Hereditary and Familial Colorectal Cancer

Hereditary and Familial Colorectal Cancer

Edited by

Éanna Ryan and Desmond Winter

Cambridge
Scholars
Publishing

Hereditary and Familial Colorectal Cancer

Edited by Éanna Ryan and Desmond Winter

This book first published 2022

Cambridge Scholars Publishing

Lady Stephenson Library, Newcastle upon Tyne, NE6 2PA, UK

British Library Cataloguing in Publication Data
A catalogue record for this book is available from the British Library

ISBN (10): 1-5275-8734-7
ISBN (13): 978-1-5275-8734-2

TABLE OF CONTENTS

FOREWORD

Over the past three decades, since the launch of The Human Genome Project and the seminal work published by Fearon and Vogelstein on the model for colorectal tumourigenesis in Cell, several ground-breaking advancements have been made relating to the molecular and genomic underpinnings of colorectal cancer. As the available technologies and research methodologies have evolved, the resultant genomic information has been produced rapidly and is expanding at a breath-taking rate.

From the initial description of the genetic basis for Familial Adenomatous Polyposis to the discovery of novel genes causing hereditary colorectal cancer predisposition syndromes via next generation sequencing, the clinical applications of these discoveries have advanced the care afforded to carriers of such mutations and their families greatly. A better appreciation of the molecular mechanisms and the implications that certain constitutional mutations have for carriers now means that patients with genetic predisposition to colorectal cancer can now be offered widely available and affordable testing, and enhanced clinical management strategies including: personalised surveillance, surgical prophylaxis, chemoprevention; and tailored adjuvant and neoadjuvant therapeutic strategies.

These advances are a result of the hard work of compassionate and dedicated scientists and healthcare professionals, technological innovations and the development of molecular genetic techniques, and most crucially from the engagement and participation of those affected by these conditions, as well as their families. Without their generous contributions none of this progress would be possible.

Despite this there is much more to be achieved. Undoubtedly, as the recent discoveries of polymerase proof reading polyposis and NTHL1-associated polyposis has demonstrated there are likely to be other yet to be discovered hereditary colorectal cancer predisposition syndromes, and elucidating their underlying genetic and molecular alterations has the potential to further our understanding of colorectal cancer, as well as improving the management of families and individual carriers.

While previous books on the topic have primarily focused on the genetic, molecular and pathological basis for these syndromes, there is a lack of information for busy physicians regarding the clinical management of hereditary cancer predisposition syndromes and colorectal cancer

occurring in the familial setting. Here the editors have been fortunate to have received contributions from a multinational panel of expert clinicians who specialise in the clinical management of such individuals. We are extremely indebted to their generous contributions.

While the historical aspects of the two most well described syndromes, Familial Adenomatous Polyposis and Lynch Syndrome, as well as the underlying basic science are all discussed, this book will specifically aim at outlining the management hereditary and familial colorectal cancer including diagnosis, clinical science and genetics, medical and surgical management options, surveillance, quality of life, patient experience, public health concerns and future developments.

We envisioned this book to be a leading manuscript and reference tool for those caring for patients and families of those with hereditary and familial colorectal cancer. We hope we have achieved our aim to consolidate the current best practice and present it in a concise manner and see it as a crucial addition to current literature available. While principally aimed at medical professionals, we trust that it will be of interest to our genetic counsellor and nursing colleagues, as well as all those affected by the conditions described herein.

We would also like to take this opportunity to express our most heartfelt appreciation to the editors at Cambridge Scholars Publishing who have been enormously helpful and patient with us throughout this project.

Lastly, we wish to mention our patients and our families whom without their support this book would have not been possible. We are forever indebted to their encouragement, kindness and support. We would like to thank them for the innumerable and constant sacrifices they have made so selflessly in supporting us throughout this and other endeavours.

Mr. Éanna J. Ryan
MB BCh, MRCSI, MD
Department of Colorectal Surgery
St Vincent's University Hospital
Elm Park
Dublin 4
Ireland

Prof. Des Winter
MB BCh, FRCSI, MD
Consultant Colorectal Surgeon
St Vincent's University Hospital
Elm Park
Dublin 4
Ireland

CONTRIBUTORS

Mohammad Ali Abbass
Department of Colorectal Surgery, Cleveland Clinic, Ohio, USA.

