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The history of familial adenomatous polyposis

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Introduction

The first convincing case of familial adenomatous polyposis was published 120 years ago, and in the first half of this period the disease was primarily described and managed by surgeons and pathologists. Since the discovery of the *APC* gene, familial adenomatous polyposis has changed into a disease, which is nowadays diagnosed, treated and controlled by a multidisciplinary team of specialists. This is undoubtedly the main cause of the exponential development of research into all aspects of the disease, which has taken place during the last two decades and has resulted in substantial improvements in treatment, survival and quality of life.

The aim of this article is to present a chronological review of the history of the disease.

Polypoid disease

The first known description of multiple colorectal polypoid lesions dates from 1721 and was published in Latin by Menzel in a medical journal from Berlin, Germany. He drew an 18-cm colonic segment with 15 wart-like mucosal and submucosal excrescences at a post mortem of a 15-year-old boy who died of dysentery [1]. The theme of polypoid projections was picked up again in 1832, when Wagner reported 20 tiny polyps as the sequelae of healed ulcers [2]. Rokitansky described the new thickened tissue forming the fibrous base from which rose projections, some of them small, some big, giving the originally rounded edges of the mucous lacunae a fringed, serrated appearance [3]. In 1847, Corvisart detailed hypertrophied features from the anatomy specimen of a 22-year-old male with more than 20 excrescences in the ascending colon. Interestingly, a colleague wondered about the malignant potential, only to be told by the author that no trace of cancerous change was to be found [4].

In that era, the purported sequence of events leading to polyps began with rectal haemorrhage, followed by mucosal prolapse, chronic inflammation, diarrhoea/dysentery, scarring, and follicular hypertrophy of the rectal mucosa (in fact this last was part of the ulcerative process). Lebert in 1857 described a 32-year-old female with a history of dysentery; autopsy showed hundreds of colorectal polyps with inflammation [5]. In 1859, a thesis on rectal polyps by Chargelaigue noted 2 living cases, both successfully treated with surgery, including a 16-year-old girl operated on by Robert for over 27 polyps and a 21-year-old male who had 80–100 polyps excised by Richet. In both cases, an early history of rectal bleeding or chronic diarrhoea was observed [6]. Autopsy case reports by Lebert and Luschka of diarrhoea-prone women in their early thirties with hundreds to thousands of polyps would come to be classified by the pathologist Virchow with a specific disease, colitis polyposa, and included Menzel's case [5, 7]. In 1863, Virchow found microscopic evidence of dilated crypts of Lieberkühn filled with mucous and the formation of retention cysts, which were later ascribed to the end stage of ulcerative colitis [8]. By 1881, Woodward classified pseudo-polyps in the submucosa of a 44-year-old female as the result of long-term inflammation, quite apart from colitis polyposa, where the mucosa between the polyps was normal. In fact, Woodward questioned whether Menzel's description did not better match that of pseudo-polyps and, though rare, was unrelated to carcinoma [9]. These early descriptions of "polyposis" are replete with misperceptions and misnomers but, clearly, histopathology remains the driving force in its evolution. Prior to the 1860s autopsy findings informed the literature but were observational in nature and linked to intestinal inflammation.

Adenomatous polyposis

Sklifasowski published the first histologically verified case of adenomatous polyposis in Russia in 1881 (Figure 1). He described a 51-year-old merchant with a history of 7 years of bloody diarrhoea and abdominal pain. Rectal examination revealed multiple excresences, and at operation with incision above the inguinal ligament and colotomy large polyps were removed. Histological examination showed multiple adenomas

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[10]. In 1882, attention would also turn toward the inherited predisposition for what Cripps termed "disseminated polypus of the rectum" on the basis of 20–30 adenomas in two affected siblings, aged 17 and 19, both of whom experienced rectal haemorrhage from prepuberty. The extreme rarity of multiple polypi, unlike the singular polyp, was emphasised [11]. Whitehead in 1884 presented a 21-year-old woman with a huge prolapsing rectal adenoma, which was resected. The patient became continent, despite the fact that the surgeon had "his arm beyond the elbow passed up the bowel" [12].

