FAMILIAL POLYPOSIS OF THE COLON

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Familial polyposis of the colon is the commonly accepted name given to a condition which should, perhaps, be more properly termed 'familial or hereditary adenomatosis of the colon and rectum'. It is a comparatively rare disease but an important one because of the development of malignancy. It is a congenitally installed disease as the polyps develop at a variable time after birth.

At Groote Schuur Hospital three White families are being investigated.

FAMILY I

This is the largest family of the three and comprises approximately 350 individuals. It is one of the largest families with this condition ever discovered.

The propositus was a 39-year-old woman, Mrs. A. W., IIIG, who was found to have carcinoma of the rectum extending down into the anal canal. Polyposis was unsuspected until the colostomy was opened at the conclusion of the abdomino-perineal resection on 30 October 1964 when the polyps were discovered. Subsequently the remaining portion of the colon was removed and an ileostomy performed on 7 January 1965.

Investigation of the family was then commenced. Several members of the preceding generation had died of 'cancer' between the ages of 35 and 47; IIA at 36, IIB at 35, IIC at 37, IID at 43 and IIE at 47. As can be seen from the family chart (Fig. 1) some of the children of these people have developed polyposis except IIB's descendants who have yet to be traced and examined. It is reasonable to conclude that the deaths were almost certainly due to carcinoma superimposed on polyposis of the colon, and that certainly they were the carriers of the polyposis gene.

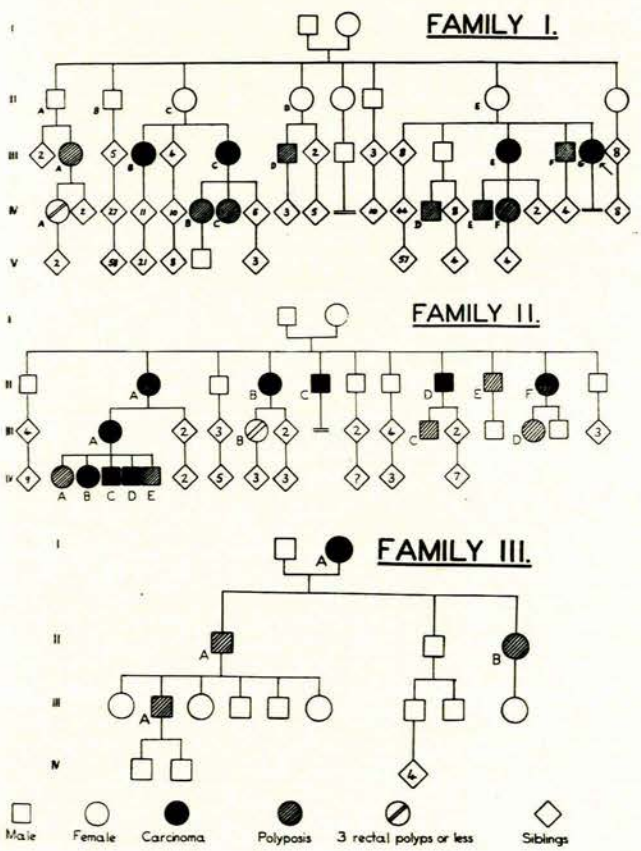


Fig. 1. Family charts. See text.

Two members of the same generation as the propositus had died of carcinoma of the rectum, verified by the death certificates—IIIC at 33 and IIIE at 42.

The family was traced back to the couple IA and B. The man died at 37 of unknown cause, the woman at 96. It is most unlikely that the woman had polyposis. The man's relatively early death may have been due to polyposis and carcinoma. Alternatively, they were free of the disease, but one of them developed the polyposis mutation which was then transmitted to the next generation as a dominant trait.

Of the 43 members of the family thus far examined, 9, possibly 10, members apart from the propositus have been discovered to have polyposis, one with carcinoma. The following are brief reports of these cases.

1. Mrs. L.L., 54, IIIA. This patient gave a history of change in bowel habit over the past 3 years with periods of diarrhoea and constipation, without blood or mucus *per rectum*. For the past 5 years she has had intermittent right-sided abdominal pain, and over the past 20 years had lost 20 lb. in weight.

Sigmoidoscopy to 25 cm. showed small, scattered polyps, and barium enema showed diffuse polyposis of the colon but no evidence of carcinoma.

Despite entreaties to undergo operation the patient has thus far refused.

2. Mrs. H.K., 27, IVA. This lady, the daughter of Mrs. L.L., has no symptoms. On sigmoidoscopy to 16 cm. 3 small polyps were seen. A barium enema was ordered but the patient has not attended for the investigation.

3. Mrs. H. van R., 63, IIIB. This lady was interviewed but refused examination. Some months later she presented with one month's symptoms of change in bowel habit to the Karl Bremer Hospital. A barium enema showed diffuse polyposis and a carcinoma of the splenic flexure. A panproctocolectomy and ileostomy were performed in December 1965.

4. Mrs. H.H., 20, IVB. This patient with glucose-6-phosphate dehydrogenase deficiency had no symptoms. Her mother, IIIC, had died of carcinoma of the rectum with secondaries at 33.

Sigmoidoscopy to 23 cm. showed small, scattered polyps, and barium enema showed diffuse polyposis of the colon. Colectomy and ileo-rectal anastomosis were performed on 7 July 1965. The specimen showed no evidence of malignancy.

5. Miss E.L., 18, IVC. The sister of Mrs. H.H., she complained of passing mucus *per rectum* for 6 months. Sigmoidoscopy to 20 cm. showed diffuse polyps. Barium enema was normal. Colectomy and ileo-rectal anastomosis were performed on 19 May 1965. The colon was diffusely involved with very small polypi (Fig. 10). There was no evidence of malignancy.

6. Mr. C.P., 51, IIID. This patient had no symptoms. His mother, IID, had died of 'cancer of the stomach' at 43. Sebaceous cysts had been removed from the neck and dorsum of the hands many years before. Sigmoidoscopy to 25 cm. and a barium enema showed diffuse polyposis. A barium meal and follow-through examination was normal. Colectomy and ileo-rectal anastomosis were performed on 1 December 1965. Four months after the operation the rectum was clear of polyps.

7. Mr. C.G., 21, IVD. This patient had no symptoms. Sigmoidoscopy to 20 cm. and barium enema showed diffuse polyposis. He is awaiting operation.

