Familial polyposis coli: heterogeneous polyp expression in 2 kindreds¹

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SUMMARY We describe 2 extended kindreds supposedly manifesting familial multiple adenomatous polyposis coli (FPC), but which show marked heterogeneity in the phenotypic expression of colorectal adenomatous polyps. In one family, 2 individuals had diffuse polyposis at very early ages (7 and 10 years), while 6 others (aged 23 to 72 years) had solitary polyps only. Of the patients with solitary polyps, 2 had associated colonic malignancies (ages 26 and 35), while another had a prophylactic colectomy performed at age 46. In the second family, 5 of the 11 patients with evidence of polyps showed the classical presentation of FPC, while the remainder showed marked phenotypic variation.

The marked variability in frequency and location of colon polyps points to the need to reassess our traditional criteria for diagnosis of FPC. The high risk of early onset colon cancer in patients from these families who have the most minimal manifestation, namely isolated polyps, recommends more careful scrutiny of supposedly unaffected members of all FPC kindreds.

Descriptions of familial adenomatous polyposis of the colon (FPC) show the classical phenotype as including myriad adenomatous polyps along the entire length of the colon and rectum. Affected patients who do not undergo prophylactic colectomy have a virtual 100% likelihood of developing colon cancer by the age of 50 (Bussey, 1975). Recently, the clinical spectrum of FPC has been expanded to include associated syndromes (Gardner's, Turcot's, and others) in which adenomatous polyps occur in the colon and occasionally throughout the gastrointestinal tract and/or which are distinguished by benign and malignant neoplasms of other anatomical sites (Yonemoto *et al.*, 1969).

To the extent that limited polyp expression occurs among supposed 'polyposis' patients, more reliable minimal diagnostic criteria characterising the phenotype will be required before the polyposis coli genotype and its cancer proclivity can be inferred. In this report we describe 2 extended kindreds showing such variable clinical expression of adenomatous polyps, ranging from the so-called classical presentation of FPC to the occurrence of only occasional or solitary adenomatous polyps in the colon.

Materials and methods

Two families (C-205, C-210) were studied in accordance with medical-genetic protocols used for acquisition of detailed genealogical and medical history. Particular emphasis was given to thorough description of the number and anatomical distribution of adenomatous polyps in the colon and other areas of the gastrointestinal tract, as well as their association with carcinoma of the colon and other anatomical sites. Questionnaires were used for the initial gathering of historical data. Signed permission forms helped in the retrieval of primary hospital, physician, and pathology records. In spite of the high rate of successful medical record retrieval in these families, a number of the medical and pathology documents contained either limited or imprecise descriptions: for example, 'huge' polyps (no precise measurements given); polyps located at the 'lower section' of the colon; or polyps described as 'multiple' but lacking more accurate quantification. These, of course, are shortcomings inherent in the retrospective method of such family studies. Consequently, classification of patients as having either isolated or diffuse polyps at a given time has in some cases been tentative and arbitrary, reflecting the incomplete and occasionally imprecise descriptions in available medical records.

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Fig. 1 Pedigree of family C-205.

Results

For purposes of brevity, much of the clinical and pathological description of pertinent conditions affecting members of kindreds C-205 and C-210 have been deleted.¹ Extended pedigrees of the subject families are shown in Fig. 1 and 2. Table 1 summarises the findings regarding age of onset for isolated and diffuse polyps, and for colon cancer in the 2 kindreds.

Fig. 3 shows the pooled cumulative age distributions of diagnosis of isolated or diffuse polyps in the 2 subject pedigrees. Both pedigrees show extreme variability in the age at which polyps were initially detected. Family C-205 had a mean onset of 28 years, with a range of 5 to 72 years. Family C-210 had a mean onset of 24 years, with a range of 14 to 53 years. In each pedigree, the occurrence of colorectal polyps spans at least 3 generations, and the age at diagnosis becomes progressively earlier in each

¹Extensive tumour registries for these families (with diagrams showing temporal polyp progression) are available from the authors on request.

Table 1 Age of onset of isolated and diffuse polyps and colon cancer in families C-205 and C-210.

Family	Isolated polyposis		Diffuse polyposis		Colon cancer†	
	No.	Age of onset	No.	Age of onset	No.	Age of onset
C-205	8	27.8	2(2)*	9	3	24.3
C-210	8	23.5	6(3)*	25	4	33.5
C-205 and C-210	16	25.6	8(5)*	21	7	29.5

*() Patients diagnosed previously with isolated polyps.

†Including carcinoma in situ of polyps.

successive generation. This latter phenomenon is probably due, at least in part, to the increased awareness of premalignant features in the younger patients, namely the appearance of isolated polyps in the colon.

