Hereditary Colorectal Cancer

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Hereditary Colorectal Cancer

Springer

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Preface

Over the last quarter of a century, significant and explosive advancements have been made regarding the study of colorectal cancer. The wealth of information evolving is far reaching. From the first case report of the loss of the long arm of chromosome 5 in a patient with Familial Adenomatous Polyposis, to the cloning and identification of multiple genes involved in hereditary colorectal cancer, the field has progressed so we can now offer our patients genetic predisposition testing and better clinical management. Molecular mechanisms and the implications that some of these changes have for our patients is better understood. Rather than only discussing therapy these advances now allow us to discuss surgical prophylaxis and chemoprevention. Advances in the knowledge of familial colorectal cancer have not come easy and are due to the hard work of inquisitive investigators and clinicians, the development of advance instrumentations and molecular genetic techniques and most importantly from our patients and families. Without them we would not have been able to achieve this feat. Still, there is more to be done in the field. There are yet undiscovered syndromes, genes and molecular alterations which can and will change the lives of families and individuals. Thus, we cannot rely solely on what has been done, but need to continue to question existing research in the future.

The lack of a comprehensive reference book on hereditary colorectal cancer has been our driving force. The editors have gathered a multinational panel of experts to address the issues in *Hereditary Colorectal Cancer*. This book goes beyond the historical aspects of Familial Adenomatous Polyposis and the Lynch Syndrome. It further encompasses the basic and clinical aspects of less common and less understood syndromes such as the Hamartomatous Polyposis Syndromes and MutYH Associated Polyposis. An important section of *Hereditary Colorectal Cancer* is devoted to genetic counseling, an evolving area. In this section, several leading authorities describe the issues pertaining to genetic counseling around the world and within registries. Also addressed are the psychosocial aspects of hereditary colorectal cancer. This book will serve as a clinical reference, however, it will be also a useful guide for basic scientists, genetic counselors, and those interested in hereditary colorectal cancer.

While the book was being edited, one of our contributors and friend passed away. Jeremy Jass was the ultimate translational scientist. He was a pathologist and a basic

scientist whose contributions to the field are too numerous to state. The editors would like to express their gratitude for his contribution as well as for all his contributions to the advancement of understanding colorectal cancer. We also would like to express our most sincere appreciation to the editors at Springer who have been immensely helpful and patient with us. Lastly we have to mention our patients and our families whom without their support this project would have not been possible.

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Part I
History

Chapter 1
History: Familial Adenomatous Polyposis

Susan K. Clark, Kay F. Neale, and Robin K.S. Phillips

> *It would be difficult to find a more promising field for the exercise of cancer control than a polyposis family, because both diagnosis and treatment are possible in the precancerous stage and because the results of surgical treatment are excellent.*
>
> C.E. Dukes 1958

Abstract This chapter sets out to describe the developments leading to our current knowledge of familial adenomatous polyposis. An appreciation of historical context allows an enhanced understanding of contemporary paradigms and management of this condition.

Keywords Familial Adenomatous Polyposis • History • Colorectal Cancer

1.1 Why Is History Important?

Some are interested in history for its own sake, but for most of us its value lies in the way in which it explains the present and points the way forward. We hope that reading this chapter will give inspiration to those interested in learning more about this fascinating condition.

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1.2 Early Descriptions

A handful of descriptions of patients with multiple colorectal polyps were published in the late nineteenth century, some of which were undoubtedly cases of familial adenomatous polyposis (FAP) [1–4] although others were probably inflammatory pseudopolyps. Various different terms were used to describe the condition, including "disseminated polypi", "multiple adenomas", "multiple adenomatosis" and "multiple polyposis", but it does not seem to have been recognised as a distinct entity for some time. Two authoritative textbooks of colorectal surgery from that time, by Curling [5] of the London Hospital and Allingham [6] from St Mark's Hospital, go no further than to note that polyps can be multiple.

