A Genetic Study of Multiple Polyposis of the Colon (With an Appendix Deriving a Method of Estimating Relative Fitness)[1]

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MULTIPLE POLYPOSIS of the colon is a condition characterized by the occurrence of numerous polyps throughout the colon and/or rectum. The polyps usually make their appearance during the first and second decades of life, but occasionally may not arise until the fourth decade or possibly even later. Although the polyps themselves may be associated with symptoms referable to the large bowel, the disease is of clinical significance primarily because of the tendency of one or more of the polyps to become malignant, with death from carcinoma of the colon or rectum at a relatively early age. The disease has long been known to have a familial distribution (cf. Cripps, 1882), with Cockayne (1927) apparently the first to point out that this distribution was characteristic of a trait dependent on a dominant gene. Dukes (1952) has provided an excellent review and bibliography of the disease.

Approximately 10 per cent of all adults can be demonstrated by combined sigmoidoscopic and X-ray studies to possess one or more polyps of the colon (cf. Helwig, 1947; Swinton and Haug, 1947; Bacon, 1949; Gianturco and Miller, 1953). However, only a small fraction of these persons has true multiple polyposis. When appropriate diagnostic studies are carried out, there is seldom any problem involved in differentiating between the person who has hundreds or even thousands of polyps—and has multiple polyposis—and the person who has two or three, or even five polyps, but does not have the multiple polyposis with which this study is concerned.

The two diseases with which multiple polyposis can most readily be confused are the so-called Peutz-Jeghers syndrome of diffuse intestinal polyposis and abnormal pigmentation (cf. Jeghers, McKusick, and Katz, 1949), and the syndrome of polyposis of the colon associated with osteomatosis and fibromatosis (Gardner and Richards, 1953). Both of these diseases are apparently much rarer than classical multiple polyposis, and were not encountered in the course of this study.

The present investigation was undertaken in an effort to develop a more rounded picture of the genetics of this disease than is currently available. More specifically, in addition to accumulating further data concerning the inheritance of this condition, we have attempted to evaluate the biological handicap it imposes on affected persons,

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and to estimate the frequency of the trait in the general population. Assuming genetic equilibrium, these data permit certain preliminary speculations concerning the rate with which the gene or genes responsible for this trait are appearing through mutation. Although, as will be pointed out in due course, large errors are inevitable in certain of these calculations, it is felt that to the extent that they contribute to arriving at an order of magnitude for a basic biological phenomenon, the calculations are worthwhile and of general interest.

GENETIC STUDIES ON MULTIPLE POLYPOSIS

The 23 kindreds on which genetic studies have been carried out were located in the following ways:

1. A survey of the records of the University Hospital of the University of Michigan for the period 1935–1950, which yielded 16 families for study. Subsequent experience has revealed that by no means all cases of polyposis seen at the University Hospital during this period were coded as such and that, further, some cases properly coded as polyposis were overlooked in the initial survey. However, so far as is known, no element of bias entered into the selection of these particular kindreds.

2. Correspondence with a number of Michigan physicians specializing in gastroenterology, which yielded three kindreds.

3. Systematic follow-up of all death certificates filed with the state of Michigan during 1950–52 inclusively on which the cause of death is listed as carcinoma of the colon or rectum and the individual was below the age of 40. This procedure, undertaken in an effort to estimate the frequency of the trait (see below), yielded four kindreds.

BASIC DATA

The basic data on the 23 kindreds studied are presented in Tables 1 and 2. Each kindred contains at least one medically diagnosed case of multiple polyposis. One hundred and nine affected or possibly affected individuals are described. Seventy of these are definitely known to have had multiple polyposis. Thirteen are known to have developed cancer of the colon or rectum and, because of their close biological relationship to an individual known to have polyposis, are assumed also to have had polyposis. The 26 remaining persons are included because of lay reports or inconclusive medical reports of polyposis, bowel cancer, or significant bowel complaints, such as rectal bleeding. There are 65 males and 44 females, and 75 of the 109 individuals were residents of the state of Michigan at the time of investigation or at death.

The kindreds can be conveniently classified into two groups according to the existence or absence of good evidence for the presence of two or more affected individuals in a kindred. This division yields 14 kindreds of the familial type and 9 which are not clearly familial. Pedigrees and data concerned with the 14 familial kindreds are presented in Figure 1 and Table 1; data on the remaining 9 kindreds are given in Table 2. As Table 2 shows, several, or perhaps most, of these 9 kindreds may well contain two or more affected persons but data required for decision are lacking. Poor cooperation from close relatives of the propositus accounts for much of this

TABLE 1.—DATA ON AFFECTED AND POSSIBLY AFFECTED MEMBERS OF 23 KINDREDS, EACH KINDRED CONTAINING AT LEAST ONE MEDICALLY DIAGNOSED CASE OF MULTIPLE POLYPOSIS OF THE COLON

Key: + = Yes; − = No or none; ? = Diagnosis made but age unknown; • = No information; P = Propositus; "definite" = Data from hospital record, patient's physician, or death certificate.

Kindred	Individual	Sex	Michigan resident	Type of Evidence				Age at				Comments
				Definite polyposis with or without cancer	Definite primary large bowel cancer; polyposis not known	Reliable lay report of polyposis or large bowel cancer	Dubious lay report of significant intestinal symptoms, polyposis or large bowel cancer	First symptoms	Diagnosis of polyposis	Diagnosis of primary large bowel cancer	Death	
A. Kindreds certainly or very probably containing two or more cases of multiple polyposis												
809	I-1	M	−	−	−	−	+	•	•	•	44	Son reports I-1 underwent abdominal surgery for unknown cause 6 mos. prior to death; hospital record unavailable.
	II-1	F	+	+	−	−	−	32	34	34	34	
	II-2	F	−	+	−	−	−	45	47	47	49	
	II-5	M	+	+	−	−	−	30	42	42	−	
	III-1(P)	M	+	+	−	−	−	25	25	32	−	Underwent subtotal colectomy with ileosigmoidostomy at age 26. Rectal polyp removed age 32 thought to be malignant. Asymptomatic when last seen age 33.
832	I-1	M	−	−	−	+	−	•	−	67	70	At operation for carcinoma of sigmoid colon at age 67, history obtained of other bowel surgery 17 yrs. previously—?carcinoma. Operation age 67 only palliative colostomy. Polyposis not diagnosed.
	II-5	M	−	−	−	−	+	•	•	•	•	Reported by mother, on dubious grounds, to have had polyposis.
	II-7(P)	M	+	+	−	−	−	43	44	44	45	
	II-8	F	−	+	−	−	−	38	41	41	42	
	III-22	M	+	+	−	−	−	20	20	−	−	No symptoms; studied because of disease in father.
	III-24	M	+	+	−	−	−	−	14	−	−	No symptoms; studied because of disease in father.
	III-25	M	+	+	−	−	−	−	11	−	−	No symptoms; studied because of disease in father.
	III-28	F	−	+	−	−	−	−	23	−	−	