In 1887, Smith reported three affected siblings with microscopic features of soft, vascular, gland polyps called adenoid, one of which died of cancer at age 26 years. Although three affected siblings were remarked upon, no mention is made of an affected parent [13]. In 1890, Bickersteth [14] would also document an affected mother and her 11-year-old son along with the importance of this genetic connection. Bussey, however, found this case and that of Bickersteth more in keeping with juvenile polyposis [15], and, in general, the early diagnosis of adenoma may include cases of juvenile polyps as well as Peutz–Jeghers polyps. In 1890, Cripps [16] would go on to distinguish pedunculated disseminated adenoid polypi from the villous tumour with its premalignant potential. The same year Handford would confirm the association with cancer in his autopsy report of a 34-year-old woman, noting the absence of a family history of disease, setting the stage for more accurate histological investigation [17]. Dalton [18] in 1893 described a woman aged 28 years with a congenital predisposition to growth of multiple adenomas of the large bowel.

In 1895, Hauser [19] noted gastroduodenal polyps in a 33-year-old patient with multiple colorectal polyps, and histological examination showed no difference from the colorectal polyps. A severe prognosis due to malignant degeneration of the adenomas was stated in 1896 by Port [20], and in 1903 Zahlmann [21] found that only a local bowel resection was possible. In the first review of the literature in 1907, Doering [22] found 44 references to FAP. Among the patients reported, 31/37 had died from cancer. The first report of osteomas was made in 1912 by Devic & Bussy [23], and in 1916, Lillienthal [24] performed the first colectomy with ileosigmoidostomy in a 20-year-old patient who had an uneventful recovery.

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 ипрямой 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 состоянія кишекъ вообще; въ дѣйствительности же оно поддерживается мѣстнымъ патологическимъ процессомъ—почечуйнымъ перерожденіемъ слизистой оболочки прямой кишки. Почечуйное перерожденіе слизистой оболочки развивается въ самой нижней части прямой кишки, и рѣдко можно наблюдать расширеніе венъ выше, чѣмъ сантиметра на три надъ жомомъ (sphincter ani). Но воспалительные процессы и новообразованія могутъ распространяться выше по кишеч-

Figure 1. The first article on FAP by Sklifasowski [9].

Polyposis registry and prophylactic surgery

In 1925, Lockhart-Mummery stated that adenomas should be distinguished from inflammatory polyps, and that the hereditary factor in FAP is not cancer, but multiple adenomas having a marked tendency to undergo malignant change. On the basis of his early polyposis series the polyposis registry was established at St. Mark's Hospital (Figure 2) as the first in the world [25]. The first 3-stage proctocolectomy was performed in 1924 by Coffey [26].

In 1927, Cockayne [27] stated that FAP is inherited as a dominant condition, and Jüngling [28] recommended prophylactic sigmoidoscopy in the offspring of affected family members. In an extensive review, Dukes (Figure 3) named the condition "polyposis" and stated that pedigrees in a FAP family "are photographs: they record the state of affairs at a given point of time" [29]. In Leipzig, Nissen [30] published the first proctocolectomy with a straight ileoanal anastomosis, which was carried out in 1933 as a 3-stage procedure and (surprisingly) left the 10-year-old patient with normal solid stools. The first report of a periampullary cancer came from the Massachusetts General Hospital in 1935 [31].

In 1939, Lockhart-Mummery & Dukes published results from the St. Mark's Hospital Polyposis Registry, which included 10 families and the common use of prophylactic sigmoidoscopy. Five patients had a colectomy (Figure 4), and four had survived [32]. Fitzgerald published the first odontomas in 1943 [33], and in 1947, Ravitch & Sabiston [34] presented a rectal resection (pull-through procedure) and ileo-anal anastomosis carried out after a previous colectomy and ileorectal anastomosis. Lloyd-Davies carried out the first colectomy and ileorectal anastomosis at St. Mark's Hospital in 1948 [35]. In 1950, Halsted et al. [36] described the first patient with gastric polyposis diagnosed by gastroscopy, and according to the description this may represent the first case of fundic gland polyposis, but no histology was reported.