Mohamad M. Adada
Department of Hematology & Oncology, Mayo Clinic, Rochester, Minnesota, USA.

Susan Aherne
Department of Pathology, St. Vincent's University Hospital, Dublin, Ireland.

Emma Anthony
Department of Clinical Pathology, The University of Melbourne, Melbourne, Australia.

Mark Arends
Department Division of Pathology, MRC Institute of Genetics & Molecular Medicine, The University of Edinburgh, Edinburgh, United Kingdom.

Paul Armstrong
Department of Gastroenterology, St. Vincent's University Hospital, Dublin, Ireland.

Helena C. Bartels
Gynaecological Oncology Group, University College Dublin School of Medicine & St. Vincent's University Hospital, Dublin, Ireland.

Nancy N. Baxter
Division of General Surgery, St. Michael's Hospital, Toronto, Ontario, Canada & the University of Toronto, Ontario, Canada.

Andrew Beggs
Department of Surgery at the Queen Elizabeth Hospital; & Department of Surgery & Cancer Genetics, University of Birmingham, Birmingham, UK.

Lisa A. Boardman
Division of Gastroenterology and Hepatology, Department of Internal Medicine, Mayo Clinic, Rochester, Minnesota, USA.

Donal J. Brennan
Gynaecological Oncology Group, University College Dublin School of Medicine & St. Vincent's University Hospital, Dublin, Ireland.

Daniel D. Buchanan
Department of Clinical Pathology, The University of Melbourne Department of Clinical Pathology; Centre for Cancer Research, the University of Melbourne& Genomic Medicine and Familial Cancer Centre, the Royal Melbourne Hospital, Melbourne, Australia.

Gabriel Capellá
Hereditary Cancer Program, Catalan Institute of Oncology, IDIBELL, Hospitalet de Llobregat, Barcelona, Spain & Centro de Investigación Biomédica en Red de Cáncer (CIBERONC), Spain.

Sue Clark
Department of Surgery, St Mark's Hospital, London, UK
& Department of Surgery and Cancer, Imperial College, London.

Maura B. Cotter
Department of Pathology, St. Vincent's University Hospital, Dublin, Ireland.

Ben Creavin
Department of Surgery, Surgical Professorial Unit, St. Vincent's University Hospital, Dublin, Ireland.

Noelle M. Cullinan
Department of Paediatric Oncology, Children's Health Ireland at Crumlin.

Quentin Denost
Bordeaux Colorectal Institute, Clinique Tivoli, Bordeaux, France.

Noel E. Donlon
Department of Surgery, St. James' Hospital, Dublin, Ireland.

Brooke R. Druliner
Department of Internal Medicine, Mayo Clinic, Rochester, Minnesota, USA.

D. Gareth Evans
Department of Medical Genetics and Cancer Epidemiology, The University of Manchester & Department of Medical Genetics and Cancer Epidemiology, Manchester Hospitals NHS Foundation Trust and The Christie NHS Foundation Trust, Manchester, UK.

Christina Fleming
Department of Colorectal Surgery, University Hospital Limerick, Ireland.

Michael Flood
Department of Surgery, Peter MacCallum Cancer Centre, Melbourne, Australia.

Ian Frayling
Department of Genetic Pathology, Inherited Tumour Syndromes Research Group; & Institute of Cancer & Genetics, School of Medicine, Cardiff University, Cardiff, United Kingdom.

Rondell P. Graham
Department of Laboratory Medicine and Pathology, Mayo Clinic College of Medicine & Division of Anatomic Pathology, Department of Laboratory Medicine and Pathology, Mayo Clinic, Rochester, Minnesota, USA.

Ann Hanly
Department of Surgery, Surgical Professorial Unit, St. Vincent's University Hospital, Dublin, Ireland.

Usman M. Haroon
Department of Urology, St. Vincent's University Hospital, Dublin, Ireland.

Alexander Heriot
Department of Surgery, Peter MacCallum Cancer Centre, Melbourne, Australia.

James Hill
Department of Colorectal Surgery, Central Manchester University Hospitals NHS Foundation Trust, Manchester, United Kingdom.

Gareth Horgan
Department of Gastroenterology, St. Vincent's University Hospital, Dublin, Ireland.