1554	I-2	F	−	−	−	+	−	•	•	•	50	Son reports I-2 died of large bowel cancer at age 50. The physician of II-17, 18, and 22 confirms this report. Hospital record unavailable.
	I-4	M	−	−	−	+	−	•	•	•	42±	Nephew and physician of II-17, 18, and 22, familiar with family, report I-4 died of large bowel cancer. Detailed medical record not available.
	I-7	M	−	−	+	−	−	60	−	60	62	Found to have inoperable carcinoma of colon; underwent only palliative colostomy. Polyps not reported on sigmoidoscopy or barium enema.
	II-6	M	−	+	−	−	−	•	36	37	−	
	II-8	F	−	+	−	−	−	29	31	29	40	
	II-9	M	−	−	−	+	−	•	•	•	33±	Brother and physician of II-17, 18, and 22 report cancer of colon. Detailed medical records unavailable.
	II-17	M	−	+	−	−	−	40	40	−	−	
	II-18	F	−	+	−	−	−	•	37	−	−	
	II-19	M	−	−	−	−	+	•	−	−	−	According to physician of II-17, 18, and 22, II-19 had rectal bleeding at about age 41. No examination is known to have been made.
	II-20	M	−	+	−	−	−	33	33	−	−	
	II-21	F	−	−	+	−	−	29	−	29	29	Pathology report on resected sigmoid colon fails to mention polyposis.
	II-22	F	−	+	−	−	−	•	32	33	33	
	II-23	M	−	+	−	−	−	−	27	28	29	
	II-25(P)	M	+	+	−	−	−	24	24	−	−	
	III-12	F	−	+	−	−	−	−	27±	−	−	
1801	I-1	M	+	−	+	−	−	•	−	?	37	Father of I-1 said to have died at about age 35, cause unknown to informants. Mother of I-1 died about age 60. No information about sibs of I-1.
	I-3	M	+	−	−	−	−	−	−	−	81	I-3 had no gastrointestinal complaints but 1 of his 6 sibs is said to have died at age 66±, possibly of "cancer of the liver." Father of I-3 is known to have had bloody diarrhea and a rectal mass before his death at age 74.
	I-4	F	+	−	−	−	−	−	−	−	−	I-4 was in good health at age 72 but had a half-sister who is known to have died at age 59 of cancer of the large bowel.
	II-2	M	+	−	−	−	−	•	−	−	37	Surgery revealed neoplasm involving stomach and transverse colon, thought by surgeon to be primary in stomach.
	II-3	F	+	+	−	−	−	•	55	55	−	Sibs II-4, 6, and 7 were medically examined and found normal at ages 58, 57, and 53 respectively. II-5 died at 6 mos.

TABLE 1.—*Continued*

Kindred	Individual	Sex	Michigan resident	Type of Evidence				Age at				Comments
				Definite polyposis with or without cancer	Definite primary large bowel cancer; polyposis not known	Reliable lay report of polyposis or large bowel cancer	Dubious lay report of significant intestinal symptoms, polyposis or large bowel cancer	First symptoms	Diagnosis of polyposis	Diagnosis of primary large bowel cancer	Death	
A. Kindreds certainly or very probably containing two or more cases of multiple polyposis—*Continued*												
1801	III-9(P)	F	+	+	−	−	−	15	15	17	18	
	III-10	M	+	+	−	−	−	13	13	14	19	
	III-11	F	+	−	+	−	−	8	−	9	9	
	III-12	F	+	+	−	−	−	−	28	−	−	Diagnosed during this study
1824	I-1	M	+	−	−	+	−	•	•	•	45	Hospital record of II-1 states that I-1 died of cancer of the rectum.
	II-1	M	+	−	+	−	−	26	−	27	27	Polyp removed on biopsy; when cancer of rectum diagnosed, only palliative colostomy performed.
	III-1(P)	F	+	+	−	−	−	−	23	−	−	
1826	I-1	M	+	−	−	−	+	•	−	−	54±	Reported by a daughter-in-law and a granddaughter-in-law to have died of cancer of bowel in 1896.
	II-1	F	−	−	−	+	−	•	−	−	40±	Reported by a daughter and a sister-in-law to have died of cancer of bowel.
	II-5	M	+	−	+	−	−	•	−	46	47	Death certificate filed in 1916 lists cancer of lower bowel, bladder, and kidney as cause of death.
	II-7	F	+	+	−	−	−	•	40	40	40	
	II-8	M	+	+	−	−	−	41	44	−	46	Presented with pelvic abscess, which was drained. Sigmoidoscopic and X-ray studies revealed obstructive lesion in colon; patient died without definitive surgery.
	III-1	F	−	−	−	+	−	•	−	−	30	Reported by a brother, sister, and a sister-in-law to have died following diarrhea and abdominal cramps. Death certificate dated 1911 gives cause of death as tuberculosis of the bowels.
	III-2	M	−	−	−	−	+	•	−	−	33	Reported by a brother, sister, and a sister-in-law to have died following diarrhea and cramps. Death certificate dated 1921, however, gives pulmonary tuberculosis as the cause of death.