Fig. 3 also contrasts the cumulative age of onset distribution of initial colon polyps in the 2 subject pedigrees with that of diffuse polyps in familial polyposis coli. The age of onset curve for FPC is based upon figures for 281 pathologically confirmed cases of FPC (Bussey, 1975). The curves reflect

Fig. 2 Pedigree of family C-210.

Fig. 3 Age of onset of isolated polyps in families C-205 and C-210 (pooled) and of diffuse polyps in patients with FPC. 1, 2, and 3 denote onset of isolated polyps in progenitors, their progeny, and grandchildren, respectively. * = onset of diffuse polyposis in FPC.

earlier diagnosis of isolated polyps in the subject families, preceding diagnosis of diffuse polyps in FPC by a span of about 10 years, consistent with generally accepted notions regarding the temporal progression from isolated polyps of the distal colon to diffuse polyps in the entire large bowel. This does not imply that it always takes 10 years for isolated polyps to increase in number to a pattern resembling diffuse polyposis coli. Indeed, affected members of the subject pedigrees show extreme variability in the interval of time between diagnosis of isolated polyps and later symptoms of either diffuse polyps or cancer. This ranges from probably less than 2 years (patient V.1, family C-205), to those patients highlighted in this report who will probably never develop diffuse polyposis (patient IV.3, family C-205, developed one polyp 21 years ago).

The most extreme heterogeneity in polyp expression is seen in family C-205. For our purposes, the putative syndrome progenitor is considered to be patient III.4 who had only isolated polyps occurring at the advanced age of 72. Her husband died of a myocardial infarction at 56, with no known personal or family history of gastrointestinal disorders. Though 4 of their 5 children had isolated polyps, a fifth (IV.5) had diffuse polyposis of the colon at age 10, and a grandson (son of isolated polyp patient IV.1) was similarly affected at age 7.

Discussion

The first familial description of FPC was by Cripps in 1882. Its cancer association was established by Handford in 1890. Research into the aetiology and control of this disease was facilitated by the establishment of the St. Mark's Hospital (London) registry of families with FPC by Lockhart-Mummery (1925). Families comprising this registry have been described by others (Lockhart-Mummery, 1925; Dukes, 1930; Veale, 1965; Bussey, 1975). Dukes (1951) recognised variability in the clinical expression of adenomatous polyps in FPC families, but emphasised a narrow set of criteria for its classical presentation: onset of isolated adenomatous polyps by approximately age 20, usually in the rectum and sigmoid colon, followed by a fairly rapid increase in number, to cover most or all of the colon by age 30. This, if untreated by colectomy, is then followed almost invariably by colonic cancer, generally by age 40 or 45. Because this phenotype has generally been regarded as a clearly defined entity, FPC has frequently been cited as a model for the study of hereditary cancer predisposing disease (Dukes, 1930).

With increasing interest in FPC, attention gradually became focused upon kindreds with extracolonic associated features. This in turn led to the supposition

that distinct clinical entities exist, consistent with genetic heterogeneity (McKusick, 1969). Gardner and Stephens (1950), in describing the triad of polyposis coli, osteomas, and sebaceous cysts (Gardner's syndrome), were among the first to describe the sometimes multifaceted clinical associations in this syndrome. The genetic basis for several other polypoid disorders with extracolonic manifestations has been explored by many investigators, though debate continues over the question of whether Gardner's syndrome and FPC are distinguishable genetic entities (Utsunomiya and Nakamura, 1975; Danes *et al.*, 1977).

The extensive phenotypic features seen in the disorders listed in Table 2 contrast sharply with the observation of familial aggregation of solitary polyps in a single extended pedigree (Woolf and Gardner, 1950; Woolf *et al.*, 1955). These authors considered the aggregation of solitary polyps to be a distinct genetic entity, rather than the result of incomplete penetrance of the polyposis gene. This supposition was undoubtedly reinforced by the absence of diffuse polyposis coli in any patients from the family.

Maintenance of the clear distinction between FPC and the described solitary colorectal polyp syndrome (McKusick, 1962) has been made difficult by our observation of the 2 families which include both patients with diffuse polyposis coli (classical FPC) and patients with only solitary polyps, but in whom the colon cancer predisposition appears to be equally high.