Jihoon E. Joo
Department of Clinical Pathology, The University of Melbourne, Melbourne, Australia.

Matthew F. Kalady
Comprehensive Colorectal Cancer Program Cleveland Clinic; Sanford R. Weiss, MD, Center for Colorectal Neoplasia, Cleveland Clinic, Ohio, USA; & Department of Surgery Cleveland Clinic, Ohio, USA.

Michael E. Kelly
Department of Surgery, St. James' Hospital, Dublin, Ireland.

Rory Kennelly
Department of Surgery, Surgical Professorial Unit, St. Vincent's University Hospital, Dublin, Ireland.

Neeraj Lal
Institute of Cancer and Genomic Sciences, University of Birmingham, Birmingham, UK.

Andrew Latchford
Department of Gastroenterology, St Mark's Hospital, London, United Kingdom.

Brandie Leach
Cleveland Clinic Center for Personalized Genetic Healthcare, the Genomic Medicine Institute, Cleveland Clinic, Ohio, USA.

Finlay A. Macrae
Department of Medicine, University of Melbourne's Royal Melbourne Hospital; & Department of Colorectal Medicine and Genetics, Genomic Medicine and Familial Cancer Centre, the Royal Melbourne Hospital, Melbourne, Australia.

Séan T. Martin
Department of Surgery, Surgical Professorial Unit, St. Vincent's University Hospital, Dublin, Ireland.

Barry B. McGuire
Department of Urology, St. Vincent's University Hospital, Dublin, Ireland.

Terri P. McVeigh
Cancer Genetics Unit, The Royal Marsden NHS Foundation Trust & Division of Genetics and Epidemiology, The Institute of Cancer Research, London, United Kingdom.

Ruaidhri McVey
Gynaecological Oncology Group, University College Dublin School of Medicine & St. Vincent's University Hospital, Dublin, Ireland.

Helen M. Mohan
Department of Surgery, Surgical Professorial Unit, St. Vincent's University Hospital, Dublin, Ireland.

Kevin Monahan
Family Cancer Clinic & Wolfson Unit for Endoscopy, St Mark's Hospital, London, United Kingdom.

Julie B. Moskowitz
Clinical Cancer Genetics Program, The University of Texas MD Anderson Cancer Center, Houston, Texas, United States.

Maartje Nielsen
Department of Clinical Genetics, Leiden University Medical Center, Netherlands.

Benjamin Norton
Department of Gastroenterology, St Mark's Hospital, London, United Kingdom.

Lachlan O'Connell
Department of Medicine, The Royal Melbourne Hospital, Melbourne, Australia.

Grainne M. O'Kane
Department Gastrointestinal Oncology, The Princess Margaret Hospital, Toronto, Ontario, Canada.

Adesola Ogunsakin
Department Gastrointestinal Oncology, The Princess Margaret Hospital, Toronto, Ontario, Canada.

Vanessa Palter
St. Michael's Hospital, Toronto, Ontario, Canada; & Department of Surgery, University of Toronto, Toronto, Ontario, Canada.

Susan Parry
Clinical Director of the New Zealand Familial Gastrointestinal Cancer Service, Auckland, New Zealand.

Sheron Perera
Department Gastrointestinal Oncology, The Princess Margaret Hospital, Toronto, Ontario, Canada.

Christophe Rosty
Department of Clinical Pathology, The University of Melbourne, Melbourne, Australia.

Eric Rullier
Colorectal Unit, Magellan Surgical Center, Haut-Lévèque Hospital, Bordeaux, France.

Éanna J. Ryan
Department of Surgery, Surgical Professorial Unit, St. Vincent's University Hospital, Dublin, Ireland.

Odhrán K. Ryan
Department of Surgery, Surgical Professorial Unit, St. Vincent's University Hospital, Dublin, Ireland.

Tarik Sammour
Department of Surgery, Royal Adelaide Hospital & St Andrew's Hospital, Adelaide, Australia.

Kieran Sheahan
Department of Pathology, St. Vincent's University Hospital, Dublin; & University College Dublin School of Medicine, Dublin, Ireland.

Antonino Spinelli
Director of the Division of Colon and Rectal Surgery and Full Professor of Surgery at Humanitas University, Pieve Emanuele, Milano.

Áine Stakelum
Department of Surgery, Surgical Professorial Unit, St. Vincent's University Hospital, Dublin, Ireland.