	III-3	M	−	−	−	+	−	•	−	−	39	Reported by a brother, sister, and a sister-in-law to have died following diarrhea and cramps. Death certificate dated 1925 gives cause of death as tubercular peritonitis.
	III-4	F	−	−	−	−	+	•	−	−	30	Reported by a brother, sister, and sister-in-law to have died following intestinal complaints. No medical record available.
	III-5	F	+	+	−	−	−	57	58	−	−	First diagnosed during this study.
	III-7(P)	M	+	+	−	−	−	37	37	37	51	One of the 2 separately ascertained propositi in this kindred. Had subtotal colectomy at 37.
	III-21(P)	M	+	+	−	−	−	50	50	50	51	One of the 2 separately ascertained propositi in this kindred.
	III-23	M	+	+	−	−	−	•	51	?	−	Cancer of the cecum was diagnosed some time before diagnosis of polyposis was made.
	III-27	M	+	−	−	−	+	•	−	−	35	Hospital report states III-27 died shortly after arrival, apparently of general peritonitis. There was no autopsy.
	III-29	M	+	−	+	−	−	39	−	39	−	Presented with symptoms of large bowel obstruction. At operation a malignancy involving splenic flexure was resected. Pathology report fails to mention polyposis.
	III-30	F	+	+	−	−	−	26±	38	38	38	
	III-34	M	+	−	−	−	+	•	−	−	−	Examined twice following discovery of multiple polyposis in sibs. First examination negative; second exam (barium enema) revealed solitary polyp at hepatic flexure.
	III-35	F	+	+	−	−	−	•	31	32	33	
	III-36	M	+	+	−	−	−	•	32	32	−	Examined following death of sister.
	III-37	M	+	+	−	−	−	−	31	31	−	Examined following death of sister.
	III-40	F	−	+	−	−	−	−	38	−	−	Diagnosed during this study.
	III-41	M	+	+	−	−	−	−	35	−	−	Diagnosed during this study.
	IV-9	M	+	+	−	−	−	−	19	−	−	Diagnosed during this study.
	IV-24	M	+	+	−	−	−	−	22	−	−	Diagnosed during this study.
	IV-26	F	+	+	−	−	−	−	17	−	−	Diagnosed during this study.
	IV-27	M	+	+	−	−	−	−	15	−	−	Diagnosed during this study.
	IV-28	F	+	+	−	−	−	−	12	−	−	Diagnosed during this study.
1861	I-2	M	+	−	−	−	−	−	−	−	−	I-2 described himself as being healthy at age 47. His mother died at 30 from unknown causes. His sister is healthy at 45.
	I-3	F	+	−	−	−	−	−	−	−	−	I-3 described herself as being in fair health at age 44. A hospital report states that at age 43 X-rays of the colon were normal. Her 10 sibs are reported normal. Father is said to have died at 52 from heart trouble, mother at about 63 following an operation for hernia.

TABLE 1.—*Continued*

Kindred	Individual	Sex	Michigan resident	Type of Evidence				Age at				Comments
				Definite polyposis with or without cancer	Definite primary large bowel cancer; polyposis not known	Reliable lay report of polyposis or large bowel cancer	Dubious lay report of significant intestinal symptoms, polyposis or large bowel cancer	First symptoms	Diagnosis of polyposis	Diagnosis of primary large bowel cancer	Death	
A. Kindreds certainly or very probably containing two or more cases of multiple polyposis—*Continued*												
1861	II-1(P)	F	+	+	−	−	−	10	10	−	10	Presented with bloody diarrhea. Died of a transfusion reaction following subtotal colectomy.
	II-3	M	+	+	−	−	−	9	9	−	−	Was in good health at age 19. No surgery has been performed.
1862	I-1	M	+	−	−	+	−	•	•	•	60	Reported by 5 of his children to have died in 1919 of cancer of the intestinal tract following symptoms including massive rectal bleeding. Hospital record and death certificate not available. Had 9 sibs, 3 of whom are reported to have died from cancer of the colon. The parents of I-1 are both reported to have died in their 40's.
	II-1	M	−	−	+	−	−	•	•	?	40	Death certificate lists cancer of colon as cause of death; further details unobtainable.
	II-2	F	+	−	+	−	−	•	−	?	49	Death certificate lists cancer of rectum as cause of death; further details unobtainable.
	II-4	F	+	−	−	−	+	•	−	−	37	Several sibs report that II-4 had much rectal bleeding but death certificate gives cause of death as carcinoma of the spleen.
	II-12(P)	F	+	+	−	−	−	25	25	32	34	
	III-26	M	−	+	−	−	−	−	21	−	−	Polyposis detected during examination because of anal condylomas.
1928	I-1	M	+	−	+	−	−	•	−	?	59	Reported by his daughter to have undergone abdominal surgery, resulting in a "short circuit" of the intestine. Hospital records not available. Death certificate gives cause of death as cancer of the rectum.
	II-1	F	+	+	−	−	−	30±	38	−	39	Following several months of bloody diarrhea and abdominal cramps, developed a pelvic abscess, which was immediate cause of death. X-rays showed persistent narrowing of sigmoid colon. Autopsy report describes abscess and polyposis but does not mention neoplasm.

	II-2	M	+	+	−	−	−	•	42	−	42	Died following subtotal colectomy because of intractable diarrhea. No malignancy of colon.
	II-5	F	+	+	−	−	−	26	44	−	44	Died following 18 yrs. of intermittently bloody diarrhea. Autopsy revealed multiple polyposis without malignant degeneration.
	III-1(P)	F	+	+	−	−	−	17	25	−	−	Polyposis diagnosed during work-up for chronic diarrhea.
1982	I-1	M	−	−	+	−	−	•	−	44	47	The wife of I-1 states that his mother died of cancer and the wife of II-1 says that I-1's mother died of cancer of the intestine. This second informant also states that I-1 had several sibs who died of "intestinal ailment." I-1 underwent resection at age 44 for carcinoma of descending colon; pathology report fails to mention polyposis. Second (?) malignancy detected 3 yrs. later, with death shortly thereafter.
	II-1(P)	M	+	+	−	−	−	30	30	30	32	
	II-2	M	−	+	−	−	−	•	36	−	−	
	III-1	F	+	+	−	−	−	•	19	−	−	Asymptomatic; diagnosed during this study.
2070	I-1	M	−	−	−	+	−	•	•	•	39	When admitted to hospital, II-2 stated that I-1 died from cancer of the bowel, that the mother of I-1 died from cancer involving the pelvic organs, and that at least one sib died from cancer of the bowel. No hospital record on I-1 is available.
	II-2	M	+	+	−	−	−	32	32	32	42	Suicide was cause of death.
	III-1(P)	M	+	+	−	−	−	17	17	−	−	Diagnosis was made following rectal bleeding.
3361	I-2	F	+	−	−	−	−	•	−	−	73	Hospitalized shortly before death with findings of partial intestinal obstruction. No operation was performed.
	II-2	F	+	−	−	−	−	•	−	−	35	Exploratory laparotomy shortly before death revealed multiple metastatic nodules in liver. Pathologist's report suggests primary in gastro-intestinal tract.
	II-4	F	+	−	+	−	−	41	−	41	−	On two occasions a rectal polyp was removed; last specimen reported as showing malignant degeneration. However, diagnosis of multiple polyposis not made.
	II-5(P)	F	+	+	−	−	−	24	39	39	−	
3496	I-2	F	+	+	−	−	−	−	49	−	−	An orphan with no knowledge of parents or sibs; polyposis diagnosed during this study.
	II-2(P)	M	+	+	−	−	−	28	30	30	30	
	II-5	F	+	+	−	−	−	−	23	−	−	Diagnosed during this study.