Variation in the phenotypic presentation of polyps in a kindred raises a question as to the minimal frequency and/or distribution of colon polyps required to establish an FPC diagnosis. In other words, is there some arbitrary minimum number of polyps and/or a particular anatomical site distribution required for securely establishing the FPC diagnosis (and, hence, genotypic status)? As recently as 1970, it was stated (Morson and Bussey, 1970) that in polyposis coli 'evidence suggests that there are never fewer than about 200 polyps', though 100 may be a more generally accepted figure. In a family which has members with known diffuse polyposis and others with only isolated colonic polyps, this distinction is particularly critical since reliance upon an arbitrary minimum number may cause the physician to overlook the potentially harmful character of isolated polyps, if they should in fact represent limited expression of FPC in carriers of the deleterious gene.

Conversely, it is known that more than 5% of the adult American population have one or more solitary polyps (Swinton, 1954; Myers and Bacon, 1960). Therefore, the indiscriminate assumption that isolated polyps in a first degree relative of an FPC proband necessarily represent reduced penetrance

Table 2 Genetic disorders which include colonic polyps. (In all of the following, mode of genetic transmission known or presumed to be autosomal dominant.)

Disorder (common name)	Usual features and differential diagnosis	Cancer association
(1) Familial multiple adenomatous polyposis (many other names)	Diffuse covering of colon and rectum with adenomatous polyps; onset between 10–20 years of age most common (we question the invariability of this phenotype)	Carcinoma (often multiple) of the colon at a significantly early age
(2) Gardner's syndrome	Adenomatous polyposis involvement as in no. 1, though greater variability in expression generally acknowledged. Distinguished from no. 1 by presence of sebaceous cysts, osteomas (generally of cranium, mandible, and long bones), abnormal dentition (supernumerary and impacted teeth), fibromas (usually abdominal), desmoid tumours and incisional scarring (keloids)	Carcinoma of the colon, mesenteric tumours of abdomen, possibly others
(3) Turcot's syndrome* (Turcot <i>et al.</i> , 1959)	Adenomatous polyposis involvement as in no. 1. Distinguished by presence of brain or spinal cord tumours	Carcinoma of colon, brain tumours
(4) Generalised gastrointestinal polyposis (many reports)	Diffuse adenomatous polyposis of entire gastrointestinal tract. May be result of more careful scrutiny of patients believed to have FPC	Carcinoma of colon, stomach, and, to lesser extent, small bowel and oesophagus
(5) Juvenile polyposis with mixed adenomatous polyp involvement	As reported by Stemper <i>et al.</i> (1975), family whose members showed variable expression of juvenile and adenomatous polyps	Carcinoma of colon
(6) Hereditary isolated polyps (Woollf <i>et al.</i> , 1955; Lynch <i>et al.</i> , 1977, 1978)	Isolated polyps of colon, usually fewer than 10 in number	Carcinoma of colon, possible proximal colon predilection
(7) Peutz-Jegher's syndrome (Jeghers <i>et al.</i> , 1949)	Generalised gastrointestinal hamartomatous polyposis, particularly small bowel. Melanin spots of mucosal surfaces and distal phalanges; occasional adenomatous polyps	Traditionally considered benign condition, though cancer, particularly of the duodenum and ovary (Christian 1971) have been reported
(8) Mixed solitary and diffuse polypst	Variable polyp expression, possibly related to no. 1 or no. 6	Carcinoma of colon
(9) Multiple polyposis and sarcomas (Fraumeni <i>et al.</i> , 1968)	Multiple adenomatous colonic polyposis with an excess of sarcoma (in one kindred); may be variant of Gardner's syndrome	Carcinoma of colon, sarcomas

*May be recessively inherited.

†Subject of this report.

of the polyposis coli gene must be avoided. Consequently, in the absence of reliable biological markers and/or distinguishing physical signs signifying the genotypic status (as in Gardner's syndrome), it may not be possible to discriminate between those patients who may have reduced penetrance of the FPC gene (yet with high colon cancer risk) and the patient who is free of the deleterious gene, but has sporadic polyps of an unknown aetiology. Patients whose genetic cancer risk is uncertain may one day be reliably distinguished through such markers as the colonic mucosa proliferation index (Lipkin and Deschner, 1976).

The description of families with variable polyp expression has been hampered by the reluctance or inability of many investigators to focus on the problem of heterogeneity *per se*. This has been due in part to: (1) inadequate or non-existent surgical pathological description of the quantity, distribution, and histological classification of colonic polyps, particularly in patients affected before the advent of modern diagnostic and surgical techniques; and (2) uncritical acceptance by geneticists and clinicians of such inadequately documented cases to which diffuse polyposis with its genetic implication is evidently ascribed.

Asman and Pierce (1970) reported a large kindred which included 8 patients categorised as having 'deduced polyposis', that is, those who died of colon cancer and had a child with polyposis, notwithstanding the fact that records of the patients with 'deduced polyposis' showed no documented evidence of this trait. They also described a class of 'polyposis carriers', that is, those having no clinical evidence of a gastrointestinal tract disorder, but who had children with polyposis.