Elena M. Stoffel
The University of Michigan Cancer Genetics Clinic; & Department of Internal Medicine at the University of Michigan, Ann Arbor, Michigan, United States.

Sanne W. Ten Broeke
Department of Clinical Genetics, University Medical Center Groningen, the Netherlands.

Selvi Thirumurthi
Department of Gastroenterology, Hepatology and Nutrition, Division of Internal Medicine, MD Anderson Cancer Center, Houston, Texas, United States.

Laura Valle
Hereditary Cancer Program, Catalan Institute of Oncology, IDIBELL, Hospitalet de Llobregat, Barcelona, Spain. Program in Molecular Mechanisms and Experimental Therapy in Oncology (Oncobell), IDIBELL, Hospitalet de Llobregat, Barcelona, Spain. Centro de Investigación Biomédica en Red de Cáncer (CIBERONC), Spain.

Anne-Sophie Van Der Werf- 'T Lam
Department of Clinical Genetics, Leiden University Medical Center, Netherlands.

Desmond C. Winter
Department of Surgery, Surgical Professorial Unit, St. Vincent's University Hospital, Dublin, Ireland; & University College Dublin School of Medicine, Dublin, Ireland.

Emma R. Woodward
Manchester Centre for Genomic Medicine, Manchester University Hospitals NHS Foundation Trust, Manchester, United Kingdom, and Division of Evolution and Genomics Sciences, The University of Manchester.

Xiaoyu Yin
Department of Medicine, The Royal Melbourne Hospital, Australia.

Yi-Qian Nancy You
Department of Surgical Oncology, Division of Surgery, The University of Texas MD Anderson Cancer Center, Houston, Texas, United States; & Clinical Cancer Genetics Program, The University of Texas MD Anderson Cancer Center, Houston, Texas, United States.

Alexandra Zaborowski
Department of Surgery, Surgical Professorial Unit, St. Vincent's University Hospital, Dublin, Ireland.

INTRODUCTION

ÉANNA J. RYAN, DESMOND C. WINTER

Introduction

The majority of colorectal cancers arise from sporadic colorectal polyps that likely arise due to a combination of underlying acquired molecular genomic changes that are accelerated by aging and environmental exposures according to the known major pathways of colorectal cancer carcinogenesis. A cancer predisposition syndrome is a genetic condition in which an inherited mutation predisposes affected individuals to cancer development, often at a young age. We now know that 10% of all colorectal cancer arises in the setting. Most mutations are autosomal dominant with high penetrance and affected patients benefit greatly from appropriate management. Genetic conditions, such as Lynch syndrome (formerly hereditary non-polyposis coli [HNPCC]) or Familial Adenomatous Polyposis [FAP]), increase the lifetime risk of developing CRC and some other cancers by as much as 70%-100% respectively. Furthermore, up to a third of colorectal cancer cases exhibit a more moderate, familial form of inheritance. These numbers may increase with technological advances and evolving knowledge as those colorectal cancers that are regarded as sporadic cases now may well be reclassified to familial or heritable cancers in the future.

At present, classification of a patient into a specific cancer predisposition syndrome is based on both clinicopathologic characteristics and, where possible, genetic testing for underlying causative constitutional mutations. However, determining the exact diagnosis is fraught with difficulty given the complexity of the possible histopathological variants at presentation and multiple clinical features that may exist within and between these syndromes. Similarly, the risks for extracolonic polyps or cancers as well as the risk for the development of colorectal cancer necessitate an extensive knowledge of how best to recognise and manage these patients.

This book outlines the known hereditary colorectal cancer predisposition syndromes with a focus on their clinical management. The

first chapter explores the two most well described syndromes, Familial Adenomatous Polyposis and Lynch Syndrome, in their historical context. The second chapter is an overview of the known cancer predisposition syndromes that may serve as an introduction to those not yet well versed in these conditions or as a refresher to those that are already aware of them. Following these introductory chapters, the book is divided into further sections, the first of which outlines what is known about syndromes characterised by deficient DNA mismatch repair mechanisms from the perspective of the various specialties that are involved in the care of patients with Lynch Syndrome and Constitutional Mismatch Repair Deficiency.