8. Mr. K.P., 27, IVE. This patient's mother died at 42 of carcinoma of the rectum. He gave an 18 months' history of intermittent bleeding *per rectum*. There was a small sebaceous cyst on the left forearm. On rectal examination a large polyp was palpable, and sigmoidoscopy to 20 cm. showed many

polyps, some quite large. A barium enema was not performed as he was returning to the Transvaal. Operation was advised and it has since been learned that colectomy and ileo-rectal anastomosis were performed in Johannesburg.

9. Mrs. M.M., 23, IVF. The sister of Mr. K.P. For 3 months in 1961 she had passed, intermittently, blood and mucus *per rectum*. She also had numerous lumps on the head, body and limbs since she was a child. Examination confirmed the presence of many surface tumours—sebaceous cysts, lipomas and ill-defined hard tumours (Figs. 2 - 6). Sigmoidoscopy to 23 cm. and barium enema showed diffuse polyposis. A skeletal X-ray survey was performed and X-ray of the mandible showed an almost edentulous jaw with 2 dentigerous cysts and an area of increased bony density (Figs. 7, 8). A colectomy and ileo-rectal anastomosis were performed on 22 December 1965. The specimen showed no evidence of malignancy.

10. Mr. F.G., 46, IIIF. The brother of the propositus. He had occasional loose stools over the previous few years with blood and mucus *per rectum*. Sigmoidoscopy to 21 cm. and barium enema showed diffuse polyposis. On 28 April 1965 colectomy and ileo-rectal anastomosis were performed. There was no evidence of malignancy in the colon specimen.

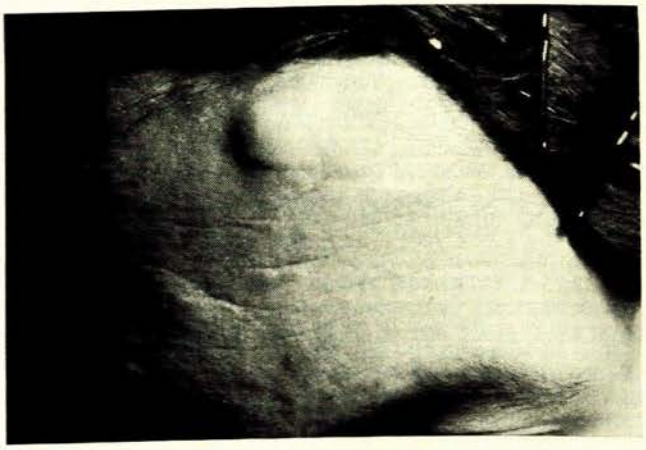


Fig. 2

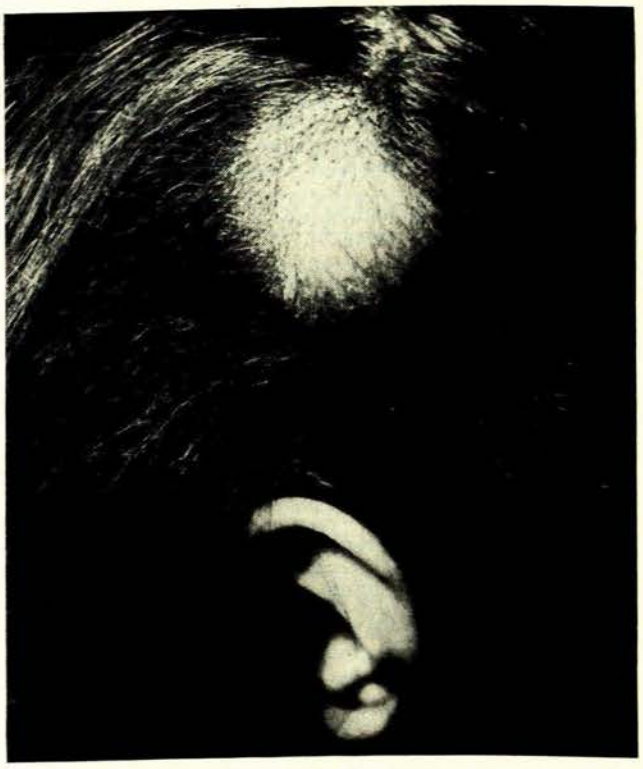
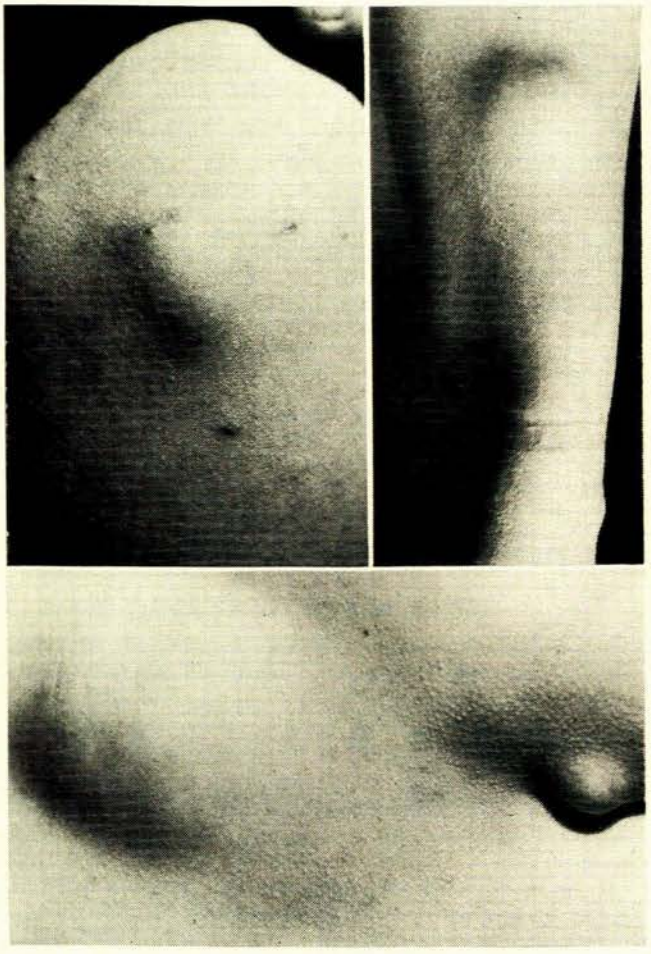


Fig. 3

Figs. 2 and 3 show a keloid above right eyebrow and sebaceous cysts of the forehead and scalp



Figs. 4, 5 and 6 show sebaceous cysts and lipomas on the upper arm, forearm, dorsum of wrist, and over the sacrum and at the natal cleft.

