, half were symptomatic, had a higher prevalence of large bowel cancer at diagnosis and were on average 10 years older than the asymptomatic patients (Table I).

Operations: Short-term results

In all, 99 operations were performed in 67 patients (1.5 operations/patient) (Figure V). A further three patients have refused both surgical management and follow up, of whom two are lost, while another died 6 years after diagnosis aged 55 years of colon cancer. The most common operation performed to prevent large bowel cancer was a colectomy and ileo-rectal anastomosis in 58 patients, one of whom had a prior colostomy for an obstructing carcinoma of the descending colon. Of these patients 15 (26%) have subsequently had at least one other operation for familial adenomatous polyposis, excluding fulguration of rectal polyps, during a median follow up of 10 years. Two of these patients and two unoperated cases underwent ileo-anal pouch procedures. Table II contrasts the complications which followed colectomy and ileo-rectal anastomosis and ileo-anal pouch procedures. Two of 58 patients (3%) have undergone revision of colectomy and ileo-rectal anastomosis to proctocolectomy with ileostomy, 1 for rectal cancer after 12 years and the other for multiple large polyps with severe dysplasia 10 years after colectomy and ileo-rectal

anastomosis. Two of four patients have had their ileal pouch removed for incontinence for which no organic cause could be found.

Long-term results

Histological material from the first operation could be reviewed in the 59 of the 67 operated patients. Fifty-one had adenomas. The remaining eight (16%) had cancer and the stage at diagnosis was Dukes A in two, C in four and two had residual intra abdominal disease at operation with an overall 5 year survival of 50%.(Table VI) Reliable data on examination of the retained rectum after colectomy and ileo-rectal anastomosis was available for 22 patients. Only nine (40%) had undergone sigmoidoscopy at least once a year. Figure VII shows the incidence of carcinoma of the rectal remnant after colectomy and ileo-rectal anastomosis. The duration of follow up of all 70 patients is shown in figure VIII. Nine have been lost to follow up after 1, 1, 10, 10, 10, 12, 21, 23 and 24 years (mean 11 years), while of the remainder 14 have died. The cause of death is unknown in five patients and one died of ischaemic heart disease. The remaining eight patients (57%) died as a result of familial adenomatous polyposis: six of carcinoma of the large bowel (present at diagnosis in five), one patient of cancer of the duodenum and another of a desmoid causing perforation of the small bowel. In 18 patients, gastroscopy with an end-viewing instrument identified adenomatous polyps in four, of whom one had an antrectomy. Five patients have had retention polyps. No duodenal polyps were found.

Since a systematic screening programme was resumed in 1988 the median age at diagnosis has fallen, and the number of new cases identified annually has risen as has the proportion without symptoms or cancer (Table III).

The outcome of all 70 patients is summarised in table IV.

Table I: Symptoms at presentation vs age

	Number	Mean age (years)	Large bowel cancer at diagnosis
Symptomatic	30	34	7
Asymptomatic	30	24	1
Unknown	10	24	0
Total	70		

p = 0.0005 age, symptomatic vs asymptomatic.
p = 0.02 age, symptomatic vs unknown.
p = 0.04 proportion with cancer at diagnosis.

Table II: Complications after total colectomy and ileo-rectal anastomosis (n = 58) and ileal pouch (n = 4)

Complication	IRA	Pouch
Anastomotic leak (no stoma)	1	
Wound dehiscence	1	
Wound infection	4	
Small bowel obstruction (within 30 days)	4	
Death	0	0
Deep vein thrombosis		1
Intra-abdominal sepsis		1
Eventual permanent ileostomy*	2	2

*p = 0.02

Table III

	Screening Programme		
	Before (1964-87)	After (1988-89)	p
Total diagnosed	60	10	
Diagnosed per annum	2.3	5	<0.006
Age at diagnosis (years, median)	29	21	<0.01
Without symptoms	31 (52%)	9 (90%)	<0.001
Cancer at diagnosis	8 (13%)	0	n.s.

Table IV: Outcome in 70 patients with familial adenomatous polyposis.

a) Refused surgery			3
died, large bowel cancer	1		
lost after 0.5 yrs (age 39) & 24 yrs (age 78)	2		
b) Total colectomy and ileo-rectal 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		
c) Other operations			9
died, large bowel cancer	3		
died, unknown cause	3		
well	3		