By 1901, a standard German text book [7] differentiated adenomatous polyposis clearly from sporadic adenomas and other types of polyps. In the following three decades, pathological classification [8] formalised the distinction between adenomatous polyps and inflammatory pseudopolyps, resulting in a well-described disease entity [9, 10], often known as "polyposis coli" or "polyposis intestini", defined by the macroscopic and microscopic appearances and inheritance.

Although Cripps' early description of the disease [2] was in a brother and sister, and others described three members of the same family [11] and a mother and child [12] with the condition, the Mendelian dominant mode of inheritance was defined by Cockayne [13] in 1927 (Fig. 1.1).

The observation that patients with this condition developed cancer [14] sparked interest in the relationship between adenomatous polyps and large bowel cancer. Lockhart-Mummery [15] recognised that it was the propensity to form polyps, and subsequently cancer, which was inherited, rather than the cancers themselves. He noted that polyps tend to appear in late childhood, and that death from multiple colorectal cancers at a young age is almost inevitable. He also commented on cases of colorectal cancer apparently developing from sporadic adenomas.

1.3 Foundation of Registries and Collaborative Groups

The St. Mark's Hospital Polyposis Register [later to become Registry in 1985] [16] was established in 1924 as a laboratory to examine the polyps taken from Lockhart-Mummery's first three families, the results of which were published the following year [15] (Fig. 1.2). The staff set about clarifying pedigrees and identifying at-risk family members, keeping meticulous records. Over the years, the role of the registry has expanded to include call-up, counselling, surveillance and genetic testing of at-risk relatives, provision of prophylactic surgery and recall for regular follow-up. The resulting database is an invaluable source of information, and the centralisation of care facilitates prospective research.

A number of other such registries have been developed around the world, but the first national register was established in Sweden [17]. There is evidence that patients