Extracolonic manifestations – Gardner's syndrome

In 1951, Gardner [37] (Figure 5) described what was later termed "Gardner's syndrome" including colorectal adenomas, desmoid tumours, bone tumours, and soft

Figure 2. The old St. Mark's Hospital at City Road.

cyst-like surface tumours. Dukes was the first to describe the psychological aspects of the disease in 1952 and stated that "in the study of polyposis scientific enthusiasm must always be tempered with sympathy and tact" [38] Furthermore, in this article Dukes presented his poetic visions about future gene therapy:

> You are old, Father William, the young surgeon said,
> And your colon from polyps is free.
> Yet most of your sibling are known to be dead –
> A really *bad* family tree.
> In my youth, Father William replied with a grin,
> I was told that a gene had mutated,
> That all who carried this dominant gene
> To polyps and cancer were *fated.*
> I sought for advice from a surgical friend,
> Who sighed and said – Without doubt
> Your only escape from an untimely end
> Is to have your intestine right *out*.
> It seemed rather back luck – I was then but nineteen –
> So I went and consulted a quack,
> Who took a firm grip on my dominant gene
> And promptly *mutated it back*.
> This, said the surgeon, is something quite new
> And before we ascribe any merit
> We must see if the claims of this fellow are true,
> And observe what your *children* inherit!

The same year Dukes [39] presented detailed results based on 156 cases from 41 families in the St. Mark's Hospital Polyposis Registry. In 1955, Reed & Neel [40] presented a detailed genetic study and calculated the frequency at birth to be 1:8,300.

Figure 3. Cuthbert Dukes.

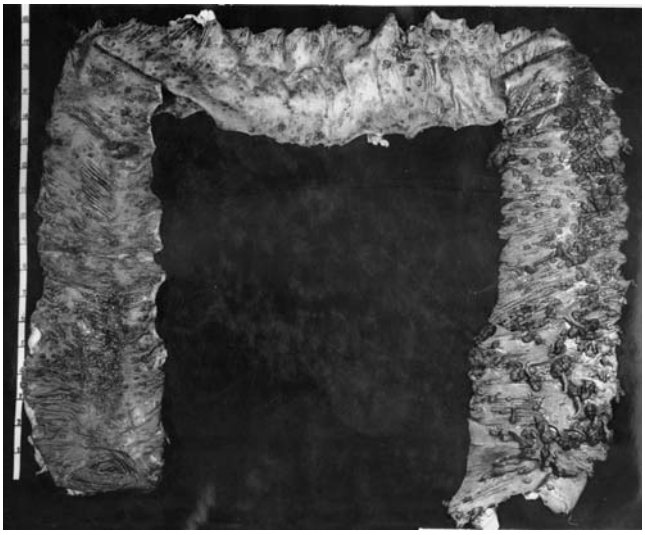

Figure 4. Old colectomy specimen from St. Mark's Hospital.

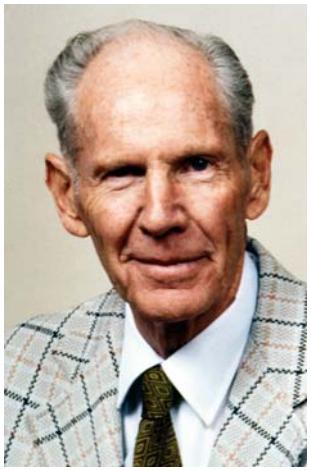

Figure 5. Eldon Gardner.

Lockhart-Mummery et al. reviewed the surgical treatment in 1956 on the basis of the St. Mark's series. Proctocolectomy with a straight ileoanal anastomosis was considered technically difficult with a high risk of complications and unsatisfactory functional results, whereas colectomy with an ileorectal anastomosis resulted in a "probably small" risk of rectal cancer, provided there was adequate supervision every 3–4 months. The operation should be carried out in the teens and the anastomosis should be made 10–12 cm above the anal verge [41]. Hubbard [42] noted spontaneous regression of rectal adenomas after colectomy and IRA in 1957. 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. The article described in detail the early years of education and psychology [43]. On the basis of a pedigree study, Veale in 1960 stated the necessity of examining all accessible relatives in a polyposis family [44]. Morson [45] presented a new histopathological classification of colorectal polyps in 1962, and, in the same year, dental abnormalities were diagnosed by Fader et al. [46]. Drobni [47] published a one-stage proctocolectomy with a pull-through anal ileostomy in 1964, and Camiel et al. [48] presented the association with thyroid carcinoma in 1968.