TABLE 1.—*Concluded*

Kindred	Individual	Sex	Michigan resident	Type of Evidence				Age at				Comments
				Definite polyposis with or without cancer	Definite primary large bowel cancer; polyposis not known	Reliable lay report of polyposis or large bowel cancer	Dubious lay report of significant intestinal symptoms, polyposis or large bowel cancer	First symptoms	Diagnosis of polyposis	Diagnosis of primary large bowel cancer	Death	
A. Kindreds certainly or very probably containing two or more cases of multiple polyposis—*Continued*												
3498	I-1	M	−	+	−	−	−	•	46	41	46	According to I-1, his mother and 3 of his sisters died from cancer of the rectum. This is confirmed by I-1's daughter, II-5, who also states that a brother of I-1 has had a colostomy.
	II-1	M	−	−	−	+	−	•	•	•	−	Son of an apparently normal brother of I-1. According to II-5, II-1 had 6 rectal polyps removed at age 29±.
	II-3(P)	M	+	+	−	−	−	30	30	33	33	
	II-5	F	−	+	−	−	−	•	26±	−	−	
B. Kindreds not certainly or very probably containing two or more cases of multiple polyposis												
1825		F	+	+	−	−	−	5	8	−	−	
1963		M	+	+	−	−	−	•	27	28	−	
2067		M	+	+	−	−	−	5	5	−	−	See text.
2068		M	+	+	−	−	−	25	28	−	−	
2069		M	+	+	−	−	−	•	27	−	−	
2071		M	+	+	−	−	−	•	23	23	31	
4029		F	+	+	−	−	−	23	25	25	26	
4057		M	+	+	−	−	−	28	30	−	−	
4103		M	+	+	−	−	−	39	39	39	39	

uncertainty. Particular aspects of Tables 1 and 2 are considered in subsequent sections.

The familial kindreds are represented in the pedigrees and table as far as the data seem to warrant. It should be emphasized that the nature of the trait is such that pedigrees alone represent only a portion of the pertinent data; for more complete information the table should be consulted. Two of the 14 familial kindreds are of particular interest. Kindred 1826 has recently been described by Neel, Bolt, and Pollard (1954) and is noteworthy for its size, including 17 medically diagnosed cases of multiple polyposis. Another kindred, 1801, is remarkable for having a sibship of four persons (III, 9–12), all of whom have or have had diagnoses of multiple polyposis and/or cancer of the large bowel, three of them dying of cancer of the bowel under the age of 20 (at ages 9, 18, and 19). The earliest age at death from cancer of the large bowel among the other 22 kindreds is 26. The other unusual feature of this kindred is that in addition to diagnosed multiple polyposis in the mother of this sibship, the family physician reports that the father, II-2, was found at exploratory laparotomy to have cancer involving the stomach and transverse colon, appearing to be primary in the stomach, and the father's father had cancer of the colon. Both men died at age 37. In addition, the father's paternal grandfather is reported to have died at about the age of 35 of unknown causes. Since in none of the other 13 familial kindreds is there an affected sibship having one parent with multiple polyposis and the other with a history comparable to the above mentioned one, the question arises whether this parental history is related to the three early deaths in the sibship. It is conceivable that the father's cancer was primary in the colon like that of his own father, both arising from multiple polyposis, in which case some or all of the three early deaths in sibship III, 9–12 may have been of persons homozygous for the polyposis gene. This conjecture can neither be proved nor disproved at present.

One kindred (2067) of the nine described in Table 2 also deserves special comment because it illustrates the diagnostic difficulties which occasionally arise. At age 6 the propositus came to medical attention because of a mass protruding from the rectum; this was found to be a prolapsed polyp. After sigmoidoscopic and X-ray studies, a surgeon made a diagnosis of multiple polyposis and performed a hemicolectomy with anastomosis of the mid-transverse colon and distal sigmoid. The pathologist's report on the specimen reads as follows: "Specimen consists of a 40 cm. segment of colon with attached mesentery and a separate pedunculated polypoid granular reddish-grey lesion about 1 cm. in gross diameter. On section, the wall is essentially normal in thickness. The mucosa of the specimen contains 5 reddish-grey granular lesions varying from 5 to 10 mm. in gross diameter. Three of the specimens have very long, soft pedicles. . . ." Microscopic sections of these lesions were typical of polyps of the colon. The boy was seen by us at age 10; sigmoidoscopic examination revealed no polyps, and two barium enemas, although demonstrating a shortened colon, likewise failed to provide evidence for polyposis. A brother, aged 7, his father, aged 38, and his mother, aged 31, were all negative to sigmoidoscopy and barium enema. The maternal grandmother underwent an exploratory laparotomy at about age 60 and was found to have "generalized metastatic adenocarcinoma of the abdominal cavity" (hospital report); a maternal great aunt is reported by a physician to have undergone surgery because of carcinoma of the bowel at age 67. While there is no doubt that the propositus had multiple polyps of his distal colon, the complete absence of polyps in the remaining large bowel at the time of our examination raises doubt as to whether this is the type of multiple polyposis with which this study is otherwise concerned. It should be noted that the inclusion of this dubious case in the series does not affect any of the calculations to be presented below.

TABLE 2. FURTHER DATA ON KINDREDS IN WHICH NO MEMBERS IN ADDITION TO THE PROPOSITUS ARE KNOWN OR STRONGLY BELIEVED TO HAVE MULTIPLE POLYPOSIS

(Propositi are described in Table 1-B.)

Key: L = Living at time of investigation; D = Deceased at time of investigation, from non-violent cause; K = Deceased at time of investigation, from violent, accidental cause.

Kindred	Parents of propositi (Age at time of investigation or at death)		Sibs of propositi		Significant intestinal symptoms in near relatives of the propositus	Details (All relationships refer to propositus)
	Father	Mother	No. living to age 5 or more (full & half-sibs)	Age range		
1825	K36	L35	1	10	+	Father had good health until accidental death. Mother in good health; normal sigmoidoscopic examination at 35. Father had 2 sibs, now aged 43 and 36, the older found to have cancer of recto-sigmoid colon at age 41, which was resected. Barium enema, sigmoidoscopy, and pathology reports on this man did not mention multiple polyposis. Paternal grandfather was drowned at about 30; paternal grandmother, according to death certificate, died at 55 from cancer of cervix. Mother has one sib, normal at 29. Maternal grandfather in good health at 59; maternal grandmother at age 55 reports having had "colon trouble" for 15 yrs. but sigmoidoscopy revealed no polyps.
1963	L69	L69	9	25–40	−	7 full sibs, 2 half-sibs. Sibs and parents live out of Michigan. Mother writes that she, father, and all sibs are in good health.
2067	L38	L31	1	7	+	See text.
2068	L58	L51	3	25–32	+	(All information from the propositus): Sibs appear to be normal. Father in good health no bowel symptoms known among his sibs and parents. Mother has had "stomach and bowel upsets" for some time. Sibs and parents refuse examination. Mother has 7 sibs, one of whom is reported to have had a colectomy like that of propositus; he refuses to allow his medical record to be examined. No other persons with gastro-intestinal complaints are known.
2069	L55	L51	2	26–32	+	(All information from propositus and one sib): Sibs and parents appear normal. Father has 4 sibs, one of whom is reported to have died at 63± from intestinal obstruction. This report cannot be confirmed or refuted. No other persons with g.i. complaints are known.