The survey of the St. Mark's polyposis registry (Dukes, 1951) showed colonic polyposis in only about 60% of the patients with colorectal cancer. Furthermore, there was insufficient description of cases of 'polyposis' to determine how many of these patients definitely exhibited the classical phenotype.

Bussey (1975), using more recent data from the St. Mark's registry, established 5 classes of 'polyposis' patients, according to criteria similar to that of Asman and Pierce (1970). Four of the 5 classes of patients (about half of the subject population) lacked histological evidence of polyposis, but were included because of symptoms consistent with it, that is, colon cancer or polyps of unknown histological status and/or pedigree relation to a known affected patient. In terms of genotype status such

classifications may be valid; nevertheless, inferences about their phenotype must be made with caution.

The marked heterogeneity of polyp expression in families has led to the establishment of at least one genetic model to explain this variability. Veale (1965) has proposed a model in which one of three allelic genes may occur at a particular gene locus: P (classical polyposis); p (recessive, causing only solitary polyps in the pp state), and x (normal). The observation of multiple polyposis and isolated polyps in a single sibship could thus be explained in terms of segregation of P, p, and x alleles.

Critical analysis of actual pedigree data, however, suggests three limitations in this simple genetic model. (1) The portion of family C-205 shown in Fig. 1 shows a mother (III.4) known to have only solitary polyps (putative pp), and a son (IV.1) with classical polyposis (putative Pp or Px). Assuming that the contribution of a P from the father is excluded and reduced penetrance of a P in the mother is ruled out, those elements of Veale's hypothesis which attribute isolated polyps to a Mendelian recessive gene would have to be largely refuted. In other words, segregation of P, p, and x alleles in this kindred would be impossible in the light of the known polyp expression in several members. Thus, our data suggest that variable penetrance of the dominant P gene is a more valid (though obviously less elegant) explanation of the patterns seen in these pedigrees. (2) Veale's model could not explain the apparent dominant transmission of solitary polyps in families reported previously (Woelf *et al.*, 1955). Furthermore, in our own family 'R' (Lynch *et al.*, 1977, 1978) there were 34 cases of gastrointestinal tract carcinoma (only 4 of which were by history alone). None of the more than 20 patients for whom adequate pathological description was available had more than 10 polyps located in the colon. Yet, autosomal dominant transmission of colon cancer has been supported through genetic analysis (Lynch *et al.*, 1977, 1978), and more recently by segregation analysis (R. C. Elston *et al.*, 1978, unpublished data) using maximum pedigree likelihood methods (Elston and Stewart, 1971). (3) The high degree of verification required for reliable classification (polyposis versus isolated polyps versus normal) is extremely difficult, if not impossible, to obtain on a retrospective basis for more than two consecutive generations (as our own somewhat arbitrary categorisations have shown).

It is noteworthy that in family C-205, the progenitor female (Fig. 1, III.4) exhibited findings so minimal (isolated colonic polyps at the advanced age of 72, and with a negative family history) that one might legitimately doubt her status as a gene carrier. Her husband, who died at 56 of a myocardial

infarction and who had a negative family cancer history, was also unlikely to be such a carrier. Germinal mosaicism has been suggested (McKusick, 1969) as a possible genetic mechanism in pedigrees exhibiting such patterns of expression (that is, an unaffected parent with 2 or more affected children, who, in turn, transmit the trait as an autosomal dominant). The mutation would occur during the embryonic life of the patient, but would only affect the primordial oocytes or spermatogonia, and not somatic tissue. The parent would thus appear normal while transmitting the deleterious gene to some (or, as in this case, all) progeny.

In conclusion, the variable colon polyp expression described in the 2 subject kindreds raises several issues which have serious implications for patient management. Therapeutic and cancer surveillance options which could be presented to the patient include: (1) prophylactic colectomy in the presence of isolated colon polyps, notwithstanding a degree of uncertainty as to the patient's genotypic status; (2) longitudinal surveillance by periodic colonoscopy and/or barium enema with air contrast, and biannual evaluation for occult blood in the stool, with consideration given to eventual prophylactic colectomy should polyps show a progressive increase in number and/or size approaching the classical features of FPC.

We believe that our data, while limited to only 2 families, indicate the need for a more careful description of clinical signs, particularly the number, site, and distribution of colon polyps in high risk patients from families with a tendency to colon cancer and/or so-called classical FPC. These data also clearly show the need for research into the development of reliable biological markers to aid the recognition of genotype status and hence colon cancer risk.

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