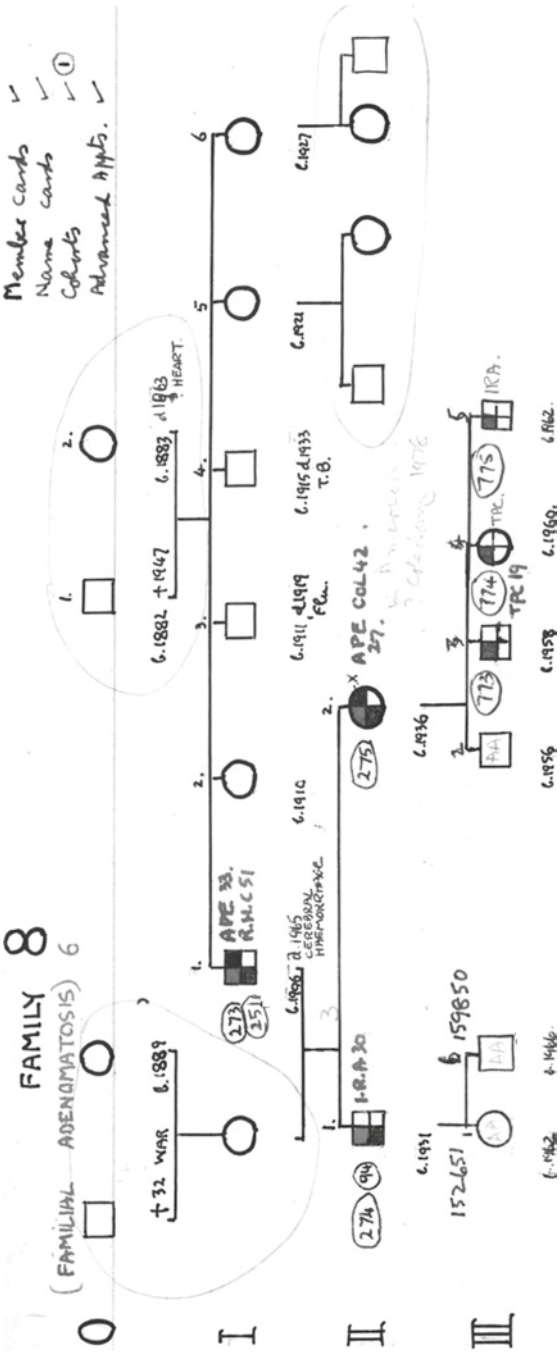


Fig. 1.1 An original family tree as drawn by Dr. HJR Bussey

Fig. 1.2 Dr. HJR Bussey in St Mark's Hospital Pathology Department 1992

with FAP cared for in a registry have a much lower chance of having colorectal cancer at the time of diagnosis of FAP [18] and higher life expectancy [19, 20] than those not cared for in such a setting.

1.3.1 The Leeds Castle Polyposis Group and International Society for Gastrointestinal Hereditary Tumours

In June 1985, the Leeds Castle Polyposis Group, an international group of clinicians from polyposis registries around the world, met for the first time [21]. The meeting was initiated by Ian Todd, a surgeon at St. Mark's Hospital, who despite many years of experience in caring for patients with FAP found that he did not know how to treat a young woman with a large desmoid tumour. The meeting agreed that an international group should be formed to promote understanding of the rarer manifestations of this uncommon condition. By 1992, 51 centres around the world were involved, and meetings were held every 2 years. In 1995, the group met jointly with the International Collaborative Group for HNPCC, and in 2003, the two organisations merged to form the International Society for Gastrointestinal Hereditary Tumours (InSiGHT) (Fig. 1.3). As the Society's name suggests, it is an international, multidisciplinary, scientific organisation. Its mission is to improve the quality of care of patients and their families with any condition resulting in hereditary gastrointestinal tumours. More information can be found on the website (www.insight-group.org) with details regarding membership and the biennial scientific meetings (Table 1.1) (Fig. 1.4).

Fig. 1.3 The first meeting of InSiGHT, Newcastle, UK, 2005

Table 1.1 LCPG and Insight biennial scientific meetings

Year	Chairman	Location
1985	Ian Todd	Leeds Castle, Kent, UK
1987	Jerome DeCosse	Washington, USA
1989	James Thomson	Broadway, UK
1991	David Jagelman	Fort Lauderdale, USA
1993	Steffen Bülow	Copenhagen, Denmark
1995	Hartley Stern	Toronto, Canada
1997	Hans Vasen	Noordwijk, The Netherlands
1999	Finlay Macrae	Lorne, Australia
2001	Luccio Bertario	Venice, Italy
2003	James Church	Cleveland, USA
2005	John Burn	Newcastle, UK
2007	Takeo Iwama	Yokohama, Japan
2009	Gariela Moeslein	Dusseldorf, Germany
2011	Partrick M. Lynch Miguel A. Rodriguez-Bigas	San Antonio, USA
2013	Alan Spigelman Finlay Macrae	Melbourne, Australia

Fig. 1.4 The InSiGHT logo

1.4 Development of Clinical Understanding of FAP

Collection together of multiple families with FAP and an increasing awareness of polyposis in the medical community facilitated observation and documentation of the extra-colonic manifestations of the condition. Examples include the first description of congenital hypertrophy of the retinal pigment epithelium (CHRPE) in a patient with FAP in 1935 [22], who also had duodenal cancer, and the documentation of the co-existence of FAP and desmoid tumour [23]. Gardner's description [24] of individuals with FAP, epidermoid cysts, osteomas and desmoids was for a time thought to be a distinct syndrome, but since the identification of the APC gene this is no longer considered to be the case (Fig. 1.5). In 1983, Judith Kingston noted that children with hepatoblastoma were likely to have a parent with FAP [25] and 2 years later an increased risk of thyroid cancer was reported by Plail [26].

Refinement of understanding the phenotype has progressed hand-in-hand with advancing medical technology. In particular, gastroduodenoscopy [27] has allowed an appreciation of duodenal polyposis, and cross-sectional imaging has enabled visualisation of desmoids and adrenal adenomas [28]. As screening and prophylactic surgery have been increasingly employed, reducing early deaths from colorectal cancer, duodenal and periampullary cancers and desmoid disease have emerged as important causes of death [29] in patients with FAP.