Of the 11 cases, 2 had carcinoma, and panproctocolectomy and ileostomy were performed. Five cases have been subjected to colectomy and ileo-rectal anastomosis at Groote Schuur Hospital, and 1 in Johannesburg. Mrs. H.K., IVA, is virtually certain to develop polyposis, if this is not already present. Three cases had sebaceous cysts and 1 of these cases, Mrs. M.M., IVF, with other soft- and hard-tissue surface tumours and dental involvement, is a case of Gardner's syndrome though without osteomata. Mr. C.P., IIID, had no symptoms at the age of 51, which is unusual at this age.

FAMILY II

This family has recently been reported by Thompson, Roberts and Comline.[6] Of the original couple the man died at 73 of 'arteriosclerosis' and the woman at 80 of heart failure, so it is uncertain who was the carrier of the polyposis gene.

Several of their children developed polyposis with or without carcinoma. Case IIA died at 44 from a carcinoma of the colon; she also suffered from amoebic dysentery. Case IIB died at 56 from carcinoma of the colon superimposed on

polyposis. Case IIC died at 46 from an annular constricting carcinoma of the rectosigmoid junction and secondaries; multiple polypi were present. Case IID died at 54 from a 'bleeding bowel', almost certainly due to polyposis and carcinoma. Case IIE had polyposis for which a colectomy had been performed. Case IIF had a laparotomy at 46; carcinomatosis peritonei and secondaries in the liver were found. The primary site was unknown at the time, but it was most probably from a carcinoma of the colon.

Fig. 7

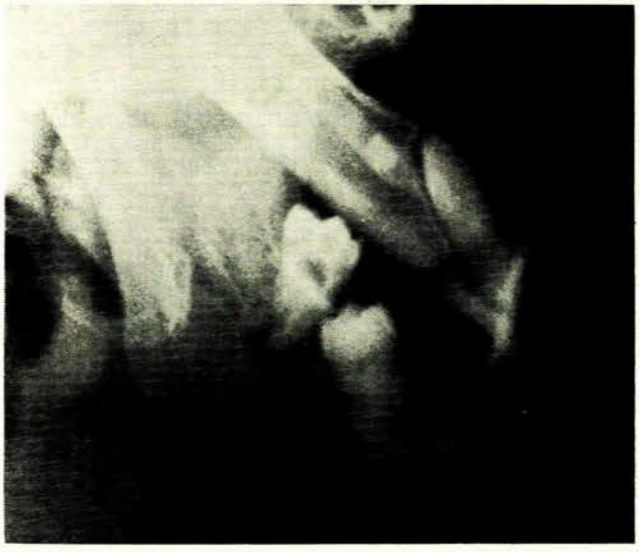


Fig. 8

Figs. 7 and 8 show an almost edentulous jaw, with dentigerous cysts and an island of bony density in a woman of 23.

Case IIIA died at 41 with polyposis and carcinoma. All her 5 children have developed polyposis and each child has had a colectomy and ileo-rectal anastomosis. Three of the children, IVB,C,D, were reported to have carcinoma *in situ*. Case IIIC has had a colectomy and ileo-rectal anastomosis for polyposis.

Since this family was reported, a further case has been discovered, and possibly another.

1. Miss K.K., 20, IIID. This young girl had no symptoms. On examination there was a large sebaceous cyst on the scalp, and a multinodular goitre. Sigmoidoscopy to 15 cm. showed some small scattered polyps in the rectum. Barium enema was normal.

In March 1966 a total thyroidectomy for carcinoma of the thyroid was performed. The polyposis operation has been deferred.

2. Mrs. J.N., 47, IIIB. This lady had no symptoms. Her mother had died of carcinoma of the colon with polyposis at the age of 56.

On sigmoidoscopy to 15 cm. two very small polyps were seen. The patient is being followed up. She is very likely to develop polyposis at a later date.

FAMILY III

This is the smallest family. Of the original couple, the wife, Mrs. N.S., IA, died at the age of 50 in 1932 following an operation for carcinoma of the colon. Two of her children have developed polyposis.

1. Mr. H.S., 59, IIA. This patient had a colectomy and ileo-rectal anastomosis performed by Mr. W. G. Schulze in January 1961. This patient is of interest in that following a cholecystostomy at 19 a desmoid tumour developed in the wound. He has two small sebaceous cysts on the scalp.

2. Mrs. M.H., 50, IIB. This lady has no symptoms, but on sigmoidoscopy to 17 cm. many polyps were noted, some quite large. A barium enema and operation were advised, but as yet no decision has been made by her.

3. Mr. R.S., 29, IIIA. This young man, the son of Mr. H.S., has no symptoms. Several years ago 4 superficial lumps —probably sebaceous cysts—were excised. Sigmoidoscopy to 21 cm. showed several small polyps. A barium enema showed no abnormality. Operation has been advised.

HISTORY

Menzel, in 1721, described a case of polypoid disease of the colon occurring in a soldier with chronic dysentery; this was, however, probably inflammatory pseudopolyposis.[1]

Corvisart, in 1847, described a case with tumours involving the terminal ileum and the first 10 cm. of the colon, with normal intervening mucosa. The pathologist, Cruveilhier, who examined the specimen, stated that the tumours were decidedly prone to malignant transformation.[1]

In 1859 Chargelaine presented an irrefutable case of diffuse polyposis.[1]

In 1861 Lebert and Luschka published cases, and Virchow, in 1863, observed a 15-year-old boy with polyposis.[61]

Harrison Cripps, in 1882, called attention, for the first time, to the familial nature of the disease, describing polyposis in a boy of 19 and a girl of 17, brother and sister.[16]

Handford, in 1890, noted the association of polyposis and carcinoma, as did Hauser in 1892.[26]

Lockhart-Mummery, in 1925, again underlined the predisposition to carcinoma.[41]

Cockayne, in 1927, was apparently the first to point out that this familial distribution was characteristic of a trait dependent on a dominant gene. Cockayne stated that 'in the more complete pedigrees such as published by Lockhart-Mummery, Niemach and Bickersteth, it is evident that the condition is inherited as a dominant'.[8]

Dukes, in 1930,[26] and Lockhart-Mummery and Dukes,[42] in 1939, showed that the disease was transmitted as a Mendelian dominant.