2071	L56	L54	5	21–33	–	One sib killed in accident at 21. Two sibs examined at ages 30 and 29 were normal by sigmoidoscopy and barium enemas. Fairly detailed family history through grandparental generation reveals no person with significant intestinal symptoms.
4029	L60	L57	5	16–35	+	One half-sib aged 35 normal to sigmoidoscopy and barium enema. Three full sibs, ages 23, 21, and 18 at time of examination; barium enema on the oldest, barium enema and sigmoidoscopy on the middle sib, and sigmoidoscopy on the youngest all reveal normal colons. The youngest full sib, not examined, appears normal at 16. The parents do not have significant g.i. complaints but each is vaguely reported to have a sib with possible intestinal symptoms. No other persons with significant intestinal complaints are known.
4057	K53	L50	2	25–32	–	Father normal; killed in accident. Mother normal. Older sib normal by sigmoidoscopy and barium enema. Younger sib has had some rectal bleeding but will not be examined. No other persons with g.i. complaints are known.
4103	D48	L64	1	33	+	Father probably died of heart disease. Mother well. Sib well. No relatives with g.i. complaints known.

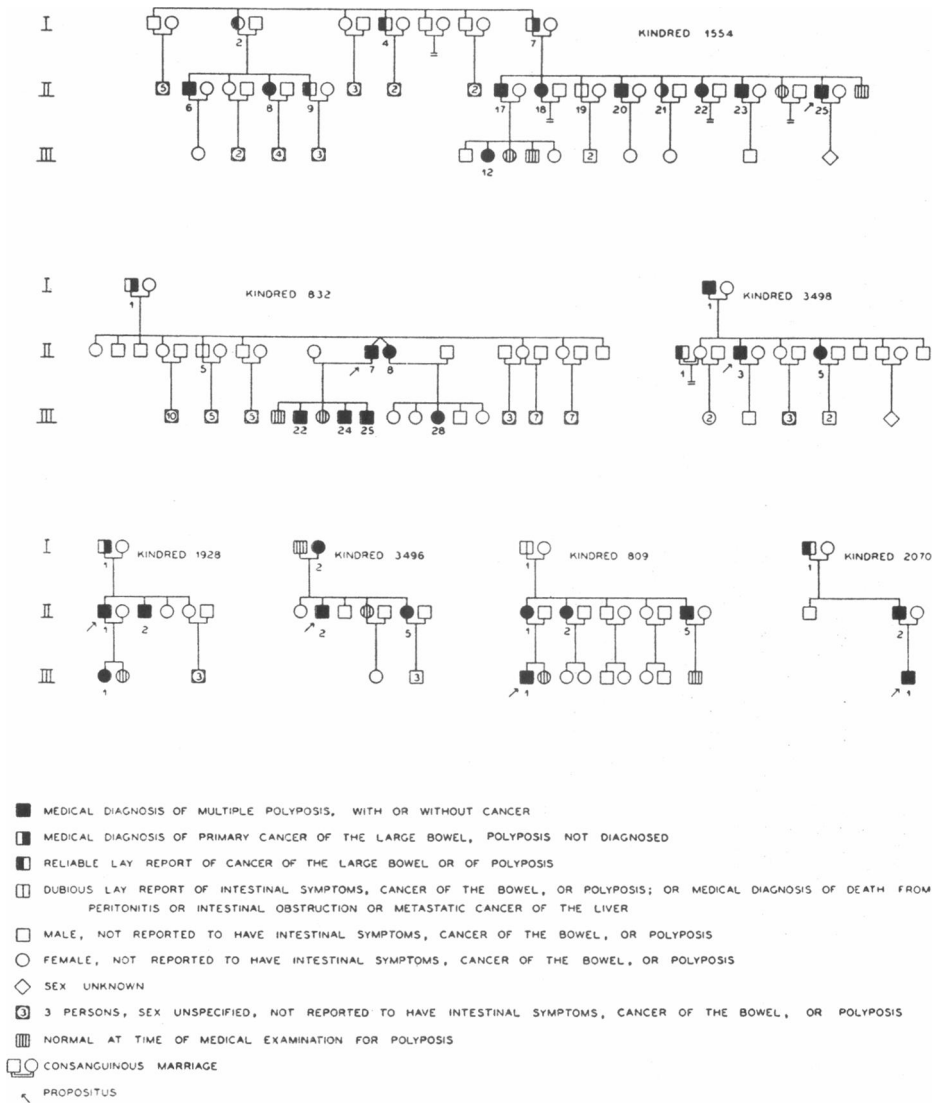

FIG. 1. Pedigrees of kindreds which contain two or more individuals with multiple polyposis.

INHERITANCE

The published pedigrees of multiple polyposis clearly indicate that this trait is usually, if not always, determined by a dominant gene of fairly high penetrance. The distribution of affected persons within the kindreds of the present study is in keeping with the reports in the literature, medically diagnosed polyposis occurring in two generations of 10 kindreds and in three generations of one.

Unfortunately, a precise calculation of the proportion of affected and unaffected sibs within sibships having a parent with polyposis, desirable as a check on the