Figure I: Number of patients diagnosed per year

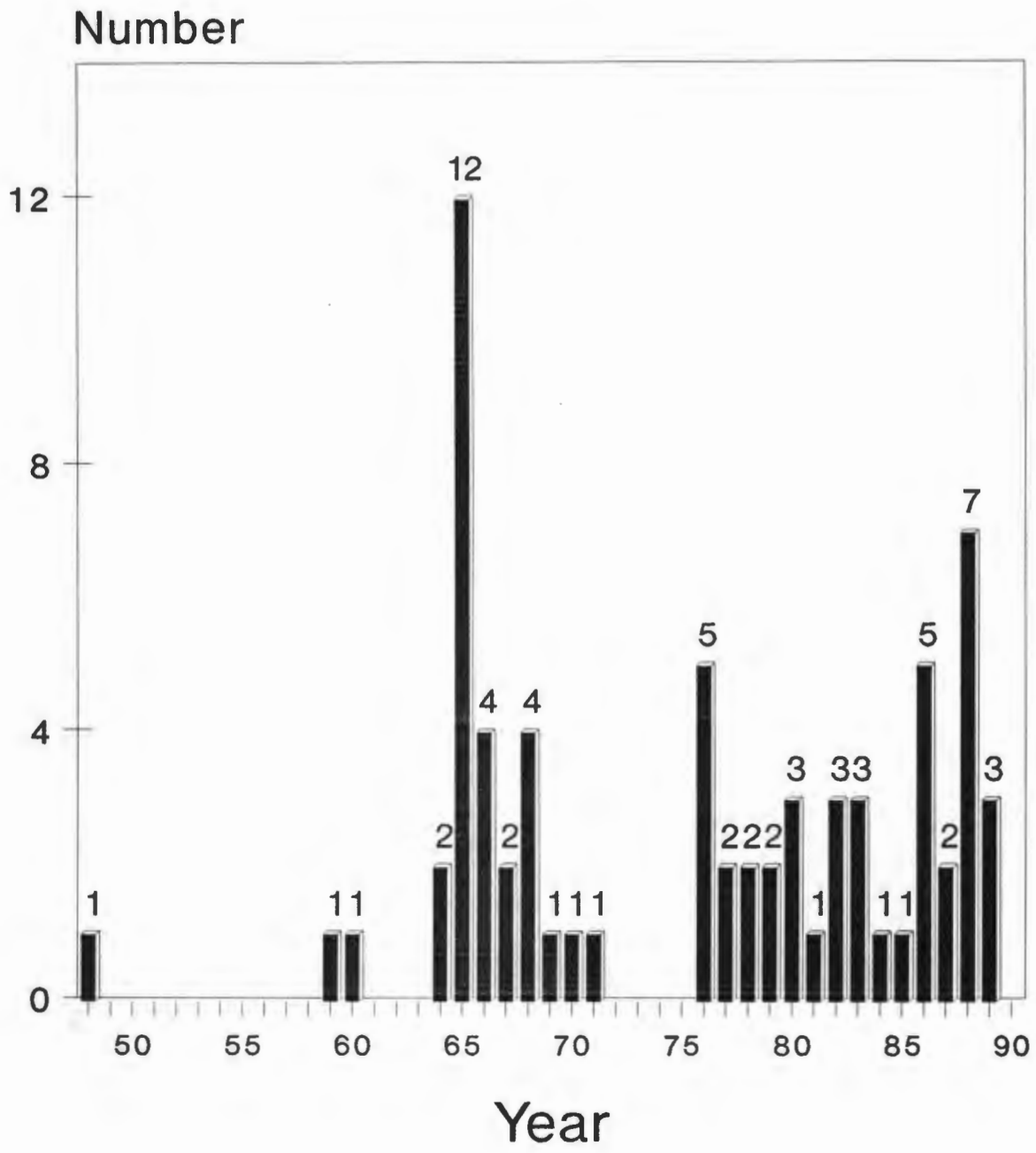


Figure II: Age at diagnosis

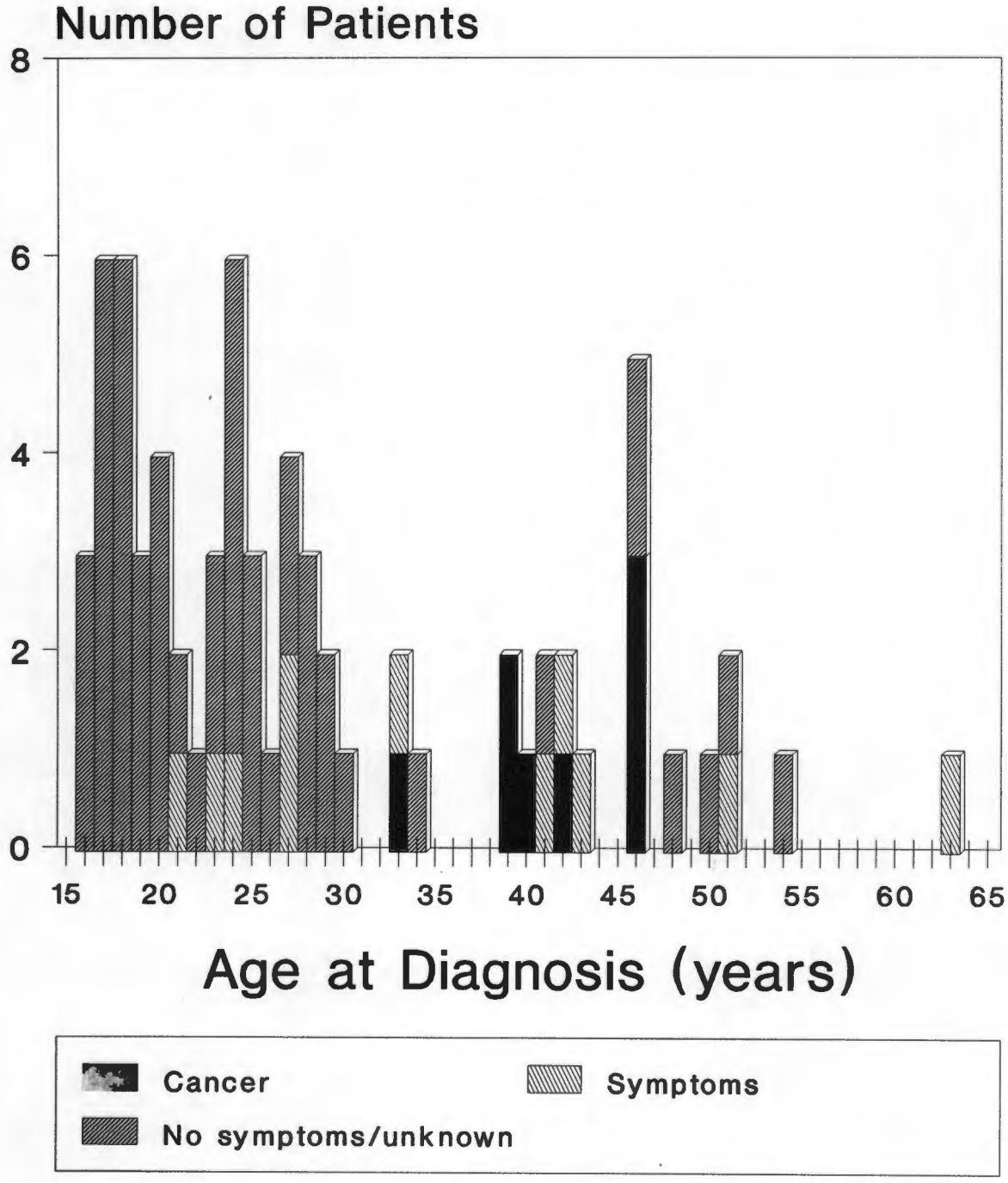
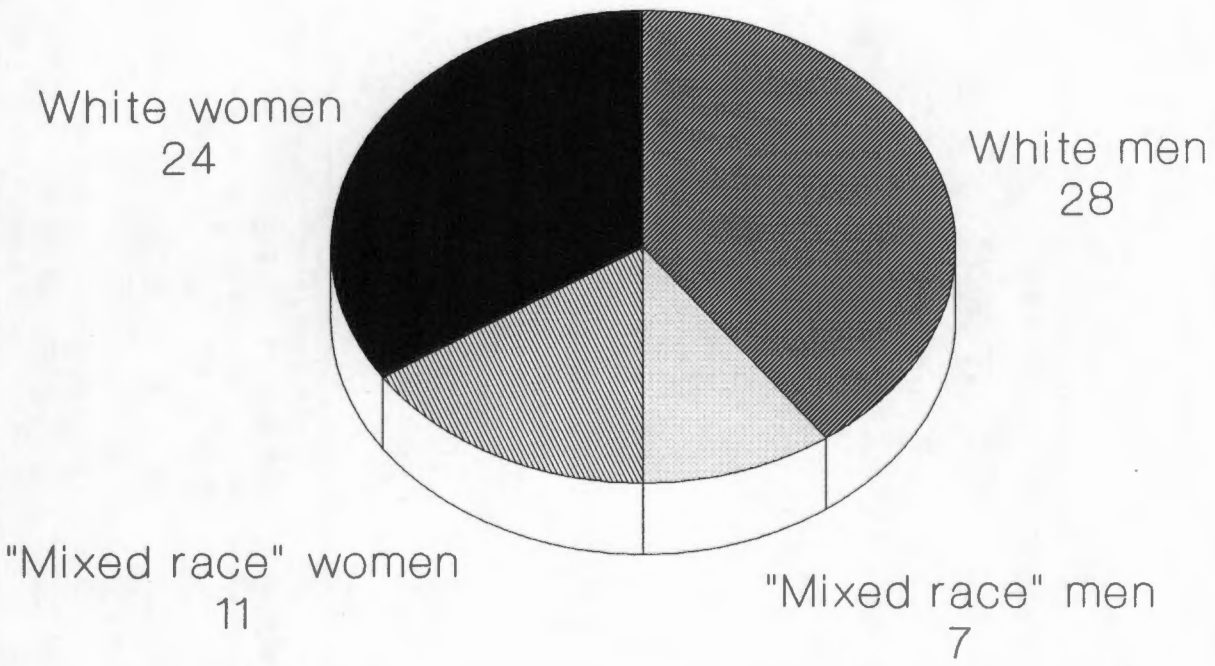