Later sections group the known polyposis syndromes based loosely on polyp type including: adenomatous polyposis syndromes; hamartomatous polyposis syndromes; mixed polyposis and serrated polyposis. These chapters describe the presenting clinical and histologic features, the underlying known molecular genetic mechanisms that lead to polyp development and ultimately the associated malignancies that increase the risk for colorectal and other extraintestinal cancers. There is a particular focus on the management of these syndromes including medical and surgical management, cancer surveillance and screening recommendations.

At present, inconsistencies in the approach to patients with a known or suspected hereditary colorectal cancer predisposition syndrome are a result of poor clinical and public awareness, patients not being seen in a timely fashion, inadequate access to specialist and cancer genetic services, and a failure to provide adequate surveillance and follow up. An inconsistent approach to managing people at higher risk of inherited gastrointestinal cancer undermines efforts to prevent morbidity and mortality from cancer screening. There has been a strong recommendation for the management of these individuals be coordinated in specialised cancer clinics such as the FORESIGHT Clinic at St. Vincent's University Hospital, Dublin, Ireland. Studies consistently report that the appropriate management of patients and families with predisposed susceptibility to cancer, through the use of registries and dedicated clinics, result in a reduction of cancer incidence and mortality. With this in mind the next section of the book deals with the specialist colorectal cancer predisposition syndrome and familial cancer clinic from the perspectives of the various clinicians involved in the running of such a service. Multidisciplinary management, universal tumour screening, risk estimation, the obtaining and use of genetic information and appropriate high-risk population screening and surveillance are all discussed.

In tandem, genetic testing has grown from a niche specialty for rare disorders to one that has a broad scope of applications for both complex

disease and more routine clinical uses. Advances in technology have resulted in widely available, inexpensive next-generation sequencing genetic screening panels for cancer predisposition syndromes. This has resulted in the identification of new pathogenic constitutional mutations, as well as, the prospect of a paradigm shift in the management of these patients to a new model, where accessibility is no longer the limiting factor with regards to genetic evaluation. The future for those who have a constitutional mutation causing hereditary predisposition to colorectal cancer and those who care for them will evolve as these syndromes are more accurately classified, diagnosed, surveyed and managed. The final section of the book outlines future developments and how these may relate to this exciting and evolving field. Ultimately, the molecular aetiologies and even the definition of how few polyps constitute a polyposis syndrome will be expanded as whole genome and other "omics" technologies are applied to all patients who developed colorectal polyps and/or cancer. The long-term hope for patients with polyposis syndromes may be met by further development of chemopreventive agents directed at genetically relevant targets, more tailored screening and surveillance programs, and possibly methodologies for gene editing or correction of genetic defects that may ultimately help these patients avoid the need for invasive surgeries.

The St Vincent's University Hospital Clinic for Formally Overseeing Risk Evaluation and Surveillance of Intestinal and Gastric Hereditary Tumours (FORESIGHT) Logo

INTRODUCTORY CHAPTERS

CHAPTER ONE

HISTORICAL ASPECTS OF HEREDITARY COLORECTAL CANCER

ÉANNA J. RYAN, ODHRÁN K. RYAN & DESMOND C WINTER

Introduction

This chapter describes the developments leading to our current knowledge of **Lynch Syndrome** ((LS) formerly Hereditary nonpolyposis colorectal cancer (HNPCC)) **(Chapters 3-7)** and **Familial Adenomatous Polyposis (FAP) (Chapters 9-11)**, the two most well described hereditary colorectal cancer (CRC) predisposition syndromes. An appreciation of the historical context that led to the recognition and characterisation of these entities should allow an enhanced understanding of contemporary management paradigms for these and related conditions. Moreover, it is hoped that this will serve as a reminder of how the advances of today are only possible due to the dedication of many compassionate researchers, and most crucially from the engagement of those affected by these conditions.