1.5 FAP as a Model of Sporadic Colorectal Cancer

Dukes, Morson and Bussey [30] in the pathology department at St Mark's saw relatively large numbers of cases of FAP and of sporadic colorectal cancer. Their observations led to the description of the adenoma–carcinoma sequence [31, 32]

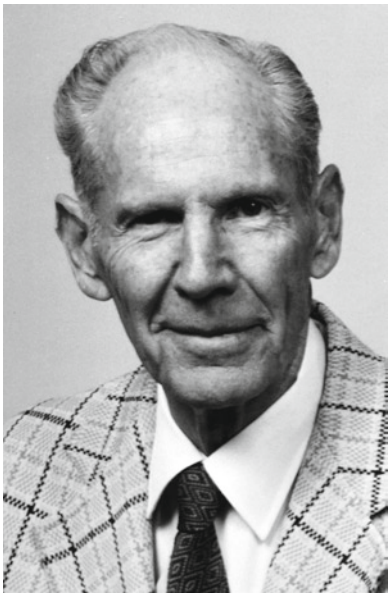


Fig. 1.5 Dr. Eldon Gardner

and the realisation that FAP can be viewed as a human model of colorectal cancer development. In 1968, Smith wrote that it would be "reasonable to hope that any significant discovery regarding familial multiple polyposis might have a bearing on the much larger problem of carcinoma of the colon" [33], and in 1975, Bussey expressed a similar view [30]: "it is the possibility of helping so many that justifies a study in depth of the few".

Much of the work underpinning Fearon and Vogelstein's proposed genetic pathway of colorectal cancer development [34] involved a study of the chromosomes and DNA from polyps removed from patients with FAP. Studies assessing potential chemopreventive agents for colorectal cancer have been undertaken on patients with FAP [35] who make an ideal model for this type of work.

1.6 Prophylactic Surgery

Lilienthal in North America performed the first recorded colectomy for FAP [36], the first operation in the UK being done on 18th March 1918 by JP Lockhart-Mummery at St Mark's Hospital [37]. The surgery was hazardous, and often done in stages. Rankin [38] described a three-stage proctocolectomy, in which an ileostomy was performed first, with a colectomy a few months later, and finally a perineal proctectomy. Mayo [39] reported a five-stage colectomy and ileosigmoidostomy done in two patients, one of whom died after the second stage from small bowel adhesions.

The introduction of prophylactic surgery followed an appreciation that pre-malignant adenomas inevitably progressed to invasive carcinoma, and an understanding of the inheritance of FAP provided the opportunity to identify asymptomatic patients in adolescence or early adulthood. While many patients diagnosed with FAP demanded that something be done, others either would not come for clinical assessment and screening or refused surgery [40].