Figure III: Race and Sex distribution



Blacks = 0

Figure IV: Number of affected members in each family

Family history unknown - 2
No family history - 7

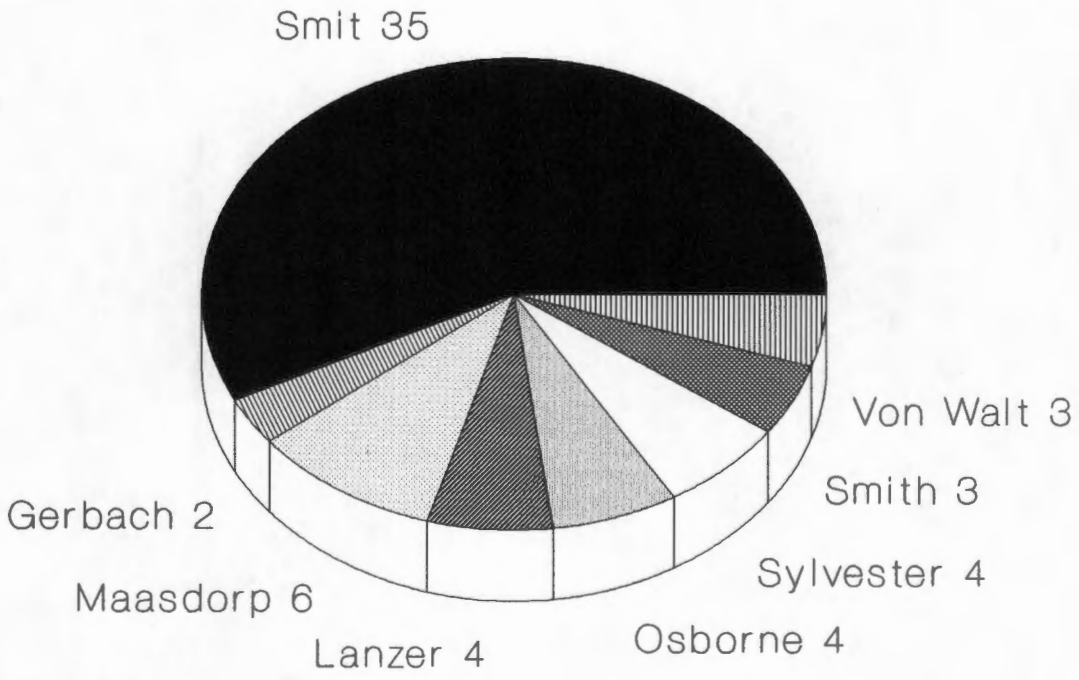


Figure V: Operations performed on all patients.

Numbers indicate patients who underwent each operation. Numbers in parenthesis indicate total operations, where a patient had more than one operation of the same type.