Familial Adenomatous Polyposis

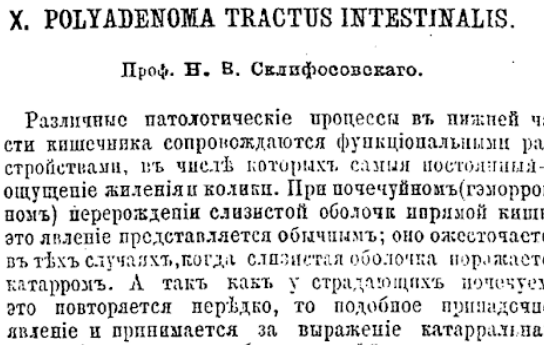
The first credible report of FAP was published over 130 years ago, and initially the disease was described and managed by surgeons and pathologists[1]. Since the breakthrough discovery of the APC gene in 1992, FAP has transformed into a disease requiring management by a wide variety of multidisciplinary specialists. This transformation in understanding and care has led to a major increase in research into all aspects of the disease over the last three decades, and has resulted in considerable progresses in management, survival and quality of life for affected carriers.

Early Descriptions of "Polyposis Coli"

Recognition and early descriptions

The first description of multiple colorectal polyps was published by the German Menzel in 1721[2]. However, most early descriptions were replete with inaccuracies and the majority described "pseudopolyps" related to intestinal inflammation[1]. The Russian Sklifasowski published the first histologically verified case of "adenomatous polyposis" managed successfully by surgery in 1881[3]. In the late 1800s, at least some of the earliest descriptions of patients with multiple colorectal polyps were likely cases of FAP[4-6]. Various terms were used to describe these presentations but the phenotype of multiple colorectal polyps received little recognition even in the definitive surgical textbooks[7,8].

By the turn of the century, there was a recognition that adenomatous polyposis constituted a separate entity from sporadic adenomas and other types of polyps[9]. Pathological classification in the early 1900s formalised these distinctions[1]. While early descriptions did identify the familial clustering of the disease[1], the autosomal dominant Mendelian mode of inheritance was not defined until 1927 by Edward Alfred Cockayne (London, United Kingdom(UK))[10]. Interest in the relationship between adenomatous polyps and the development of CRC grew as it was recognised by among others, John P. Lockhart Mummery(London, UK) consulting surgeon at St Mark's Hospital, that patients with this condition inevitably developed CRC due to the tendency of adenomatous polyps to undergo malignant change[11].



X. POLYADENOMA TRACTUS INTESTINALIS.

Проф. Н. В. Склифосовскаго.

Различные патологическіе процессы въ нижней части кишечника сопровождаются функціональными разстройствами, въ числѣ которыхъ самыя постоянныя— ощущеніе жиленія и колики. При почечуйномъ(гэморройномъ) перерожденіи слизистой оболочк прямой кишки это явленіе представляется обычнымъ; оно ожесточается въ тѣхъ случаяхъ, когда слизистая оболочка поражается катарромъ. А такъ какъ у страдающихъ почечуемъ это повторяется нерѣдко, то подобное припадочное явленіе и принимается за выраженіе катарральнаго

Figure 1-1: The first article on FAP by Sklifasowski[12]. [Reproduced by kind permission of *"Springer Nature"*]

The Polyposis Registry and Characterising FAP

Foundation of The Polyposis Registry at St Mark's Hospital, London

"The Polyposis Registry" at St. Mark's was subsequently established when consultant pathologist, Cuthbert Dukes, began to collect data with his then teenaged assistant, Richard Bussey, later Dr. HJR "Dick" Bussey, as a laboratory to examine the polyps taken from Lockhart-Mummery's original families with "polyposis coli". The result of these initial investigations were published in the Lancet the following year[11].

Figure 1-2: The old St. Mark's Hospital at its City Road site. [Reproduced by kind permission of St. Mark's Hospital, London, Prof. Sue Clark and Ms. Kay Neale.]

Prophylactic surgery and screening of asymptomatic relatives

Howard Lilienthal (New York, United States(US)) performed the first recorded colectomy for multiple colorectal polyps[13], while the first UK operation was performed in 1918 by Lockhart-Mummery[14]. Due to the complexity of the surgery it was frequently performed in stages. The first 3-stage proctocolectomy was performed in 1924 by Robert C. Coffey (Portland, US)[15]. Later, Fred W. Rankin (Louisville, US)[16], described a 3-stage proctocolectomy, where an ileostomy was performed first, with colectomy later, and finally completion proctectomy. Charles W. Mayo (Rochester, US)[17], son of the Mayo clinic founder, reported a 5-stage colectomy and ileosigmoidostomy performed in two patients, one of whom later died of complications.