The first recorded case in South African literature was described by York Mason[46] in 1939, and Muller[51] in 1964 described the first case of Gardner's syndrome in the Republic.

PATHOLOGY

The disease is characterized by excessive epithelial proliferation in the mucosa of the rectum and colon, leading to the formation of multiple sessile and pedunculated growths. The polyps vary in size, shape, number, distribution and development.

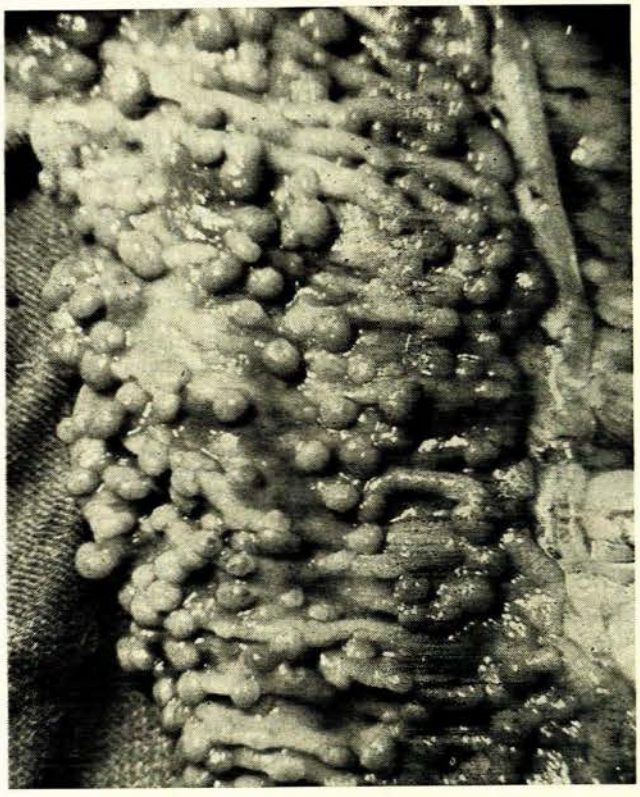


Fig. 9

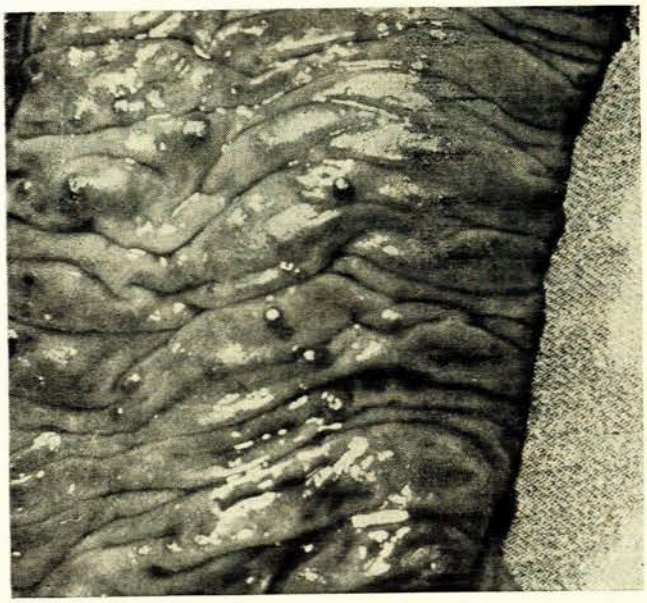


Fig. 10

Figs. 9 and 10 illustrate the disparity in size and number of the polyps in two patients.

The smallest lesions when examined microscopically appear as scattered patches of epithelial hyperplasia. Larger lesions show the histological structure of adenomata. The mucosa between the tumours may appear normal, apart from showing areas of hyperplasia. The number may vary from a few score, scattered in the rectum and sigmoid colon, to many thousands, extending all the way to the ileo-caecal valve, of such density that no normal mucosa is visible (Figs. 9 and 10). Grossly contrasting numbers of polypi may be found in related individuals.

The distribution of the polyps in the large bowel is variable, but they tend to be more numerous in the rectum and in the distal colon. In some cases the adenomas are most numerous in the ascending colon, although at the time of examination focal mucosal hyperplasia may be found throughout the remainder of the bowel.[3,11] These variations may be observed within the affected members of the same family.[11]

There is considerable variation, too, in the age at which polypi appear. The condition has been described in a child of 4 months,[59] and there is one verified case in which the polyps did not appear until the age of 39.[71] The polyps usually develop during childhood, probably about the time of puberty.[31,67]

All the tumours are at first non-malignant and most of them remain so, but after an interval of a few months or years carcinoma develops in one or more of these adenomas, the onset of malignancy being indicated by an increase in size, a darker colour, a firmer consistency and later by frank ulceration. The development of a carcinoma may occur at any time. In some patients who have relatively few polypi when the condition is first detected, malignancy is found to be already established. In others, who have widespread polyposis, malignancy does not develop for many years. This is one of the most baffling features of the condition.[71]

The classical villous papilloma is occasionally found in familial polyposis.[60,71] Moreover, it is quite common to find tumours in familial polyposis which have gross and microscopical features intermediate between adenoma and villous papilloma described by the term 'papillary adenoma'. Juvenile polyps may also occur in familial polyposis.[71]

GENETICS

The condition is transmitted as a Mendelian dominant. Males and females are equally affected and either may transmit the disease. In most polyposis families only half the children are likely to inherit the disease, the remainder being normal. The manifestation, or penetrance, of the polyposis gene has been estimated at 80%,[18] thus the over-all incidence of polyposis would be 40%. Thus, if there are 10 children of an affected parent, approximately 5 of the children, according to Mendelian law, are likely to inherit the disease. However, as the penetrance is only 80%, only 4 of the children, on the average, develop the condition.

As a rule only those who have inherited polyposis can transmit the condition to the next generation.