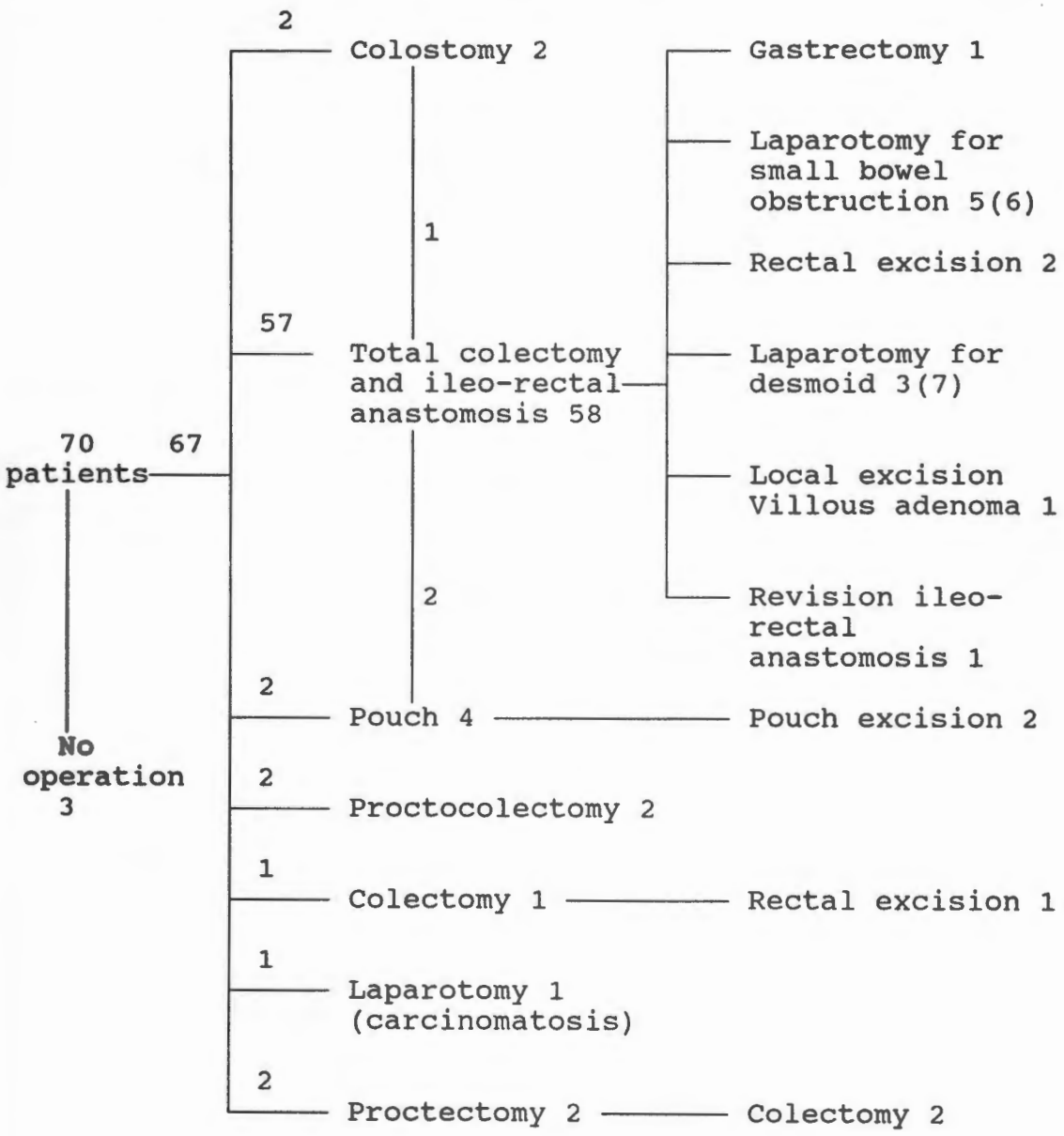


Figure VI: Survival if large bowel cancer present at diagnosis

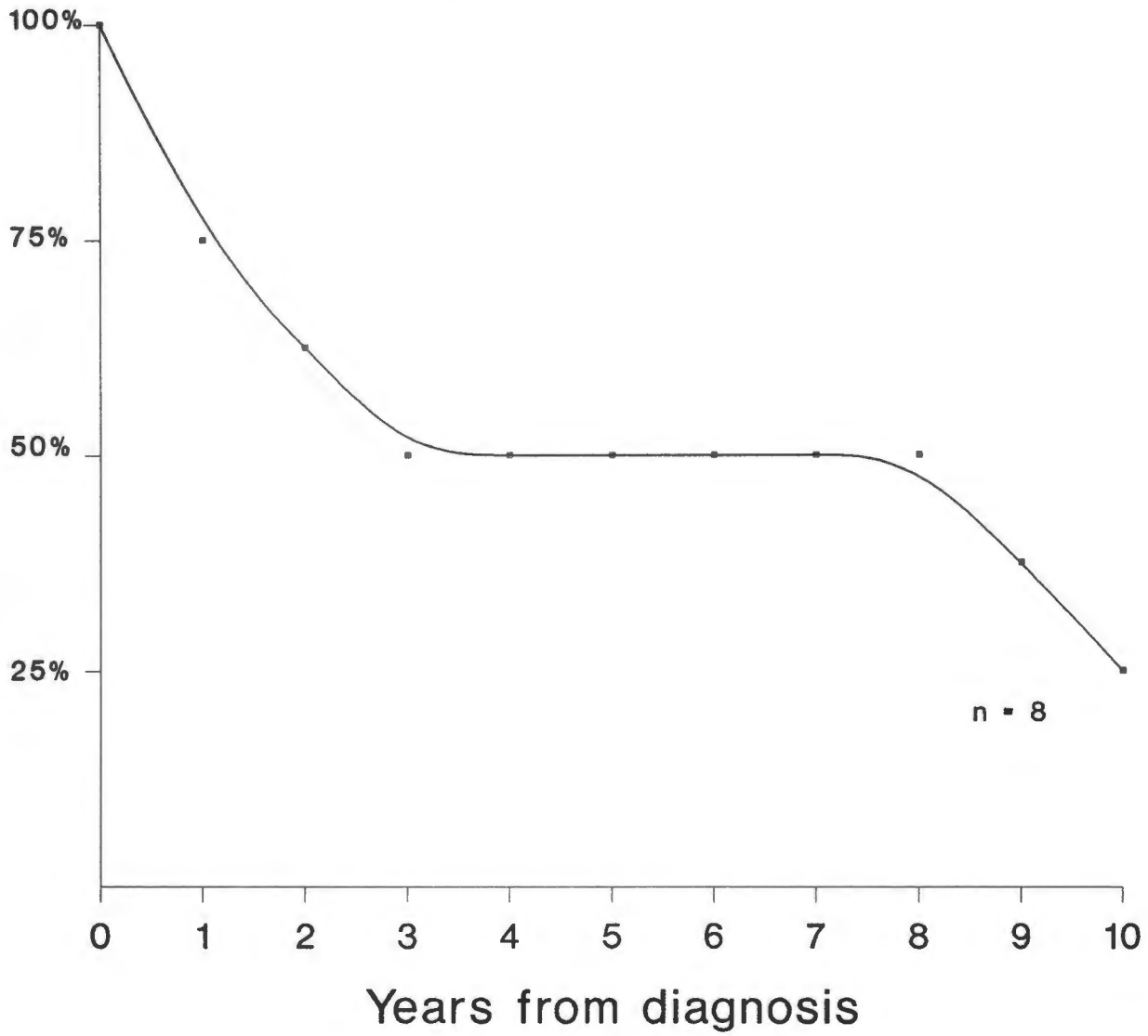


Figure VII: The incidence of cancer of the rectal remnant after ileo-rectal anastomosis (with 95% confidence limits)

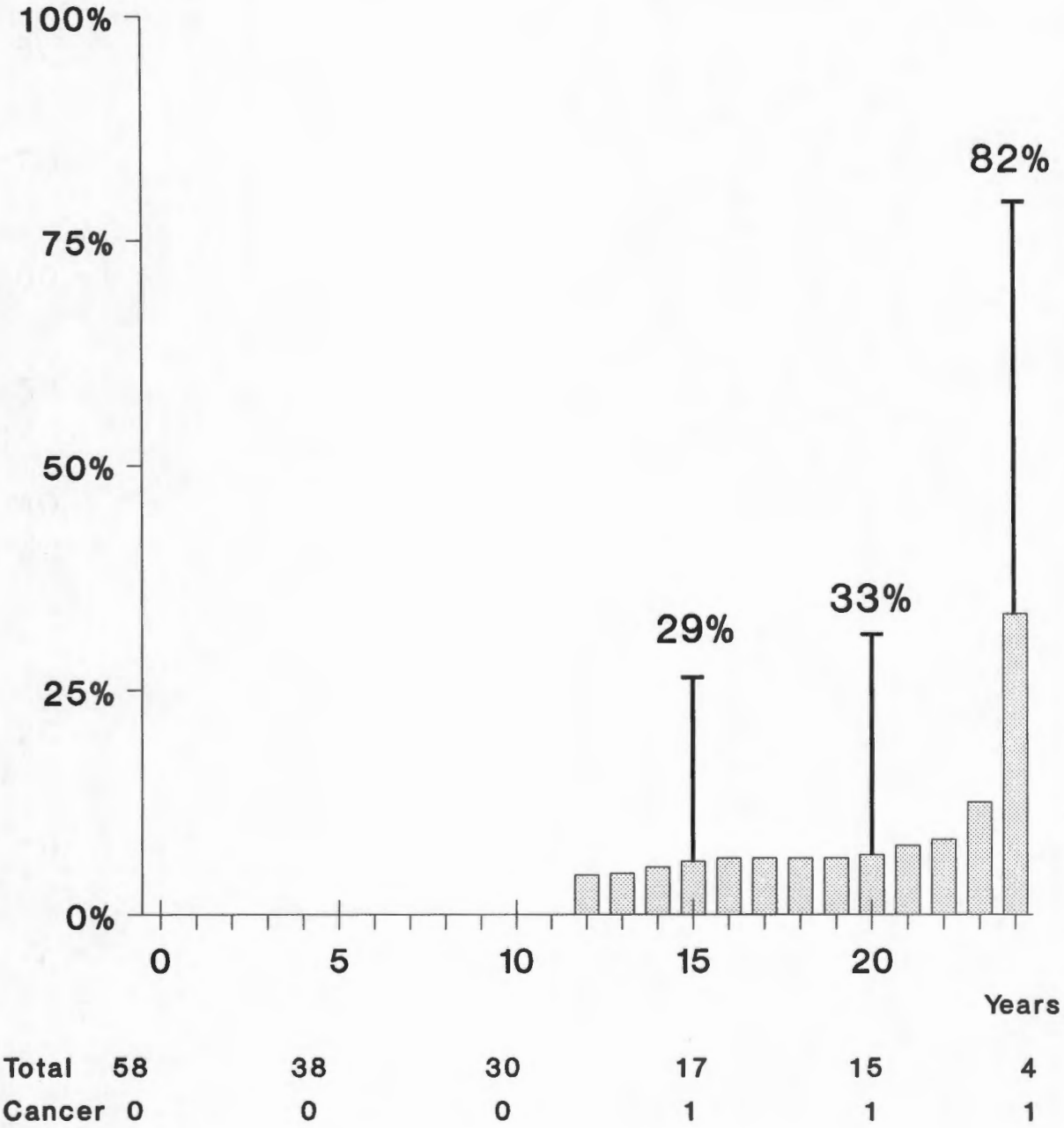
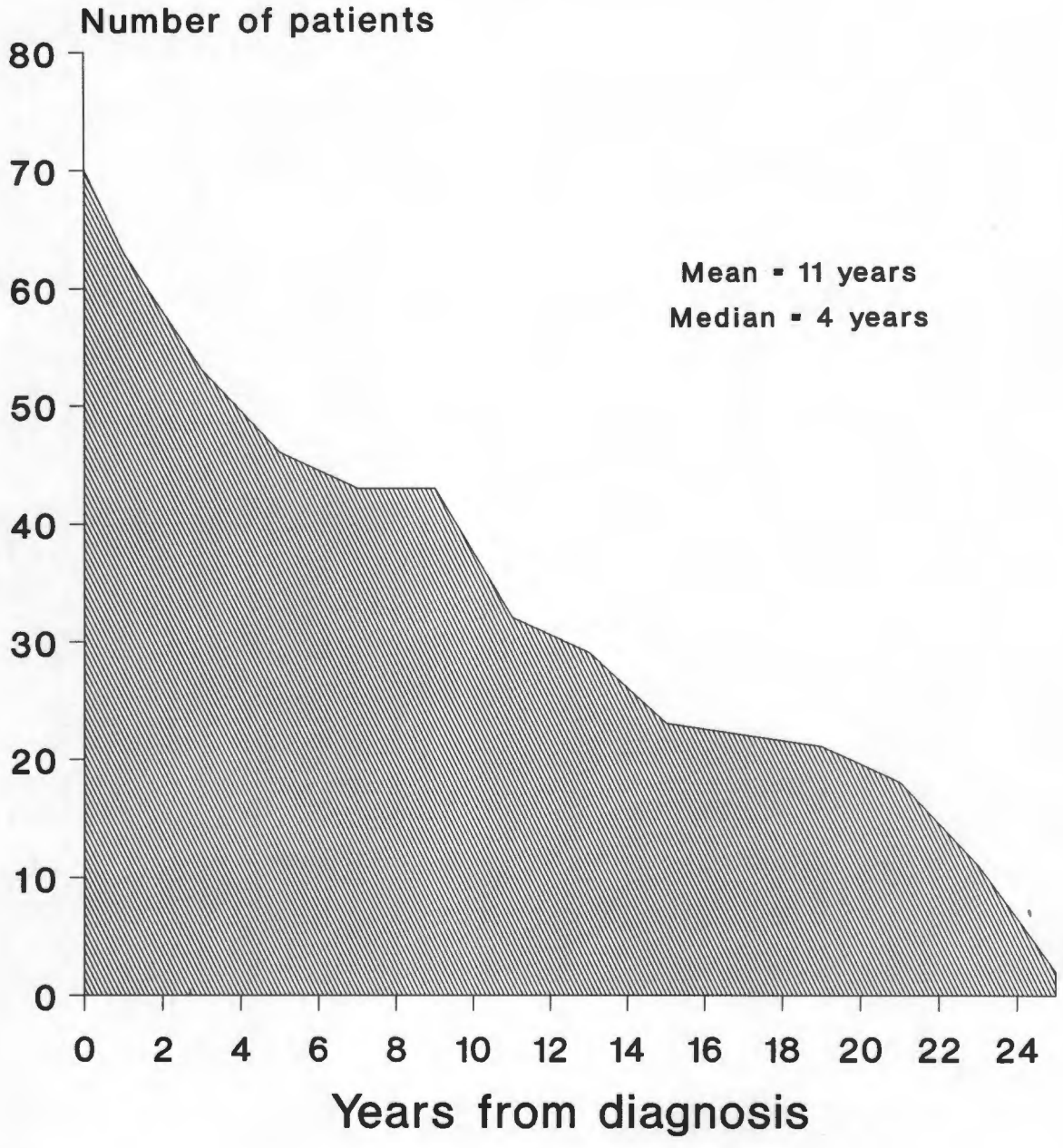