Figure 1-3: Cuthbert Dukes (Left) and Richard Bussey (Right) at work in the St Mark's Polyposis Registry. [[Reproduced by kind permission of St. Mark's Hospital, London, Prof. Sue Clark and Ms. Kay Neale.]

Once the inherited nature of FAP [10] and the concept that adenomas inevitably progressed to invasive CRC gained credence, it was realised that there was an opportunity to identify young asymptomatic patients. In an extensive review, Dukes outlined how pedigrees in a FAP family ''are photographs: they record the state of affairs at a given point of time''[18]. These observations led the German physician, Otto Jüngling, to recommend prophylactic sigmoidoscopy for children of affected family members[19]. However, while many patients diagnosed with FAP sought medical attention, others were more reluctant to undergo surveillance[20]. In 1939, Lockhart-Mummery and Dukes published results of 10 families and the use of surveillance sigmoidoscopy and prophylactic surgery. Five patients underwent colectomy with only one mortality[21].

Gastrointestinal (GI) surgery was revolutionised in the 1940s by the improvements in perioperative care and anaesthesia that allowed more radical resections. With these advancements, in 1947 Mark M. Ravitch (Baltimore, US)[22] presented a "pull-through" rectal procedure and ileo-anal anastomosis after a previous colectomy and ileorectal anastomosis (IRA). While, Sir. Oswald V. Lloyd-Davies (London, UK) carried out the first single-stage colectomy with IRA at St. Mark's in 1948[23].

Clinical characterisation of FAP

The growing awareness of inherited polyposis within the medical community and centralisation of care allowed the recognition of some of the rarer clinical manifestations of the condition including congenital hypertrophy of the retinal pigment epithelium (CHRPE)[24], periampullary cancers[24] and desmoid tumours[25] in the 1920s and 30s.

One of the pioneers of radiology, Gordon M. Fitzgerald (San Francisco, US)[26] published the first report of odontomas in 1943. While initially geneticist Eldon J. Gardner's (Utah, US) description[27] of individuals with colonic polyposis, epidermoid cysts, osteomas and desmoids was thought to be a distinct syndrome, since the identification of the APC gene in the early 1990s this is now recognised as a FAP variant.

Dukes was among the first to outline the psychological and social facets of the disease. In 1952 he observed that ''in the study of polyposis scientific enthusiasm must always be tempered with sympathy and tact''. The same year he[28] presented results from 41 families in the St. Mark's Registry. Three years later, Reed and Neel (London, UK)[29] presented a genetic study that calculated the frequency of FAP to be 1:8,300.

In 1983, paediatrician Judith Kingston (London UK) et al. made the observation that children with hepatoblastoma frequently had a parent with FAP[30]. That same year surgeon Heikki Järvinen (Helsinki, Finland) et al. described biliary adenomas for the first time. Just two years later a review of the St Mark's Registry by Plail et al. revealed an association between FAP and papillary thyroid cancer[31]. However, this association was reported as early as 1968[32].

In the late 1950s, the psychological and social aspects to the condition were beginning to be appreciated. In 1958, Dukes described in detail the early years of education and psychology[33]. Social worker Anne Krush, who worked with LS pioneer Henry T. Lynch (Nebraska, US)[34] offered the first psychosocial guide to FAP 1965, and later Miller [35] would go on to describe the barriers to coping and adaptation faced by mutation carriers.

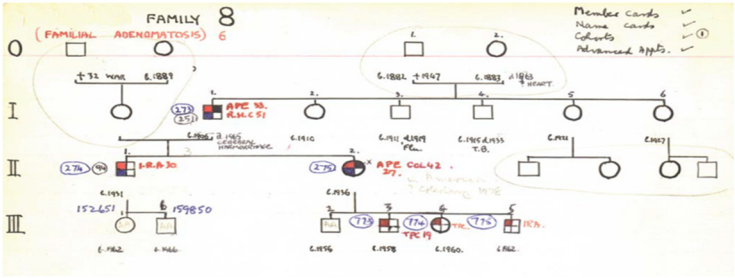


Figure 1-4: Example of one of Bussey's original polyposis pedigrees. [Reproduced by kind permission of St. Mark's Hospital, London, Prof. Sue Clark and Ms. Kay Neale.]