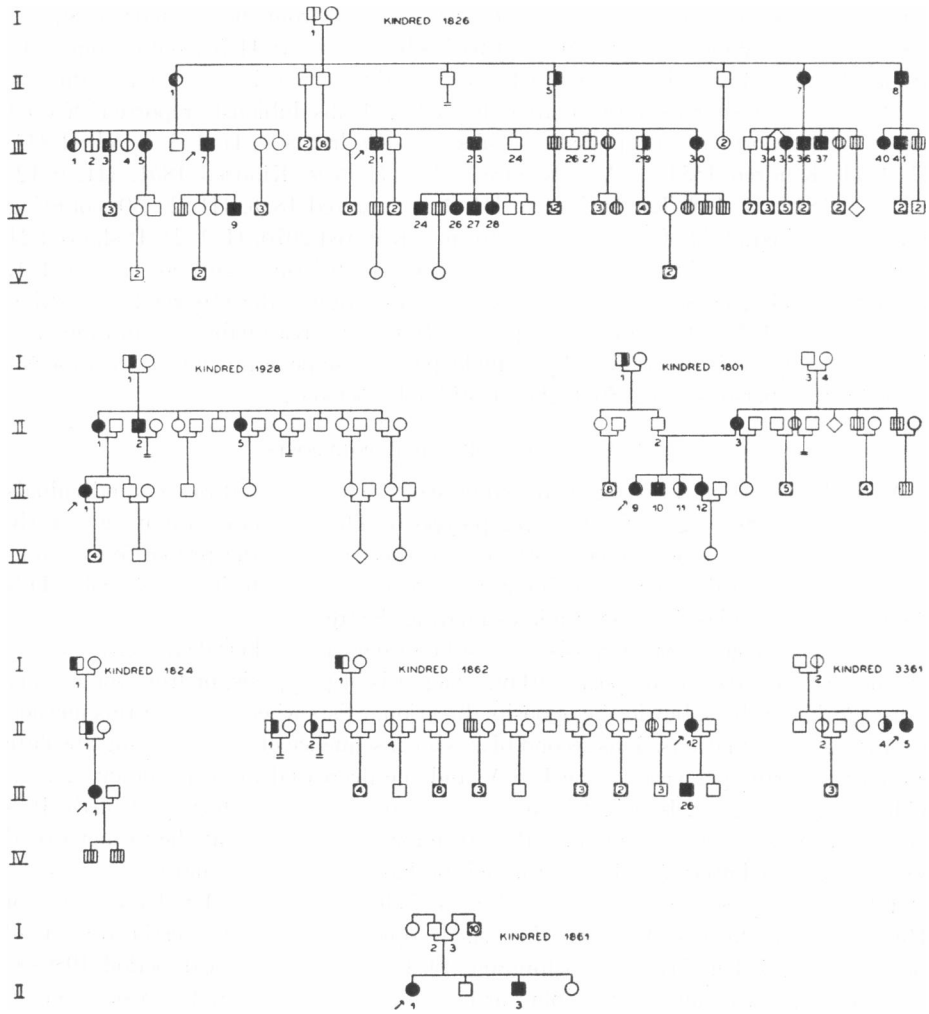

FIG. 1

hypothesis of dominant inheritance and on the degree of penetrance under this hypothesis, is not possible. The late onset of symptoms and diagnosis in some individuals (about 10 per cent of the medically diagnosed cases are first diagnosed over age 45) and the lack of diagnostic information on a number of individuals account for the fact that not one sibship in the 14 familial kindreds gives critical information on the segregation of the gene for polyposis. However, it is possible to obtain a rough test for agreement with the expected 1:1 ratio in segregating sibsips by using only sibships in which persons reported to be normal are well within the age of manifestation of the trait, and, at the same time, employing conservative criteria in classifying individuals with respect to the trait. In this calculation, two kinds of sibships—that of the propositus and, where possible, that of his affected parent—have been utilized;

the propositus and affected parent have been excluded from the calculation. Such a test, in which the minimum age of "normal" sibs was set at 41 (except for one individual, Kindred 1826, III-24 described below), and in which sibs reported as affected by "reliable" lay sources were counted affected, and sibs dubiously reported affected were counted normal, was applied to 9 sibships (Kindred 809, II, 1–5; Kindred 832, II, 1–11; Kindred 1554, 1, 1–7; Kindred 1554, II, 6–9; Kindred 1801, III, 9–12; Kindred 1826, II, 1–8; Kindred 1826, III, 1–9; Kindred 1826, III, 20–30, counting III, 24 who died at 32 of "epilepsy" as normal; Kindred 2070, II, 1–2). It showed 24 affected persons and 36 unaffected, a proportion not differing significantly from 1:1. If there is 1:1 gene segregation and reduced penetrance, the observed proportion deviates from 1:1 in the direction expected. It seems a reasonable assumption that multiple polyposis is determined by a single gene whose penetrance is of the order of 90 per cent in persons of age 50, higher in still older persons.

FREQUENCY OF MULTIPLE POLYPOSIS

An attempt was made to obtain an estimate of the frequency at birth of individuals heterozygous for the gene for multiple polyposis. This estimate cannot be directly determined, but an approximate estimate can be based on the proportion of individuals dying within some time-interval who have had multiple polyposis. This approximation is biased toward underestimating the frequency at birth because some persons with the gene for polyposis will not be recognized at their death, either dying of cancer secondary to polyposis without diagnosis of polyposis, or from some other cause. A further bias, but in the opposite direction, exists when applying this method to American populations. This second bias is a consequence of the increasing absolute number of births per year in the U.S.A. and the decreased life expectancy of individuals with the gene. Its effect is to over-estimate the true frequency at birth. It is not possible to make any adequate allowance for these biases, but the former would seem to be more important. This estimate is probably an underestimate.

The frequency estimate was obtained in the following manner. The Department of Health of the state of Michigan furnished copies of the death certificates of all persons who died in Michigan before age 40 during the three-year period 1950–52 from primary carcinoma of the colon or rectum. One hundred and two such certificates were on file. On 25 certificates it was stated that an autopsy had been performed. The findings on these certificates were accepted as final. An effort was made to contact the next-of-kin of each of the remaining 77 deceased persons to obtain permission for the release of medical information to the Heredity Clinic. After receiving such permission, letters were written to the deceased's physician and to the hospitals where the deceased was studied, requesting copies of his medical records in order to determine whether he had multiple polyposis. In 59 cases medical reports were obtained, and in 18 they were not obtained. This procedure yielded 4 persons with multiple polyposis (Kindreds 3496, 3498, 4029, and 4103); only one (Kindred 4103) of these 4 persons had a death certificate which failed to state that multiple polyposis was present. The proportion of known cases of multiple polyposis is therefore 4/102 or 0.039 ± 0.019.