Figure VIII: Duration of follow up of all patients.



Discussion

Families affected

Although familial adenomatous polyposis has been reported in South African blacks[58,59] none have been diagnosed at our hospital. One reason may be the founder effect causing a high incidence in white immigrants, as the first affected individual in one of our families arrived from Holland about 1685.[60] Another reason is that until recently the hospital has served a population of predominantly mixed or Caucasian descent.

Implications of a Registry

That familial adenomatous polyposis should be treated before symptoms appear if large bowel cancer is to be prevented is shown by the significantly higher incidence of cancer in our patients with symptoms at diagnosis (23% with symptoms vs 3% without). Cases identified through the screening programme were younger, while almost all were asymptomatic and none had cancer in comparison with a cancer incidence of 13% in cases diagnosed earlier in the study (Table III). These data suggest that if a Polyposis Registry ensured efficient screening its cost might be justified by a reduction in large bowel cancer when familial adenomatous polyposis was diagnosed. However, calculating the likely cost of establishing and running a registry is beyond the scope of this study, as is the calculation of cost-saving which might flow from its operation. While the increase in detection of asymptomatic individuals and the decrease in the incidence of cancer at diagnosis is to be expected with the introduction of systematic screening, this has not previously been shown as there is no literature comparing patients diagnosed prior to and after the introduction of systematic screening. The success of family-based registry assisted surveillance could previously be inferred by the decrease in aggregate incidence of colorectal cancer in called up cases.[61] The longer a registry was been existence the lower the

incidence of cancer at diagnosis within that registry as fewer and fewer patients are probands and more and more are called up asymptomatic patients.

Current role of a Registry

The Registry has two main tasks, firstly, detection of asymptomatic carriers of the familial adenomatous polyposis gene and secondly the follow-up of patients who have a retained rectum.

Management of a family starts with the identification of a patient with more than 100 adenomatous polyps[2]. A complete family history is obtained and a family tree drawn up. The at-risk siblings, parents and offspring are identified. A number of questions in management however arise:

The St Mark's Registry initiates screening by sigmoidoscopy at 14 years[2] as the procedure may be less frightening at this age.[23] Some American and European centers however begin screening at 10 years in order not to miss the occasional early malignancy.[3,62]

Bussey recommends screening should be at intervals of 2 to 3 years by sigmoidoscopy alone[2] and this recommended by both the Danish and Dutch Registries.[3,5] This may however not be adequate as colon cancer has been reported in the absence of rectal polyps[63-66].

The age at which screening should be discontinued is difficult to determine. The risk of development of polyposis decreases rapidly with increasing age.[2] The Danish Registry recommends surveillance until age 40 in the usual patient but increased to age 45 or 50 in those families that have a history of late development of polyps.[3] A study of data from St Mark's and the Western Australia Registries[67] allowed calculation of the cumulative risk of developing adenomas with increasing

age. The presence or absence of CHRPE and linked markers can be added to this age specific risk.[23]

Once the disease is detected in asymptomatic individuals, the only method of prevention of large bowel cancer is prophylactic proctocolectomy. This would result in a permanent ileostomy which is unacceptable to young, well, asymptomatic patients necessitating either reconstruction with an ileal pouch or retention of the rectum and ileorectal anastomosis. This latter option is a simpler procedure than the former and can be performed by any general surgeon. It does however leave residual rectal mucosa with the possibility of later malignant change. The registry thus must ensure adequate follow up of patients who have a retained rectum by outpatient sigmoidoscopy at six to 12 monthly intervals.[68,69]

New developments in screening

Rigid sigmoidoscopic surveillance requires that all offspring of an affected family member require examination every second year from age 10 to 14 to at least 40 years old. Half will never manifest the disease but will be screened on at least 13 occasions over 26 years. At each screening session, there is a high level of patient anxiety as to the result of the screening test. Compliance over this period of time is difficult to ensure and repeated examinations become expensive.

Examination of the optic fundi for congenital hypertrophy of the retinal pigment epithelium (CHRPE) was first reported quite recently.[70] Chapman[71] found that between 2 and 40 areas of CHRPE occurred in all 40 gene carries studied while none of 35 controls had more than 2 areas. It appears that the lesions are present at birth and there may be complete consistency within families.[72] The presence of CHRPE thus strongly suggests that the individual carries the familial adenomatous polyposis gene. This ophthalmological examination requires only the mild inconvenience of pupillary dilatation during examination by an ophthalmologist. It

remains to be seen whether it is safe to not follow up family members who do not have CHRPE of families where affected members have CHRPE.