The condition may occasionally skip a generation.[18] In traits inherited as autosomal dominants, severity is widely variable. The age at onset of symptoms and the age of development may vary from childhood to old age. The phenomenon of skipped generations is largely an artefact related to the wide range of severity. The late onset in severity in some individuals can lead to an impression of normality at a given point in time when the family is studied. As a result, a grandparent and a grandchild may show the disease with an intervening generation apparently skipped.[45]

Anticipation, that is, the earlier appearance of a genetical condition, often with increased severity, in successive generations may also be found. Anticipation is another artefact based on the wide range of severity, when there is a highly variable age of onset of the disease.[45]

The incidence of the condition has been estimated variously as 1:23,000,[59] 1:16,000,[45] 1:8,300[56] and 1:7,437.[71] An estimate of the relative biological fitness (relative reproductive span) of patients has yielded a value close to 80%—0·78.[56] This means that the average polyposis patients are only able to produce 80% of their expected quota of children. This would lead to an inevitable loss of polyposis genes from generation

to generation, with ultimate extinction, unless the lost genes were replaced by mutation. The mutation rate necessary to maintain the polyposis gene at a constant frequency in the population is 3·8 mutations[59,71]—13 mutations[56] per million loci per generation.

Since mutations are thought to occur, a proportion of new cases of polyposis will have unaffected parents, and the observed frequency of such cases in the St. Mark's series is consistent with the calculated value for mutation rate, when due allowance is made for the fact that a small proportion of cases actually carrying the polyposis gene appears to escape detection. Further support in favour of isolated cases of polyposis being the result of fresh mutations is obtained from a study of parental ages of these cases. These are found to be increased when compared with average values for the population. The increases of 4 years for the fathers and 2·9 years for the mothers are both statistically highly significant. Similar effects have been observed in the parents of sporadic cases of other genetic disorders, and it appears that the probability of mutation increases with increasing age. There is thus no need to postulate the existence of a non-familial form of polyposis as the observed incidence of such cases can be satisfactorily explained by current genetic theory.[59]

Veale[71] has recently postulated the presence of 3 allelic genes: (1) The polyposis gene 'P', (2) the polyp gene 'p'—this is the unfavourable modifier in that it causes an early age of onset of polyposis when carried in conjunction with P, and (3) the 'wild type' (normal) gene '+' with no suggested pathological effect.

The following 6 genotypes are possible:

1. **PP** — this is very rare.
2. **Pp** — this is the unfavourable form of polyposis with an earlier death from cancer than individuals of the next genotype.
3. **P+** — the favourable form of polyposis in which the age at death is later than that observed in persons of genotype **Pp**.
4. **++** — these persons are normal.
5. **p+** — these persons, too, are normal and are presumed to be indistinguishable from persons of genotype **++**.
6. **pp** — persons of this genotype will inevitably tend to produce a few adenomata in the rectum and colon.

SYMPTOMS

There are 3 stages in the natural history of polyposis.[19] In the first stage, which may last throughout childhood, there are no signs or symptoms of the disease and sigmoidoscopy would not show any abnormality. In the second stage, which is very variable in duration, polyps are developing but have not yet caused symptoms. In the third stage there are both signs and symptoms.

The initial symptoms are extremely mild and consist of only slight looseness and frequency of the motions. Later this may develop into frank diarrhoea in severe cases. Excess mucus may be a symptom, and also bleeding, which is rarely severe. The development of carcinoma may lead to aggravation of these symptoms until the growth is quite large when further bleeding, alteration of bowel habit or abdominal pain may occur.

The average age at onset of symptoms is 20 years, according to Dukes[18] in 1952, and approximately 30 years, according to Veale[71] in 1965.

The presence of symptoms is highly significant. 50% of cases with symptoms had cancer at the time of diagnosis or within a period of 2 years, whereas only 6% of cases without symptoms had cancer at the time of diagnosis or within a period of 2 years.[71] This confirms the views of Dockerty who states that about 50% of patients who have familial polyposis are likely to harbour infiltrating colonic carcinoma by the time they have reached 30.[15]

The average age at diagnosis of cancer is 35 years, according to Dukes[18] in 1952, and 38·8 years, according to Veale[71] in 1965. The average age at death from carcinoma is 41·6 years (Dukes, 1952).[18]

DIAGNOSIS

Rectal examination may show the presence of polyps either as obvious masses or, if small, as imparting a feeling of granularity to the palpating finger.

Sigmoidoscopy is 'almost the only instrument needed for the diagnosis'.[22] The appearance of multiple sessile and pedunculated tumours separated by normal mucosa is characteristic. If no polyps can be seen with a 25 cm. sigmoidoscope, one can usually say that the patient is not affected by the disease at the time of the examination. Occasionally, however, segments of the colon may escape involvement, as previously mentioned, and involvement of the right half of the colon without involvement of the left is observed.[3,11]

A biopsy of a suspect carcinoma should be performed and, in any case, biopsy of a polyp should always be done to confirm the diagnosis.

Barium enema should be done if polyps are discovered on sigmoidoscopy to determine the extent and severity of the polyposis and to obtain information about the possible development of carcinoma (Figs. 11 and 12). A negative

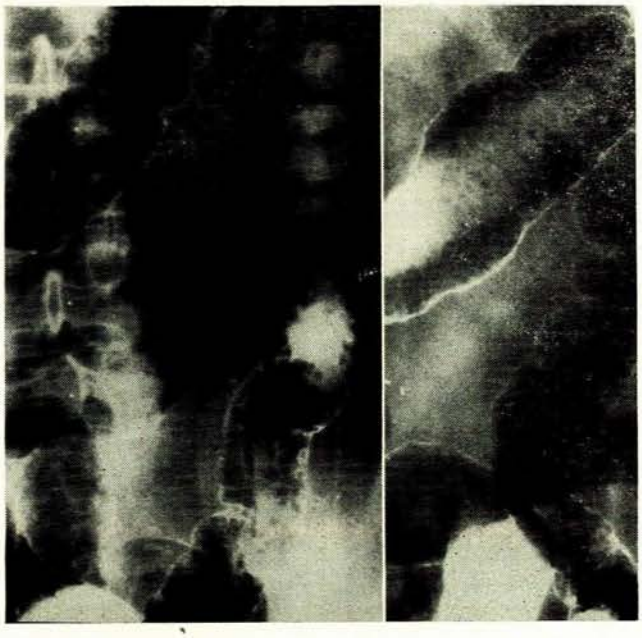


Fig. 11 *Fig. 12*

Figs. 11 and 12. Barium enema illustrating the colonic polyps.

barium enema alone does not exclude the presence of polyposis, for multiple small sessile polyps may be impossible to demonstrate by X-rays, even with the most refined techniques.