It soon became apparent that a frequency estimate based on this proportion would

be a minimal one. Thus, some death certificates fail to mention multiple polyposis even when the persons' hospital records do. Furthermore, in 3 of the 23 kindreds included in this study, the hospital records of persons who were parents of two or more children who themselves had polyposis, stated only that cancer of the large bowel was present. It is almost certain that these three persons (see Pedigrees 832, 1564, and 1982) had the gene and trait of multiple polyposis. In order to obtain a more reliable estimate of the proportion of persons dying before age 40 from primary cancer of the large bowel secondary to multiple polyposis, a survey was made of all the records of persons dying before age 40 from primary cancer of the rectum and colon who were studied at the University Hospital, Ann Arbor, in the period 1935–1944. Of 58 such persons, 6 had definite multiple polyposis and 1 had questionable multiple polyposis. Counting only the 6 definite cases, the proportion is 6/58 or 0.103 ± 0.040. It is clear that this may be an underestimate of the true proportion.[2]

In a population in equilibrium, the frequency (f) at birth of individuals with the gene for polyposis is equal to the frequency, among all deaths in a specified time interval, of individuals dying with the gene. If, for a specified population,

T = the specified time interval
P = the number of individuals with the gene for polyposis dying in T
D = the total number of deaths of all individuals in T
a = the observed proportion of individuals, among those dying before age 40 from primary cancer of the large bowel, whose cancer is secondary to multiple polyposis
b = the observed number of individuals dying before age 40 from primary cancer of the large bowel in T
c = the observed proportion of individuals, among those dying from cancer of the large bowel secondary to multiple polyposis, who die before age 40

then an approximation to P is given by ab/c. This estimate of P will be too low since some persons with the gene for polyposis fail to die from, or are not recognized as having died from, cancer secondary to multiple polyposis. For T we have used the three-year interval 1950–52. From the preceding section a is 0.103 ± 0.040; b for the state of Michigan is 102; c from Table 6 is 45/91 or 0.495 ± 0.052; D for the state of Michigan is 175,842. The frequency at birth is then approximated as

$$f = \frac{P}{D} \sim \frac{ab}{cD} = \frac{(.103 \pm .040)(102)}{(.495 \pm .052)(175{,}342)}$$

$\sim (1.21 \pm 0.49) \times 10^{-4}$ or 1 in 8,300 individuals. The expression ab/c neglects individuals with the gene for polyposis who die of causes other than cancer secondary

[2] An observation which may be pertinent here is that the frequency distribution of age at death from cancer of the large and small intestine (almost entirely due to the large intestine) shows a noticeable "bump" at the 30–34 year interval relative to the corresponding distribution for cancer of the stomach (data from Michigan Department of Health over the interval 1933–1945 inclusive.) Multiple polyposis will contribute to the former distribution but not to the latter so that it seems possible that the early age at death subsequent to polyposis may be responsible for this bump. If such is the case and if, in this age range, and in the absence of polyposis, the two frequency curves are proportional, one can estimate that cancer following polyposis may account for as much as a quarter of all cancer of the colon under age 40.

to polyposis, and a may well be an underestimate of the true proportion of individuals, among those dying before age 40 from primary cancer of the large bowel, whose cancer is secondary to polyposis. Therefore the true value of f is probably higher than the calculated value. It should be noted that because persons with the gene for polyposis have a decreased life expectancy, the frequency of such persons in the general population will be less than (approximately two-thirds) that at birth.

RELATIVE FITNESS OF INDIVIDUALS WITH MULTIPLE POLYPOSIS

Fitness, in a population sense, is measured by ability to produce children and is a function of viability (from birth through the reproductive period) and fertility (in the narrow sense, once the reproductive period is reached). The fitness of a class of individuals relative to that of another class may, under ideal conditions, be measured by the ratio of the expectation *at birth* of the number of live-born children to be produced by a live-born individual of the first class, to the corresponding expectation of the second class. If the first class is composed of heterozygotes for a rare dominant gene which lowers fitness, such as that for multiple polyposis, and the second class is the remainder, all normal in this respect, of a population in equilibrium, this estimate of relative fitness (W) is also the proportion of the dominant genes transmitted from one generation to another. An estimate of W for multiple polyposis will measure the degree of natural selection for or against bearers of the gene and is required in the indirect estimation of the mutation rate. Two independent methods of calculating W are available.

The direct calculation of relative fitness from the observed reproductive performance of affected persons and their normal sibs is complicated by the late manifestations of multiple polyposis in some individuals. Depending on the method of ascertainment of the data, a possible further complication is the tendency of members of large families to have more children than members of small families (Fisher, 1930). The first difficulty is somewhat reduced by using only sibships whose apparently normal members were all over 40 years of age at the time of investigation or at death. Six such sibships are available; they are described in Table 3. It is clear that appearance of polyposis in persons after 40 can make this estimate of W an underestimate since, on the average, these persons are very probably more fertile than persons affected before 41. In theory, this restriction introduces a possible bias from deaths before age 41 of individuals lacking the gene for polyposis. In our sample, however, there were no such deaths among the apparently normal members of these sibships, thus eliminating this source of bias. Unfortunately, the 6 sibships are heterogeneous with regard to ascertainment, 2 containing a propositus, 2 containing one parent of a propositus, 1 containing two parents of propositi, and 1 containing first cousins of the propositus. Lacking a suitable weighting procedure to correct for ascertainment and sibship size frequency, it seems best to calculate W simply as the ratio of the mean number of children from persons affected with polyposis to the corresponding mean for the apparently normal sibs, using pooled data of the six sibships. From the totals of Table 3, the mean for affected persons is $45/18 = 2.50$ and that for "normal" persons is $78/23 = 3.39$, giving an estimate of W of 0.74. If, in fact, there is no

TABLE 3.—DESCRIPTION OF SIBSHIPS USED IN DIRECT CALCULATION OF RELATIVE FITNESS
All "normal" individuals were over age 40 at time of investigation or at death. See "Remarks" for details on omission of certain individuals.

Sibship	Size	Affected		"Normal"		Remarks
		(Usable) number	No. of children	(Usable) number	No. of children	
1554 (II, 6–9)	4	3	8	1	2	All persons usable; first cousins of the propositus.
809 (II, 1–5)	5	2	3	2	4	II-1, parent of propositus, excluded.
1554 (I, 1–7)	7	2	6	4	10	I-7, parent of propositus, excluded.
1826 (II, 1–8)	8	2	9*	4	12	II-1 and II-5, parents of propositi, excluded.
1826 (III, 20–30)	11	5†	16	4	26	III-24 and III-26 excluded because of uncertain status with regard to polyposis. A propositus is included.
1862 (II, 1–12)	12	4‡	3	8	24	All persons usable; the propositus is included.
Total.....	—	18	45	23	78	

* Twins counted as one individual.
† III-27 counted as affected.
‡ II-4 counted as affected.

difference in the means, the probability of obtaining an estimate as low as or lower (single-tail test) than the one observed is 0.05.

The second method for estimating relative fitness is indirect and requires the assumptions that (1) the only effect on W of the gene for multiple polyposis is through the death, from cancer secondary to polyposis, before the end of the reproductive period, of some affected individuals, and (2) that until their death persons with the gene reproduce at the same rate as persons lacking the gene. There appear to be no data suggesting that the first assumption is incorrect with regard to the *biological* action of the gene, although the possibility of pleiotropic effects must always be considered. The second assumption, judging from the present data, appears to be reasonable for the period up to the time of first bowel complaint. The possibility exists that some children of affected parents will restrict their reproduction when they are concerned about the appearance of polyposis in their own descendants. Such restriction was not apparent in our data. Reproductive capacity is, of course, impaired in the interval between onset of symptoms and death. The bias resulting from making the second assumption, however, appears to be only several percent. This bias is discussed below.