Another recent addition to the armamentarium of the Registry is use of linked DNA markers which are becoming progressively more numerous. Recently markers have been found closer and closer to the familial adenomatous polyposis gene[73] since it was first shown to be located on the long arm of chromosome 5.[74] The recent discovery of a marker lying within rather than near the gene[75,76] should make other forms of screening obsolete. Screening for this gene at birth by a single blood test will eliminate the need for followup of unaffected family members. This should improve the acceptability of screening, as only those shown to carry the gene will ever need sigmoidoscopy, ideally performed in their early teens to identify the minority with large polyps in whom early colectomy should be considered. The remaining gene carriers will be able to choose a socially convenient time for their colectomy, usually in their late teens. This holds out the possibility of reducing the present biennial sigmoidoscopic examinations recommended[2,3,5] in all at-risk individuals to one in the early teens and another immediately before colectomy, only in gene carriers. This will greatly reduce the work load and running costs of a Registry as well as the work of surgeons caring for affected families while the role of the clinical and molecular geneticist will expand considerably. The essential work of a Registry will involve ensuring perinatal testing of offspring of affected family members, the later sigmoidoscopic examinations of gene carriers, their eventual surgery and life-long postoperative follow-up. The relatively short professional lifespan of individual doctors makes it almost impossible for them to ensure this personally, particularly now that perinatal diagnosis is a real possibility, so the role of registries will become even more important.

As it is possible to identify the gene from a blood sample immediately after birth, it should soon be possible to identify the gene by amniocentesis in early pregnancy. The difficult ethical issue of therapeutic abortion will need to be addressed.

Outcome

While 58 patients underwent colectomy and ileo-rectal anastomosis, only four (6%) had an ileo-anal pouch formed. The increased short-term morbidity associated with the latter operation is not surprising. However the poor functional results (2/4 permanent stomas) are at variance with the outcome reported after ileo-anal pouch operations elsewhere[77-79]. Our two patients who preferred a stoma had undergone the ileo-anal operation because they appeared unlikely to allow regular follow-up examinations. In retrospect both were probably temperamentally unsuited to the procedure. The ileo-anal pouch is considered to be the operation of choice to prevent large bowel cancer by a minority of surgeons. Most favour colectomy and ileo-rectal anastomosis[78,79]. The major objection to ileo-rectal anastomosis is the risk of cancer in the retained rectum, which rises steadily with time and appears to reach 8-32%[80-83] at 20 years after the operation.

However, after 20 years only one of 15 patients (7%) in this study developed rectal cancer. This would not justify a change from colectomy and ileo-rectal anastomosis as the standard procedure. It is also relevant that rectal polyps usually regress soon after colectomy and ileo-rectal anastomosis[84] and this may partly explain why rectal cancer was so uncommon in our patients despite erratic follow-up.

Foregut Lesions

Foregut cancer is likely to become a major cause of death in patients who have undergone surgery to prevent colorectal cancer[85]. However, only one of our patients died of duodenal cancer. This was diagnosed by duodenoscopy in the presence of liver metastases and had been missed with an end-viewing instrument

six months previously. Furthermore, the apparent absence of duodenal adenomas in our patients illustrates that an end-viewing instrument is probably inadequate for examination of the foregut in familial adenomatous polyposis. A study of 102 cases using a side-viewing duodenoscope to take systematic biopsies and photographs identified duodenal adenomas in 94/102 (94%) and gastric adenomas in 6/73 (8%)[86]. However, patients with confluent foregut adenomas or severe dysplasia present a difficult management problem. A prophylactic pancreaticoduodenectomy carries excessive morbidity while endoscopic destruction of adenomas is unlikely to prove adequate.

Conclusions

Systematic screening increases the proportion of patients who are asymptomatic and decreases the mean age at the time of diagnosis. It should therefore reduce the frequency of large bowel cancer.

Total colectomy and ileo-rectal anastomosis has proved to be a safe prophylactic operation in the short-term, with a low long-term incidence of rectal cancer.

Because of the limited number of ileo-anal pouch operations performed, data are too sparse to allow firm conclusions. This is particularly so because these operations were performed early in the local experience. Others have found an increase in the short-term morbidity, but the long-term function appears to be similar to that following total colectomy and ileo-rectal anastomosis.

Calculations of the likely costs and benefits of a registry are probably worth pursuing.

New developments in genetic techniques will allow identification of at-risk individuals at birth thus reducing the need for sigmoidoscopic screening and improving patient compliance. A Registry will be essential in ensuring that at-risk infants are screened and that if the gene is present they are optimally followed up.

When prenatal diagnosis by amniocentesis becomes a reality, the difficult ethical issue of therapeutic abortion will need to be addressed.

Appendix

AUDIT OF GSH FAMILIAL ADENOMATOUS POLYPOSIS EXPERIENCE
FAPFORM.DOC

SURNAME **DOB** / / **MAIDEN NAME**
mo/day/yr
FIRSTNAME **R/S** 1 2 3 4 5 6 7 8

HOSPNO Always code "unknown" as 9

FAMILY OF ORIGIN **GENERATION** I II III IV V VI

SIB NO 1 2 3 4 5 6 7 8 9 10 11 12 **CODER:** **DATE:** / /

PRESENTATION **1** propositus **2** called up, asymptomatic

3 called up, symptomatic **4** presented, asymptomatic

FIRST SEEN DATE / / **FIRST SIG DATE** / /
mo/day/yr
FIRST DIAG DATE / / **LAST SIG DATE** / /

LAST SIG RESULT **1** polyp(s) **2** ca **3** normal

9 unknown **ANAST HT ON RIGID SIG (cm):**

LAST KNOWN ALIVE DATE \ \

OP1 DATE \ \ **1** ileorectal **2** panproctocolectomy

3 pouch **4** subtot colect **5** other **9** unknown **0** no op

OP1STAY days **OP1 COMP** **1** died **2** anasleak **3** wnd inf

4 SB obst **5** abdom abs **6** bleed **7** other **9** no inf **0** nil

OP2 DATE \ \ **1** ileorectal **2** panproctocolect

3 pouch **4** subtot colect **5** other **9** unknown **0** no op

OP2STAY days **OP2 COMP** **1** died **2** anasleak **3** wnd inf

4 SB obst **5** abdom abs **6** bleed **7** other **9** no inf **0** nil

OP3 DATE \ \ **1** ileorectal **2** panproctocolect

3 pouch **4** subtot colect **5** other **9** unknown **0** no op

OP3STAY days **OP3 COMP** **1** died **2** anasleak **3** wnd inf

4 SB obst **5** abdom abs **6** bleed **7** other **9** no inf **0** nil

OP COMMENT **TOTAL OPS FOR FAP:**
(excl fulguration)

HISTO 1 adnmtous polyps 2 Ca "A" 3 Ca "B" 4 Ca "C"

5 Ca "D" 8 no polyps 9 no info **PATH NO:**

GARDNER'S SYN 1 yes 2 no 8 uncertain 9 no info

COMMENT

F-UP BY 1 GSH 2 MSE 3 WHR 5 other pvt

6 other hosp 9 no info 0 lost

SIG AT LEAST YRLY POSTOP 1 yes 2 no 3 no info

F-UP STATUS 1 A,W,f-up OK 2 A,W,not f-up 3 D,ca colon

4 A+ca colon 7 lost 8 D of other cause

DATE CA DIAGNOSED \ \ **DATE DIED** \ \

FAP DIAGNOSIS 1 proven 2 >40, no polyps 3 uncertain

GASTROSCOPY 1 adnmtous polyp 2 other polyp

3 both types polyp 4 no polyp 5 other 8 not scoped

GENERAL COMMENTS

ON COMPUTER Y N

REFERENCES:

1. Lockhart-Mummery JP. Cancer and Heredity. Lancet 1925; 1:427-429.

2. Bussey HJR. Familial polyposis coli family studies, histopathology, differential diagnosis and results of treatment. Baltimore: Johns Hopkins University Press (1975)

3. Bülow S. The Danish Polyposis Register. Description of the methods of detection and evaluation of completeness. Dis Colon Rectum 1984; 27: 351-355.