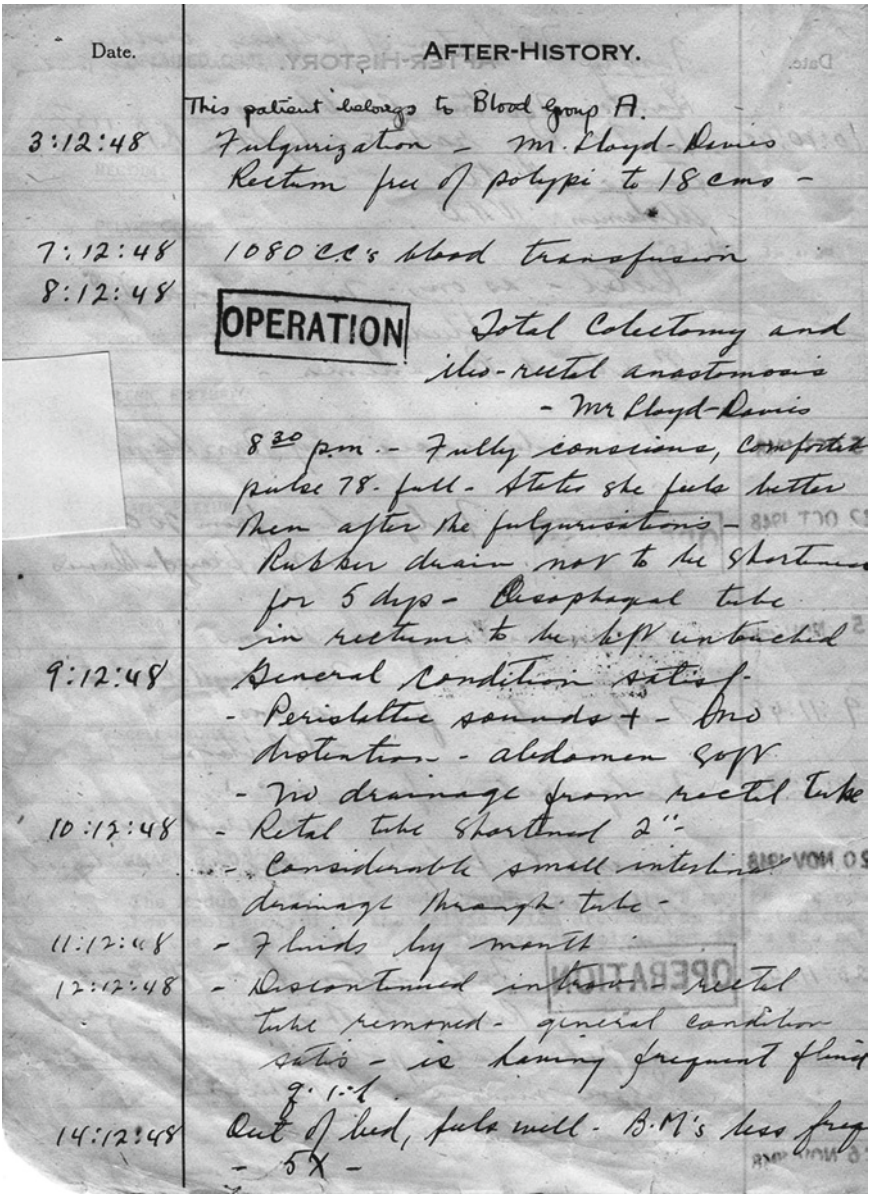
Gastrointestinal surgery was revolutionised in the 1940s by the development of antibiotics, blood transfusion and an understanding of the importance of electrolyte balance, all of which came at a time when anaesthesia was also becoming very much safer. The introduction of muscle relaxants (curare was first used in 1942) allowed much less anaesthetic agent to be used, decreasing cardiovascular depression. These advances allowed prophylactic single-stage colectomy with ileorectal anastomosis (IRA) to be performed relatively safely, with the great advantage of avoidance of an ileostomy. The first such procedure at St Mark's was carried out in 1948 by OV Lloyd-Davies [41] (Fig. 1.6).

1.6.1 Post-operative Follow-up

Patients after IRA required regular follow-up [42], done at that time with rigid sigmoidoscopy, much inferior to modern flexible endoscopes. In the early years, it was considered important to clear the rectum of polyps before colectomy and remove them on a regular basis afterwards. They were destroyed by fulguration [42], leading to considerable scarring, which made assessment of the state of the rectal mucosa more difficult in later years. Initial proctocolectomy or subsequent completion proctectomy was undertaken reluctantly, because of the resulting permanent ileostomy. While the risk of developing rectal cancer after IRA varies from series to series, probably in part due to different operative technique and follow-up protocols, the Mayo clinic reported a 59% risk after 23 years of follow-up [43], while at St Mark's [44], the equivalent figure was 10% by the age of 50 years and 29% at 60 years.