Nationwide registration and a new surgical option

In 1975, Bussey [49] (Figure 6) published his comprehensive thesis on the basis of the St. Mark's series, which was based on his meticulous recording of the families (Figure 7) and became a milestone in the FAP literature. Utsunomiya & Nakamura [50] reported the finding of multiple subclinical mandibular osteomas detected by pantomography. In the same year Alm in his thesis presented the results of the national registration in Sweden and calculated an incidence rate of 1:7,646 [51]. In 1977, Yao et al. [52] published the first series of patients with endoscopically diagnosed duodenal adenomas, and Watanabe et al. [53] described fundic gland polyposis in 1978. In 1979, Hamilton et al. [54] published the first report of ileal adenomas after colectomy.

In 1980, Parks et al. [55] and Utsunomiya et al. [56] simultaneously presented a new surgical procedure: restorative proctocolectomy with mucosectomy and ileo-pouch-anal anastomosis. Blair & Trempe [57] described congenital hypertrophy of the retinal pigment epithelium (CHRPE) in 1980. Baron & Lee [58] introduced CT scan for the evaluation of mesenteric desmoid tumours in 1981, and the combination of an NSAID (clinoril) and tamoxifen was presented by Waddell et al. [59] as a treatment for a desmoid tumour. Kingston et al. [60] described the association with hepatoblastoma in 1983, and Järvinen et al. [61] described biliary adenomas in 1983. Krush et al. [62] offered the first psychosocial guide to FAP, and Miller et al. [63] described barriers to coping and adaptation. Bülow [64] published the first calculations of national survival rates in 1986.

The *APC* gene

In 1986, Herrera et al. [65] presented the possible association to a deletion in chromosome 5q, and in 1987, Bodmer et al. and Leppert et al. [66, 67] independently presented the location of the *APC* gene at chromosome 5q21–22. The Leeds Castle Polyposis Group (LCPG) was established in 1985 as an international research forum [68], and a multicenter LCPG study described the prevalence of upper gastrointestinal malignancy [69]. Tops et al. [70] presented presymptomatic diagnosis on the basis of DNA markers in 1989, and Spigelman et al. [71] published a new staging of duodenal adenomatosis, which was later named the Spigelman Classification. In 1990, Neal & Berrey [72] introduced MRI scanning for the evaluation of growth of a desmoid tumour, and textbooks were published by Herrera [73] and by Utsunomiya [74]. In 1991, Groden et al., Kinzler et al. and Joslyn et al. [75–77] characterised the APC gene in detail. Screening guidelines for molecular genetic diagnosis were published in 1991 by Petersen et al. [78], and Bradburn et al. [79] introduced the detection of microadenomas in the diagnosis of FAP. Tsukuda reported the use of systemic cytotoxic chemotherapy for desmoids [80]. In 1992, a murine FAP model (min mouse) was introduced by Su et al. [81], and Nugent & Phillips [82] stated that the risk of rectal cancer after ileorectal anastomosis was sharply rising after age 50. Levitt et al. [83] explored coping styles and highlighted problems such as cancerophobia. Spirio et al. [84] found that an attenuated form of FAP was linked to the APC locus, and in 1993 Nugent et al. [85] described the development of adenomas in the ileoanal pouch. A European Union research group (EuroFAP) published guidelines for the establishment of polyposis registers [86].

Figure 6. H. J. R. Bussey in the Polyposis Registry.

The latest decade

Olschwang et al. [87] published the first reported evidence of a genotype-phenotype correlation in 1994, and Giardiello et al. [88] presented sulindac as treatment for colorectal adenomatosis. Bertoni diagnosed jejunal polyps by push-enteroscopy [89]. In 1994, Lynch et al. [90] described the effect of doxorubicin and dacarbazine on unresectable desmoids, and Hoehner & Metcalf [91] described a carcinoma of the ileoanal anastomosis after restorative proctocolectomy. Also the use of the protein truncation test as a rapid method for the detection of an *APC* gene mutation was presented by van der Luijt et al. [92]. In the same year Phillips, Spigelman and Thomson from St. Mark's Hospital published the most recent textbook on all major aspects of FAP [93]. In 1995 the APC protein product was identified by Rubinfeld et al. [94], and Chung et al. [95] described the pancreas-sparing duodenectomy as a cancer prophylactic procedure for severe duodenal adenomatosis. Lynch et al. [96] published the first report of an attenuated subgroup of the disease, which is now known as attenuated familial adenomatous polyposis (AFAP). Vasen et al. [97] presented molecular genetic testing as a possible guide to surgical decision making (ileorectal anastomosis versus ileoanal pouch) in 1996, and in the same year Healy et al. [98] published the first report of MRI scan for evaluation of the growth of a desmoid tumour.