4. Utsunomiya J, Iwama T: Adenomatous coli in Japan. In: Winawer S, Schottenfeld D, Sherlock P eds. Colorectal cancer: prevention, epidemiology and screening. New York: Raven Press. 1980: 83-95.

5. Vasen HFA, Griffioen G, Offerhaus GJA, Den Hartog Jager FCA, Van Leeuwen-Cornelisse ISJ, Meera Khan P, Lamers CBHW, Van Slooten EA: 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.

6. Bower C, Levitt S, Francis S: The Western Australian Familial Polyposis Registry. Med J Aust 1989; 151: 557-560.

7. Raynham WH, Louw JH. Familial polyposis of the colon. S Afr Med J 1966; 40: 857-865.

8. Menzel, D. Acta Medicorum Berlinensium 9 (1721):78. Quoted by Hewitt and Howard (1915) as quoted in Bussey 1975[2].

9. Corvisart L. Hypertrophie partielle de la muqueuse intestinale. Bull. Soc. Anat. 1847; 22: 400 as quoted in Bussey 1975[2].

10. Chargelaigue, A. "Des polipes du rectum." Thesis, Paris, 1859 as quoted in Bussey 1975[2].

11. Woodward JJ. Pseudo-polypi of the colon: an anomalous result of follicular ulceration. Amer.J.med.Sci.1881; 81: 142. as quoted in Bussey 1975[2]

12. Cripps WH. Two cases of disseminated polypus of the rectum. Trans.path.Soc.Lond.1882; 33: 165-168 as quoted in Bussey 1975[2].

13. Bickersteth RA. Multiple polypi of the rectum occurring in a mother and child. St.Bartholomew's Hosp.Rep. 1890; 26: 299 as quoted in Bussey 1975[2].

14. Niemack J. Intestinal polyposis and carcinoma. Ann.Surg. 1902; 36: 104 as quoted in Bussey 1975[2].

15. Zahlmann S. Polyposis intestini crassi. Hospitals Tidende 1903; 11: 1267-74 quoted in Bussey 1975[2].

16. Handford H. Disseminated polypi of the large intestine becoming malignant. Trans.path Soc.Lond. 1890; 41: 133 quoted in Bussey 1975[2].

17. Peutz JLA. Over een zeer merkwaardige gekombineerde familiaire polyposis van de slijmvliezen van dem tractus intestinalis met die van de neuskeelholte en gepaard met eigenaardige pigmentaties van huid en slijmvliezen. Nederl maandschr. voor Geneesk 1921; 10:134-146 as quoted in Northover[23].

18. Jeghers H, McKusick VA Katz KH. Generalised intestinal polyposis and melanin spots of the oral mucosa, lips and digits. New Engl.J.Med. 1949; 241: 993-1005.

19. Dormandy TL. Medical progress: Gastrointestinal polyposis with mucocutaneous pigmentation (Peutz-Jeghers syndrome). New Engl J Med 1957; 256:1093, 1141,1186

20. Bartholomew LG, Dahlin DC. Intestinal polyposis and mucocutaneous pigmentation (Peutz-Jeghers syndrome). Further comments and report of an additional case. Minnesota Med. 1958; 41: 848-852.

21. Rintala A. Histological appearance of gastrointestinal polyps in Peutz-Jeghers syndrome. Acta chir. scand. 1959; 117: 366-373.

22. Veale AMO, McColl I, Bussey HJR, Morson BC. Juvenile polyposis coli. J med Genet 1966; 3: 5-16.

23. Northover JMA, Murday V: Familial colorectal cancer and familial adenomatous polyposis. Baillière's Clinical Gastroenterology 1989; 3: 593-606

24. Alm T, Licznerski G: The intestinal polyposes: Clin Gastroenterol 1973; 2: 577-602

25. Gardner EJ. A genetic and clinical study of intestinal polyposis, a predisposing factor for carcinoma of the colon and rectum. Am J Hum Genet 1951; 3: 167-176.

26. Gardner EJ, Richards RL. Multiple cutaneos and subcutaneous lesions occurring simultaneously with hereditary polyposis and osteomatosis. Am J Hum Genet 1953; 5: 139-147.

27. Gardner EJ. Followup of a family group exhibiting dominant inheritance of a syndrome including intestinal polyps, osteomas, fibromas and epidermal cysts. Am J Hum Genet 1962; 14: 376-390.

28. Parks TG, Bussey HJR, Lockhart-Mummary HE. Familial polyposis coli associated with extracolonic abnormalities. Gut 1970; 11: 323-329.

29. Shepherd NA, Bussey HJR. Polyposis syndromes: An update in Gastrointestinal pathology. Current topics in Pathology. Williams GT (ed) 1990; 323-346. Springer-Verlag.

30. Bülow S. Familial polyposis coli. A clinical and epidemiological study. Denmark, 1986 Laegeforeningens Forlag as quoted in Bülow S. 1987.[33]

31. Bess MA, Adson MH, Elveback LR, Moertel CG: Rectal cancer following colectomy for polyposis. Arch Surg 1980; 115: 460.

32. Eidt S, Stolte M. Gastric glandular cysts:- Investigations into their genesis and relationship to colorectal epithelial tumours. J Gastroenterol 1989; 27: 212-217.

33. Bülow S. Incidence of associated diseases in familial polyposis coli. Sem in Surg Oncol 1987; 3: 84-87.

34. Spigelman Ad, Williams CB, Crofton-Sleigh C, et al. Gastroduodenal adenomas in polyposis:- Is bile the missing link? Int J Colorect Dis 1990; 5: 54.

35. Desigan G, Wang M, Dunn G, et al. Intramucosal gastric carcinoma in a patient with familial polyposis coli. Am J Gastroenterol 1986; 81: 19-22.

36. Krutz RC, Sternbergt SS, Miller HH, et al. Upper gastrointestinal neoplasia in familial polyposis. Dig Dis Sci 1987; 32: 459-465.

37. Spigelman AD, Williams CB, Talbot IC, Domizio P and Phillips RKS: Upper gastrointestinal cancer in patients with familial adenomatous polyposis. Lancet 1989; 2:783-785.

38. Jagelman DG. Extracolonic manifestations of familial adenomatous coli. Cancer Cytogenet 1987; 27: 319-325.

39. Sugihara K, Muto T, Kamiya J, et al. Gardner's syndrome associated with periampullary carcinoma, duodenal and gastric adenomatosis. Dis Colon Rectum 1982; 25: 766-771.

40. Spigelman AD, Thomson JPS, Phillips RKS. Cholecystectomy, duodeno-gastric reflux and polyposis. J R Soc Med 1989; 82: 437-438.

41. Hamilton SR, Bussey HJR, Mendelsohn G, et al. Ileal adenomas after colectomy in nine patients with adenomatous polyposis coli / Gardener's syndrome. Gastroenterology 1979; 77: 1252-1257.

42. Ross JE, Mara JE. Small bowel polyps and carcinoma in multiple intestinal polyposis. Arch Surg 1974; 108: 378-380.

43. Jarvinen HJ, Nyberg M, Peltokaalio P. Billary involvement in familial adenomatous coli. Dis Colon Rectum 1983; 26: 525-528.