Barium meal and follow-through examination is suggested by Mayo,[47] since in 5% of cases of colonic polyposis

there are also polyps in the stomach and small intestine.

Gastroscopy: 'Every patient with diffuse polyposis of the colon should have a gastroscopic examination.'[35] The barium meal may not show up the polyps revealed by gastroscopy. The barium meal was negative in 4 out of 5 of Halsted's cases in whom gastroscopy revealed polyposis.[35]

VARIATIONS OF FAMILIAL POLYPOSIS

Familial Polyposis and Sebaceous Cysts

Sebaceous cysts are relatively common in association with familial polyposis. The ratio of polyposis families to polyposis families with cysts at St. Mark's Hospital, London, was 12·2:1.[71] Several individuals from each of our 3 families have sebaceous cysts. The cysts seem to appear rather frequently on the face or in a peripheral distribution.[63]

Gardner's Syndrome

Gardner[27] described a family with intestinal polyposis in which several members had associated 'surface tumours'. In 1953[30] he described a family with intestinal polyposis associated with multiple osteomata and soft-tissue tumours. This triad of multiple polyposis, multiple osteomata and multiple soft-tissue tumours has been referred to as Gardner's syndrome.

The first recorded case of multiple polyposis associated with soft- or hard-tissue tumours is attributed to Devic and Bussy (1912).[13] They noted the incidental findings of exostoses of the mandible, sebaceous cysts of the scalp, multiple lipomas and a benign adrenal adenoma in a 36-year-old woman with polyposis, predominantly in the jejunum, but throughout the gastro-intestinal tract. Two other reports of cases with involvement of the small intestine as well as the large intestine were described before Gardner's report.[7,48] Gardner[28] states his cases had polyposis apparently restricted to the large intestine.

The osteomata especially affect the maxilla, mandible and sphenoid; the frontal, ethmoid, zygomatic and temporal bones are less often affected.[32] The osteomata of the jaw are particularly characteristic benign lobate projections.[45] The involvement of the calvarium and other bones, such as those of the extremities, is in some instances more diffuse, suggesting a form of osteosclerosis.[46] Some may call it a fibrous dysplasia.[45] Individual osteomata may be formed in the long bones. The bone lesions may be so flat as to escape notice unless specifically looked for by radiological skeletal survey.[54] Scoliosis has been described.[7,32]

Lipomas,[30] leiomyomas[34] and ill-defined subcutaneous connective tissue tumours (fibromas)[32,64] have been found.

The soft- and hard-tissue connective tissue tumours may appear before the development of polypi or certainly before the symptoms of polyposis. When they are encountered in clinical practice, the patient should always be sigmoidoscoped to exclude polyposis of the colon.[38]

Desmoids are most often found in abdominal incisional scars. A nodule in an incisional scar in a patient with polyposis may well be a fibroma or desmoid tumour rather than an implant of carcinoma.[63] Desmoids may also arise *de novo* from extra-abdominal sites.

Desmoids in the mesentery[32,34,62] (mesenteric fibromatosis) usually appear after intestinal surgery. Seven out of 8 cases at the Mayo Clinic had previous intestinal surgery.[62] The interval between operation and recognition of the mass varied in the Mayo Clinic series from 3 months to 5 years, and usually between 1 to 3 years. The mesenteric masses are usually asymptomatic but may cause abdominal pain. There may be multiple masses present, and on examination the abdomen may present numerous easily palpable abdominal lumps, which may be mistaken for secondary deposits. The surgical management of the mesenteric fibromas is conservative as far as possible.[62] To remove a mass would frequently result in removing the subtending portion of small bowel, and if multiple fibromas are present this is not a practicable proposition, nor necessary.

There is an increased incidence of intestinal obstruction due to postoperative adhesions in Gardner's syndrome[62] and keloid formation in scars.

The abnormal proliferation of fibrous tissue is an impressive component of the syndrome.[64] Trauma in initiating this response would appear to be an important factor as seen in the desmoids in abdominal scars, mesenteric and retroperitoneal fibromata, excessive production of postoperative adhesions, keloid formation and, in some cases, of subcutaneous fibrous masses which have followed known trauma.

Dental involvement: Gardner, in 1962,[28] following up his cases originally reported, noted that very poor teeth were common, and most who were 20 years old or older had false teeth. Supernumery teeth, unerupted teeth, impacted teeth and dentigerous cysts were also found. Irregular islands of increased bone density may be found in the mandible, maxilla and skull, and there may be bizarre bony changes resulting in thickening of the bone, as shown on X-ray.

The polyps in the colon in Gardner's syndrome do not carpet the bowel as in familial polyposis, according to McKusick.[45] In Gardner's syndrome the polyps may occur anywhere in the length of the gastro-intestinal tract. The gene that determines the Gardner syndrome is unquestionably different from that of familial polyposis according to McKusick. This statement is based on the phenotypic differences, specifically the occurrence of the osseous and soft-tissue tumours and the distribution of polyps throughout the gastro-intestinal tract in Gardner's syndrome.[45]

The Turcot Syndrome

Turcot, Despres and St. Pierre[68] described a brother and sister with polyposis of the colon in association with tumours of the central nervous system; the 15-year-old boy developed a medulloblastoma and the 13-year-old girl a glioblastoma of the frontal lobe. Also present in the girl was a small chromophobe adenoma of the pituitary.

Syndrome of Polyposis, Pigmentation, Alopecia and Onychotrophia

Cronkhite and Canada[12] described two cases with adenomatosis of the stomach, duodenum, small and large bowel, with no family history of polyposis nor pigmentation.

The pigmentation, alopecia and atrophic nails were explained by widespread structural changes in the gastro-intestinal tract mucosa which resulted in the malabsorption of vitamin A, riboflavin, nicotinic acid and vitamin C.

Familial Polyposis of Colon, Stomach and Small Bowel

Several cases have been reported.[5,35] Mayo[47] states that 5% cases of familial polyposis coli have associated polyps in the stomach and small bowel. The stigmata of Gardner's syndrome have not been present.