Success of St Mark's to the establishment of National Registries

The success of the St Mark's polyposis registry was evidenced by many international publications over this time and the role of "the Registry" was further expanded to include other necessary functions such as recall for surveillance and the provision of prophylactic surgery[1]. This resulted in increasing numbers of FAP patients being referred to St Mark's. The ensuing centralisation of care allowed the development of prospective research and suitable management strategies for these conditions. Following the success of this model a number of other similar registries were developed. Sweden was the first country to develop a national registry in the late 1950s, with the goal of promoting the screening of FAP[36]. There is ample evidence that patients with FAP cared for in the setting of a specialised registry have decreased incidence of colorectal cancer [37] and increased life expectancy [38,39].

Surveillance and Management of FAP

Post-operative surveillance

In a 1956 review of the St Mark's registry Lockhart-Mummery et al. observed that proctocolectomy with a straight ileoanal anastomosis was technically difficult. Colectomy with IRA was favoured as it preserved function and resulted in a ''probably small'' risk of rectal cancer, provided there was adequate surveillance. It was advised that the operation be carried out while patients were in their teens and that the anastomosis should be made at the level of the upper rectum[40]. Initial proctocolectomy or subsequent completion proctectomy was undertaken reluctantly because of the resulting permanent ileostomy.

Surveillance at this time was difficult due to the shortcomings of rigid sigmoidoscopy and the scarring of rectal mucosa from polyp removal via fulguration[41]. While the risk of developing rectal cancer after IRA varies from series to series, the St Mark's data demonstrated a CRC risk of 10% by the age of 50 years and 29% at 60 years[42]. In 1958, Dukes stated that if by the age of 40 there are no symptoms and sigmoidoscopy is negative, it is very unlikely that polyps will develop later[33]. On the basis of a pedigree study, Veale in 1960 outlined the need to examine all relatives in a polyposis family[43].

A greater appreciation of the phenotypes associated with FAP developed in tandem with advancements in medical technology. In particular, the development of fibreoptic endoscopes[44] enhanced the understanding of duodenal polyp development, while advances in cross-sectional imaging enabled greater characterisation and surveillance of

desmoids and adrenal adenomas[45]. As the availability of prophylactic surgery and surveillance increased, early deaths from CRC become rare; however, less frequent FAP-related malignancies and desmoids have become increasingly important causes of mortality[46].

Innovations in surgical technique

In the late 1970s and early 1980s, Parks et al.[47,48] in the UK and Utsunomiya et al.[49] in Japan reported the new technique of restorative proctocolectomy (RPC) and ileo-pouch-anal anastomosis (IPAA). This procedure seemed to offer a solution to the problem of CRC development after IRA[42]. However, IPAA is associated with greater morbidity, and a less satisfactory functional outcome[50]. There is also increased risk to male sexual function and female fertility[51]. Moreover, it is now evident that there is also a late risk of adenocarcinoma development[52]. Thus, many patients, especially those with attenuated FAP (AFAP), may be just as well served with IRA and endoscopic surveillance. In addition, surgery is increasingly being performed via minimally invasive techniques[53,54], making prophylactic surgery a more attractive option for young mutation carriers.

FAP Collaborative Groups

Leeds Castle Polyposis Group

Despite the success of polyposis registries and a growing interest in intestinal polyposis, many clinicopathologic and clinical questions remained well into the late twentieth century. One of these was how best to manage large abdominal desmoids. It was exactly this question that prompted St Mark's surgeon Ian Todd (London, UK) to convene an international meeting for clinicians with an interest in hereditary cancers at Leeds Castle in Kent in June 1985[55]. At the meeting researchers Sheila Ritchie and Kay Neale, both from St Mark's, were tasked with conducting a survey of worldwide polyposis registries in order to establish the global knowledge base. The resulting Leeds Castle Polyposis Group (LCPG) was the first major international collaboration in hereditary CRC[56].

The next meeting of the group took place two years later in Washington DC, hosted and personally funded by surgeon Jerome DeCosse (New York, US). Again, the meeting was deemed a success and it was decided that another should be held in the UK. By the time of this meeting in Worcestershire in 1989, the LCPG had almost doubled in size. By 1992, 51 centres around the world were involved, and a biennial meeting format was arranged that continues to this day, latterly under the International Society for Gastrointestinal Hereditary Tumours (InSIGHT) umbrella, after