In 1997, Milsom et al. [99] reported a laparoscopic colectomy with ileorectal anastomosis, and in 1998, Clark et al. [100] described the identification and progression of a desmoid precursor lesion. Steinbach et al. [101] described the effect of celecoxib on colorectal and duodenal adenomatosis in 2000. In 2002, Groves et al. [102] presented an evaluation of the risk of duodenal carcinoma, and Costamagna et al. [103] reported the diagnosis of ileal polyps detected by video capsule endoscopy. In 2003, Olsen et al. [104] demonstrated a reduced fertility after restorative proctocolectomy; Sieber et al. [105] and Sampson et al. [106] independently demonstrated that mutations in the MYH gene predispose to a recessive phenotype with multiple colorectal adenomas similar to AFAP, and Middleton et al. [107] demonstrated a stepwise progression of desmoid precursor lesions by a CT-scoring system. In the same year Burn et al. [108] presented the effect of resistant starch and aspirin on colorectal adenomas (CAPP 1 Study), and the Leeds Castle Polyposis Group and the International Collaborative Group for HNPCC merged into the International Society of Hereditary Gastrointestinal Tumours (InSiGHT) [109]. In 2004 Crabtree et al. [110] demonstrated the evidence of modifier loci for the severity of colonic adenomatosis, and Bülow et al. [111] presented a prospective evaluation of the natural course of duodenal adenomatosis.

It is impossible to document here all the publications on FAP over the years. To those we have omitted we

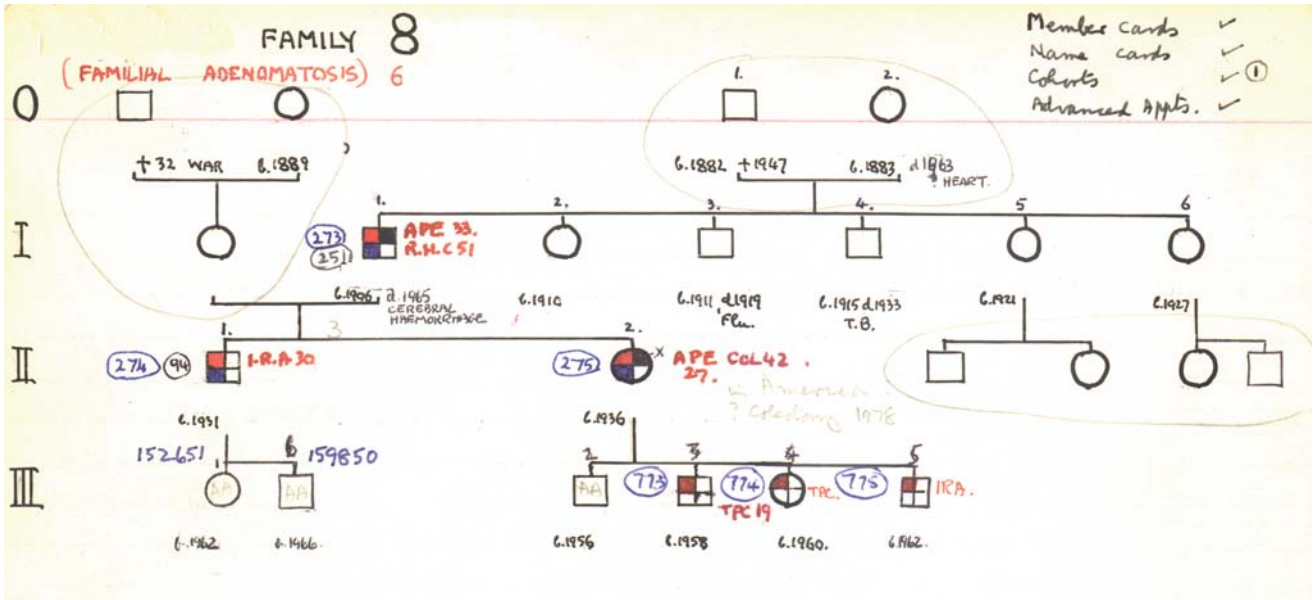

Figure 7. One of Dr. Bussey polyposis pedigrees.

offer our apologies. We have tried to represent all major advances in knowledge and understanding of the condition. It is, however, interesting to note that the truth contained in Dukes' statement of 1958 has not been altered, "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" [43].

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