DIFFERENTIAL DIAGNOSIS

The diagnosis must be made from other conditions in which multiple polyps are seen on sigmoidoscopy.

Pseudopolyposis. These inflammatory polyps occur in ulcerative colitis, Crohn's disease of the colon, bilharzia, chronic dysentery and tuberculosis.[26] In these inflammatory conditions the polyps are more irregular and rigid than the smooth, rounded polyps of familial polyposis, there is usually a great deal of mucopus present and the mucosa between the polyps is inflamed and granular and lacks the vascular pattern. In familial polyposis the adenomata extend down into the rectum, whereas in ulcerative colitis the pseudopolypi seldom affect the bowel further distally than the rectosigmoid junction.[31] A barium enema may reveal the characteristic changes of ulcerative colitis or Crohn's disease. The sigmoidoscopic findings, however, should have already revealed the differentiating features of polyposis and pseudopolyposis. Biopsy would confirm the differentiation.

Lymphomatous polyposis. Giant follicular lymphoma, lymphosarcoma, reticulum cell sarcoma and Hodgkin's disease may rarely cause multiple polyps throughout the rectum and colon and sometimes the whole gastro-intestinal tract[49,71] (Fig. 13). Biopsy of one of the polyps will establish the diagnosis.

Fig. 13. Lymphosarcomatous polyposis simulating familial polyposis of the colon. (Courtesy of E. & S. Livingstone Ltd.—from *Cancer of the Rectum* edited by C. E. Dukes.)

Peutz-Jeghers syndrome. The characteristic pigmentation of the buccal mucosa and the inconstant cutaneous pigmentation round the orifices of the face, the mouth, nostrils and eyes, and possibly of the palms, fingers, soles and toes, together with biopsy of a rectal polyp (if present), which on examination shows a hamartoma, serve to differentiate this condition from familial polyposis coli.

Juvenile polyposis. Juvenile polyps are usually single[57] but may be multiple and in some cases may number up to many hundreds.[44] In contrast to familial polyposis coli, the polyps are bright red, usually pedunculated, bleed readily on contact and can be plucked off the rectal wall with ease and with little bleeding. Histology shows the classical appearance of a juvenile polyp which is thought to be hamartomatous[50] or inflammatory[57] in origin. Congenital abnormalities, e.g. hypertelorism, amyotonia congenita, umbilical faecal fistula, malrotation of the gut and lymphangioma of the mesentery,[44] have been found in some of these cases, quite different to the associated osteomas, sebaceous cysts and connective tissue tumours of Gardner's syndrome.

Cystic pneumatosis. This may affect the left side of the colon in which the rectum is likely to be involved, and the resemblance to polyposis may be close.[26] The polyps may appear translucent on sigmoidoscopy, and biopsied specimens bisected under water may show obvious bubbles of gas. Barium enema will show the abnormal appearance in the bowel.

Other rare causes which may be differentiated are hereditary lipomatosis,[71] which may involve the large bowel as well as other parts of the body, and a condition which has been called Brock-Suchow polyposis of the colon,[6,65] where curious sessile, umbilicated, yellow-brown polyps of the large bowel have been described. In one case the polyps disappeared 7 weeks after discovery.[65] Examination showed mucosal nodules with coagulation necrosis of the mucosa superficially, degeneration of glandular structure and an occasional residual gland outlined in the remaining mucosa, diffuse oedema and infiltration of macrophages and lymphocytes. The aetiology is unknown. Brock and Suchow believe it to be due to extensive submucosal obliterative arteriolar disease.

TREATMENT

As familial polyposis is a precancerous condition, the ideal treatment is a total colectomy and excision of the rectum. However, this procedure entails the establishment of a permanent ileostomy which is not readily acceptable to a person with polyposis who is often in good general health, and who may be symptomless. Ileo-anal anastomosis has been done by some surgeons[34,35] who claim the incidence of diarrhoea is not high. Most surgeons, however, prefer an ileostomy in the right lower quadrant.[73]

The alternative, compromise procedure to a panproctocolectomy and ileostomy, is a total colectomy with ileorectal anastomosis, thus preserving the greater part of the rectum and ensuring natural continence. The disadvantage of this procedure is that the retained rectal segment is potentially liable to the development of carcinoma. This risk has been estimated at about 3·4[72] - 5·2%.[25] Thus it is essential that postoperatively the aftercare should be thorough with regular sigmoidoscopic examinations.

Age at which Colectomy Should be Undertaken

The average age of onset of symptoms is about 30 years[71] and the average age at which carcinoma is detected is 38 - 39 years.[71] In some cases, however, malignancy develops at a much earlier age. Any person above the age of 25 is clearly within the danger zones.[52] As mentioned above, the presence of symptoms is of great significance, and Veale feels that the surgical treatment of polyposis in a patient with symptoms over the age of 15 is a matter of urgency.[71] Apart from symptoms, the operation is best carried out at about 14 or 15,[31] when the cases are diagnosed on routine sigmoidoscopy.

Some Points in the Technique in Colectomy and Ileo-rectal Anastomosis

The patient is placed in the lithotomy-Trendelenburg position.[67] The advantage of this position is that an assistant can pass a sigmoidoscope from below after the rectum has been transected and the rectal mucosa can be carefully searched for polypi which can be fulgurated.[67] Another advantage is that after the rectum has been clamped off, the rectum can be washed out with mercuric perchloride 1:500 solution to prevent suture-line recurrence should a carcinoma be present proximally.

The ileum should be divided as close to the caecum as possible, for not only does it widen out near the ileo-caecal valve but subsequent function seems better if this portion of the ileum is preserved.[37,40,67]

The less the amount of rectum retained, the less will be the area of potential malignancy to be supervised postoperatively. An optimum length of rectum is about 12 - 14 cm. measured from the anal verge, which is below the rectosigmoid junction and which also makes for a technically easy anastomosis and good rectal function. Postoperatively after a variable period of frequent loose bowel actions, which is rarely more than 6 months, the patient usually has about 2 - 3 bowel actions in 24 hours.

Usually the paracolic gutters are not re-peritonealized after total colectomy, e.g. for ulcerative colitis; due to the increased risk of intestinal obstruction in operations on polyposis cases, the paracolic gutters in our cases have been re-peritonealized in an attempt to reduce this complication. We have had no obstruction in our small series to date.