44. Komorowski RA, Tresp MG, Wilson SD. Pancreaticobillary involvement in familial polyposis / Gardner's syndrome. Dis Colon Rectum 1986; 29:55-58.

45. Plail RO, Bussey HJR, Glazer G, et al. Adenomatous polyposis: an association with carcinoma of the thyroid. Br J Surg 1987; 74: 377-380.

46. Marshall WH, Martin FIR, Mackay JR. Gardner's syndrome with adrenal carcinoma. Australian annals of Medicine 1976; 16: 242-244

47. Painter TA, Jagelman DG. Adrenal adenomas and adrenal carcinoma in association with hereditary adenomatosis of the colon and rectum. Cancer 1985; 55: 2001.

48. Naylor EW, Gardner EJ. Adrenal adenomas in a patient with Gardner's syndrome. Clin Genet 1981; 20: 67-73.

49. Schnieder NR, Cubilla AL, Chaganti RSK. Association of endocrine neoplasia with multiple polyposis of the colon. Cancer 1983; 51: 1171-1175.

50. Perkins JT, Blackstone MO, Riddell RH. Adenomatous polyposis coli and multiple endocrine neoplasia type 2b. A pathogenetic relationship. Cancer 1983; 55: 375-81.

51. Utsonomiya J, Nakamura T. The occult osteomatous changes in the mandible in patients with familial polyposis coli. Br J Surg 1975; 62: 45-51.

52. Li FP, Thurber WA, Seddon J, et al. Hepatoblastoma in families with polyposis coli. JAMA 1987; 257: 2475-2477.

53. Lotfi AM, Dozois RR, Gordon H, et al. Mesenteric fibromatosis complicating familial adenomatous polyposis. Ann Surg 1986; 204: 94-97.

54. Audisio RA, Rossetti C, Bertario L, et al. 10 cases of desmoid tumours associated with adenomatous polyposis. Int J Colorect Dis 1990; 5: 53.

55. Thomson JPS. Familial adenomatous polyposis: The large bowel. Annals of the R Col Surg of England 1990; 72: 177-180.

56. Turcot J, Despres JP, St Pierre F. Malignant tumours of the central nervous system associated with familial polyposis of the colon: Report of two cases. Dis Colon Rectum 1959; 2: 465-468.

57. Aitken RJ, Elliot MS, Torrington M, Louw JH: Twenty year experience with polyposis coli in Cape Town. Br J Surg 1986; 73: 210-213.

58. Bremner CG: Ano-rectal disease in the South African Bantu - III carcinoma of the rectum. S Afr J Surg 1965; 3: 35-40.

59. McQuaide JR, Stewart AW: Familial polyposis of the colon in the Bantu. S Afr J Med 1972; 46: 1241-1246.

60. Louw JH, Raynham WH, Torrington M. Carcinoma of the Colon with particular reference to familial polyposis. Proceedings of NCA of SA 1974: 318-326.

61. Berk T, Cohen Z, McLeod RS, Cullen JB: Surveillance in relatives of patients with adenomatous polyposis. Seminars in Surgical Oncology 1987; 3: 105-108.

62. Jagelman DG. The expanding spectrum of familial adenomatous polyposis. Perspectives in Colon and Rectal Surgery. 1988; 1: 30-46 as quoted by Northover[23]

63. Perry RE, Christensen MA, Thorson AG, Williams T. Familial polyposis: Colon cancer in the absence of rectal polyps. Br. J. Surg. 1989; 76: 744

64. Moertel CG, Hill JR, Adson MA. Surgical management of multiple polyposis. The problem of cancer in the retained segment. Arch Surg 1970; 100:521-526.

65. Bess MA, Adson MH, Elveback LR, Moertel CG: Rectal cancer following colectomy for polyposis. Arch Surg 1980; 115: 460.

66. Schaupp WC, Volpe PA: Management of diffuse colonic polyposis. Am J Surg 1972; 124: 218

67. Murday V, Slack J. Inherited disorders associated with colorectal cancer. Cancer Surveys 1989; 8: 139-157.

68. 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.

69. Jagelman DG. Familial polyposis coli. Surgical Clinics of North America. 1983; 63: 117-128.

70. Blaire NP, Trempe CL. Hypertrophy of the retinal pigment associated with Gardener's Syndrome. American Journal of Ophthalmology 1980; 90: 661-667.

71. Chapman PD, Church W, Burn J, Gunn A. Congenital hypertrophy of the retinal pigment epithelium: a sign of familial adenomatous polyposis. Br Med J 1989; 298: 353-354.

72. Baker RH, Heinemman M-H, Miller HH, DeCosse JJ. Hyperpigmented lesions of the retinal pigment epithelium in familial adenomatous polyposis. American Journal of Medical Genetics 1988; 31: 427-435.

73. Dunlop MG, Wyllie AH, Steel CM, Piris J, Evans HJ. Linked DNA markers for presymptomatic diagnosis of familial adenomatous polyposis. Lancet 1991; 337: 313-316.

74. Bodmer WF, Bailey CJ, Bodmer J, Bussey HJR, Ellis A, Gorman P, Lucibello FC, Murday VA, Rider SH, Scambler P, Sheer D, Solomon E, Spurr NK. Localization of the gene for familial adenomatous polyposis on chromosome 5. Nature 1987; 328: 614-616.

75. Nishisho I, Nakamura Y, Miyoshi Y, Miki Y, Ando H, Horii A, Koyama K, Utsunomiya J, Baba S, Hedge P, Markham A, Krush A, Petersen G, Hamilton S, Nilbert M, Levy D, Bryan T, Preisinger A, Smith K, Su L, Kinzler K, Vogelstein B. Mutations of chromosome 5q21 genes in FAP and colorectal cancer patients. Science 1991; 253: 665-669.

76. Kinzler K, Nilbert M, Su L, Vogelstein B, Bryan T, Levy D, Smith K, Preisinger A, Hedge P, McKechnie D, Finniear R, Markham A, Groffen J, Boguski M, Altschul S, Horii A, Ando H, Miyoshi Y, Miki Y, Nishisho I, Nakamura Y. Identification of FAP locus genes from chromosome 5q21. Science 1991; 253: 661-665.

77. 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.

78. Williams NS (Moderator): Symposium. Surgical aspects of familial adenomatous polyposis. Int J Colorect Dis 1988; 3: 1-16.

79. Everett WG, Forty J: The functional result of pelvic ileal reservoir in 10 patients with familial adenomatous polyposis. Ann R Coll Surg Engl. 1989 Jan; 71(1): 28-30.

80. Bess MA, Adson MH, Elveback LR, Moertel CG: Rectal cancer following colectomy for polyposis. Arch Surg 1980; 115: 460.

81. 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.

82. Gingold BS, Jagelman D, Turnbull RB: Surgical management of familial polyposis and Gardner's syndrome. Am J Surg 1979; 137: 54.

83. Schaupp WC, Volpe PA: Management of diffuse colonic polyposis. Am J Surg 1972; 124: 218

84. Nicholls RJ, Springall RG, Gallagher P: Regression of rectal adenomas after colectomy and ileo-rectal anastomosis for familial adenomatous polyposis. Br Med J 1988; 296: 1707-1708.

85. Arvanitis ML, Jagelman DG, Fazio VW, Lavery IC, McGannon E: Mortality in patients with familial adenomatous polyposis. Dis Colon Rectum 1990; 33: 639-642.

86. Spigelman AD, Williams CB, Talbot IC, Domizio P and Phillips RKS: Upper gastrointestinal cancer in patients with familial adenomatous polyposis. Lancet 1989; 2:783-785.