1.6.2 Advances in Surgical Technique

The advent of the ileoanal pouch, allowing restorative proctocolectomy (RPC) in the late 1970s [45] seemed to offer a solution to the problem of polyp and cancer development in the retained rectum after IRA. This procedure, however, is associated with greater morbidity than IRA, and a less satisfactory functional outcome [46]. There is a small risk to male sexual function, and a significant reduction in female fertility [47]. It is now becoming clear that adenomas and even carcinomas can develop in ileoanal pouches, which no longer seem to be the panacea they once did [48].


Date.

AFTER-HISTORY.

This patient belongs to Blood Group A.

3:12:48 Fulgurization – Mr. Lloyd-Davies
Rectum free of polypi to 18 cms –

7:12:48 1080 c.c.'s blood transfusion

8:12:48 OPERATION Total Colectomy and ileo-rectal anastomosis
– Mr Lloyd-Davies
8.30 p.m. – Fully conscious, comfortable
pulse 78. full – States she feels better
than after the fulgurisations –
Rubber drain not to be shortened
for 5 days – Oesophageal tube
in rectum to be kept untouched

9:12:48 General condition satisf.
– Peristaltic sounds + – bowel
distention – abdomen soft
– No drainage from rectal tube

10:12:48 – Rectal tube shortened 2" –
– Considerable small intestinal
drainage through tube –

11:12:48 – Fluids by mouth

12:12:48 – Discontinued intravenous – Rectal
tube removed – general condition
satis – is having frequent fluid
q. i. d.

14:12:48 Out of bed, feels well – B.M's less frequent
– 5X –

Fig. 1.6 Documentation from the patient's hospital record

1.6.3 Impact of Genetics on Surgical Choice

An understanding of the genotype–phenotype correlation allowing the identification of aggressive FAP, best managed by restorative proctocolectomy, and the advent of

flexible sigmoidoscopy and endoscopic polypectomy techniques mean that the rectal cancer risk after IRA is now much lower than it was in the "pre-pouch era" [49], and the pendulum is swinging back to IRA as the favoured prophylactic procedure in many cases. A further refinement is that IRA is increasingly being performed laparoscopically [50], a particularly attractive option for young people undergoing prophylactic surgery.

1.7 Gene Discovery

The structure of DNA was identified in the 1950s, but it was not until 1986 that the serendipitous observation of a deletion of the long arm of chromosome 5 in a patient with mental retardation and FAP led to the suggestion that the gene responsible would be found at that site [51]. In rapid succession, linkage studies confirmed this location [52] then refined it to 5q22. In 1991, causative mutations were identified in what was now called the APC gene [53] (the FAP gene having been named earlier as responsible for familial amyloidotic polypneuropathy) opening the door to predictive genetic testing, and more recently pre-implantation diagnosis, which is now available at a number of centres. As mutation detection methods improved it became possible to identify the mutations responsible for attenuated FAP allowing a genetic diagnosis to be made in cases not fulfilling the traditional clinical criteria of FAP.

Identification of a number of different mutations in the APC gene has allowed an understanding of genotype–phenotype correlation to be developed, although the mechanisms underlying this relationship remain to be fully elucidated. APC has also been found to have a pivotal role in the wnt signalling pathway, abnormal activation of which occurs in the majority of sporadic colorectal cancers.

1.7.1 MYH-associated Polyposis

Study of a small group of patients with a phenotype similar to attenuated FAP, but with no detectable APC mutation, and the fact that the handful of families with this condition apparently had recessive inheritance, led to the discovery of mutations in the MYH gene and identification of MYH-associated polyposis [MAP] [54].

1.8 History into the Future

History should be reviewed to confirm that the basic decisions regarding clinical care are still relevant to current clinical practise. For example, pioneers of the IRA would leave the recto-sigmoid long in an attempt to improve bowel function. Once

it had been shown that cancers could develop beyond the reach of a 25-cm rigid sigmoidoscope, most surgeons fashioned the anastomosis lower; with the advent of flexible scopes, there is an argument to return to the practice of the early pioneers.

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