Diathermy of the Rectal Polyps Before or After Colectomy?

Opinion varies in this respect. Black and Hansbro[3] are strongly of the opinion that in the great majority of cases the polyps should be fulgurated after and not before the colon has been removed. They maintain that before the anastomosis has been established the exact site of resection cannot be known, and consequent needless fulguration may be carried out. They feel that 3 months should elapse after fulguration, before elective operation is performed, to permit the acute inflammatory reaction to subside. Even after this time, they say, the bowel remains thickened and scarred, and the anastomosis is less satisfactory technically and thus less safe.

Other reasons, perhaps more cogent, mentioned by Lockhart-Mummery *et al.*[43] for proceeding to elective operation first are:

(*a*) The danger in delaying the operation in older patients with an unsuspected carcinoma already present when repeated fulgurations are performed initially.

(*b*) The risk of implantation of malignant cells, when fulguration is performed initially, on the raw surfaces.

Another reason for performing the elective operation first is the phenomenon of regression of the polyps in the retained rectal segment after colectomy and ileo-rectal anastomosis.[4,9,10,23,36,72] Crude data suggests that approximately 25% patients so treated will no longer develop benign adenomas in the retained rectum. Cole and Holden[9] suggested that ileal contents might inhibit the development and growth of rectal adenomas after subtotal colectomy, since the adenomas close to the ileo-rectal anastomosis are the first to disappear after such an operation, and that the adenomas are much less common in the right side of the colon that is exposed to ileal contents.

Lockhart-Mummery *et al.*[43] feel that in any patient over the age of 25 in whom large congested polyps are seen, it would be better policy to operate without delay, and that preliminary fulguration and later colectomy be reserved for younger people and those with mild disease.

We feel that preliminary fulguration is not indicated in most cases and that fulguration be done *at the time* of the colectomy and ileo-rectal anastomosis, and thereafter as is required. Our policy is dictated for the reasons given above. The argument that anastomosis through a freshly fulgurated area is hazardous has not been borne out in our experience, and no untoward sequelae have resulted. The described difficulty of liquid motions after ileo-rectal anastomosis making fulguration awkward[31] has likewise not been a problem.

When the Rectum Cannot be Preserved

The presence of a carcinoma of the rectum may influence the above plan of treatment. Broadly speaking, a carcinoma of the lower third of the rectum would indicate a panproctocolectomy, whereas a carcinoma of the upper third of the rectum would be treated by restorative resection, i.e. ileo-rectal anastomosis. Most cases of carcinoma of the middle third of the rectum would require proctocolectomy, though in some—the more proximal growths—an ileo-rectal anastomosis may be possible; other factors such as the build and sex of the patient, the size of the growth and the degree of malignancy as shown by biopsy, would also influence the decision for or against an anastomotic procedure. More of the rectum should be preserved in ileo-rectal anastomosis than in anterior restorative resection so as to ensure continence.

Excision of the rectum may be necessary for patients in whom the polypi are so numerous in the rectum that diathermy destruction of them all would be liable to result in an uncertain anastomosis. In some cases, however, with preliminary fulguration, it is often possible with care and patience to destroy all the rectal polypi without any stenosis resulting, so that rectal preservation becomes possible.[42]

Follow-up

The follow-up after colectomy and ileo-rectal anastomosis is very important: Initially after operation the patient should attend every 3 - 4 months for the first year. Polyps are fulgurated, as is necessary. Longer intervals between visits gradually become permissible. However, it is mandatory that the follow-up should be life-long.

Management of the Polyposis Family

The surgeon treating a case of polyposis has a moral responsibility to investigate the other individuals in the family. Sigmoidoscopy of the members is usually postponed until the age of 13 - 14 unless symptoms occur earlier than this to suggest that polyps are already present. If sigmoidoscopy is negative, a second sigmoidoscopic examination should be arranged towards the end of the

teen-age period, but, if at any time they should pass blood or mucus or have suspicious symptoms, they should report immediately. If this second sigmoidoscopic examination is negative, additional examination should be performed at the ages of 20, 25 and 30 years.[19]

Dukes[19] has posed the question: 'At what age can it be assumed that an apparently unaffected member has escaped inheritance of polyposis?' He says 'this question cannot be answered by quotation of a definite figure. All one can say is that if by the age of 40 years there are no symptoms of polyposis and if the results of sigmoidoscopic examination are negative, then it is unlikely that polyposis will develop later. If sigmoidoscopy cannot be done, and the decision must rest on symptoms only, it is better to be non-committal until the patient is 50 - 55 years of age.'

Veale[69,71] has shown that symptoms may be delayed until the age of 70, and thus it would seem that an almost life-long vigil should be conducted on these patients. This indicates that not only should the affected individual's children be examined but that the apparently unaffected members of a family and their children should be followed-up till late in life.

At present the only practical method of determining what members of a polyposis family will in fact develop polyposis is by regular sigmoidoscopic examination.

A test that can be devised to prognosticate who the unfortunate members of the family will be, would obviously be a great saving in terms of anxiety from a patient's point of view, and of endless sigmoidoscopies from the clinician's.

Various tests have been investigated without success, viz. blood group systems[70]—ABO, MN, Duffy; fingerprints;[21] chromosome analyses;[70] cell-cultures[70] and enzyme studies.[71] Birbeck and Dukes[2] have discovered ultramicroscopic particles in the intestinal epithelium of polyposis patients. These are situated near to the free border of cells lining the crypts of Lieberkuhn. They are too small to be resolved with the light microscope but are clearly seen with the higher magnifications of the electron-microscope. Gorlin[32,33] has investigated the presence of urinary hydroxyproline in these patients, but found the results unsatisfactory, the hydroxyproline being raised in some cases and normal in others.

CONCLUSION

The subject of familial polyposis of the colon is reviewed, and 3 families are briefly described. The investigation of these families has yet to be completed. The members of the families, though predominantly settled in the Western Cape, are widely scattered over the country. With the aid of interested surgeons in the main centres of the Republic, it is hoped that a Polyposis Register will be formed so that the members of these families may be traced and examined. It is gratifying that with timely prophylactic surgery, cancer may be obviated in many of these cases and that these patients may continue to serve as useful members of the community.

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