This estimate of W, then, will actually be a function of relative survival to and through the reproductive period. The quantity, which we here equate with W, we may term the "relative reproductive span" or RRS.[3]

[3] Although the use of RRS as a measure of fitness appears permissible in the present context, it should be recognized that for many dominant traits this is not the case. Thus, Crowe, Schull, and Neel (in press) find that although part of the effect of the gene responsible for neurofibromatosis on

If

p_x = the proportion of births, among all births, which occur to parents of age x (mean of values of paternal and maternal age distributions),

l_x = the proportion of all live-born individuals with the gene for polyposis who survive to age x,

L_x = the proportion of all live-born individuals lacking the gene for polyposis who survive to age x, and

d_i = the proportion of deaths, among all deaths from cancer secondary to polyposis, which occur at age i,

then

$$RRS = \sum_x p_x \left(\frac{l_x}{L_x}\right) \sim \sum_x p_x \left(1 - \sum_0^{x-1} d_i\right),$$

summation extending over the longest life span. These relations are derived in the appendix.

To obtain estimates of d_i both the data of the present study and the excellent study of Dukes (1952) were used. Utilizing only individuals dying at a known age from medically diagnosed cancer of the large bowel and who either were medically diagnosed as having multiple polyposis or who were close relatives of persons so diagnosed, 29 ages at death were obtained from the present study and 62 from that of Dukes. The period over which these deaths occurred was 1916–1953, with a mean at 1940.4 for the present study, and 1882–1951, with a mean at 1930.2 for the 59 deaths of Dukes' study for which data are given. There was one other death before 1900 among these 59. The distribution of these ages is given in Table 4 and the means, standard deviations, and standard errors in Table 5. It is seen that the means and variances of males and females do not differ significantly within the two studies nor do the means and variances between the studies. It was therefore considered appropriate to combine all data, resulting in a mean age of death of 40.21 $\pm$ 1.23 years and a standard deviation of 11.77 years. In spite of a marked dip at the 35–39 year interval the combined distribution does not differ significantly from that expected of a normal curve with the same mean and variance. To reduce the effects of chance fluctuation in the proportions of deaths in the 5-year-age intervals, it seemed advisable to estimate d_i from the normal curve.[4] Values of d_i through the reproductive period are

fitness is exerted through the early death of a few individuals with the trait, the major effect is a decreased marriage rate on the part of persons with the trait, as well as impaired fertility after marriage. At the other extreme, Panse (1942) and Reed and Palm (1951) have suggested that despite the early death of some persons with Huntington's chorea, the net fertility of affected persons is actually greater than normal.

[4] It is recognized that it is unlikely that the distribution is normal. More extensive data would doubtless make this apparent and also would permit a decision as to whether or not the two observed peaks in Table 5, at 30–34 years and 45–49 years, are real. At the present stage of our knowledge the assumption of normality, for purposes of calculation, seems justified by the symmetry of the mean with respect to the extremes and by the similarity of the distributions around the modes of age-at-death curves for various diseases. The mean age at death in polyposis of 40 years, with extremes at about 10 and 70 years, suggests a symmetrical distribution, while the bell-shaped distributions around the mode found in many diseases, including various cancers, suggest that the normal distribution is not unreasonable.

TABLE 4.—DISTRIBUTION OF AGES AT DEATH OF PERSONS DYING FROM CANCER OF THE COLON OR RECTUM ARISING FROM MULTIPLE POLYPOSIS (CANCER MEDICALLY DIAGNOSED)
Present study and Dukes, 1952

Age at death	Present study*	Dukes, 1952†	Total
0–4	0	0	0
5–9	1	0	1
10–14	0	0	0
15–19	2	0	2
20–24	0	3	3
25–29	3	6	9
30–34	7	14	21
35–39	1	8	9
40–44	4	8	12
45–49	6	9	15
50–54	3	5	8
55–59	0	6	6
60–64	1	2	3
65–69	0	1	1
70–74	1	0	1
75+	0	0	0
Total	29	62	91

* Omitting the 4 persons selected for having died under 40 years of age. Multiple polyposis either medically diagnosed or inferred from existence of a parent or child with medically diagnosed multiple polyposis.

† All individuals are members of kindreds containing at least one medically diagnosed case of multiple polyposis. Diagnosis of cancer established by one of the following: medical or death certificate, medical examination, hospital record.

given in Table 6. Values of p_x for Michigan are available from the vital statistics of the U. S. Bureau of the Census for 1934 and later years. In order to make the data for p_x and d_i more comparable, p_x for Michigan in 1935 was used. The values of p_x and the calculation of the relative reproductive span are given in Table 6. This estimate is 0.78, slightly higher than the previous estimate of W of 0.74 obtained from the observed reproductive performance of 6 sibships. This latter estimate is considered less reliable than the RRS estimate because (1) it is based on few data, (2) the diagnoses of a number of individuals are not certain, and (3) the method to correct for ascertainment and sibship size is not apparent.

Two known biases of this estimate should be considered. One bias is in the formula for the RRS. The derivation of the formula used shows that it slightly underestimates the true value of l_x/L_x, and hence of RRS. A bias in the opposite direction results from the assumption that reproduction continues until death from cancer secondary to polyposis. Among the 29 cases of the present study used in estimating the mean age at death, data were available in 17 cases on the interval between onset of significant bowel complaints and death from cancer. This interval varied from less than one year to 14 years, with a mean of 3.2 years. Of these 17 cases, 10 died under age 40 and the intervals varied from less than one year to 8 years, with a mean at 2.8 years. Since, on the average, reproductive capacity does not end with onset of bowel com-

TABLE 5.—AGE AT DEATH FROM CANCER OF THE COLON OR RECTUM OF PERSONS WHOSE CANCER AROSE FROM MULTIPLE POLYPOSIS (CANCER MEDICALLY DIAGNOSED)
Present study and Dukes, 1952

Source*	Individuals	Number		All deaths		
		Dying < 40 years	All deaths	Mean	Standard deviation	Standard error
Present study	Males	6	15	42.00	13.76	3.55
	Females	8	14	35.57	11.54	3.08
	Males and females	14	29	38.90	12.93	2.40
Dukes, 1952	Males	18	34	40.24	10.59	1.82
	Females	13	28	41.54	12.17	2.30
	Males and females	31	62	40.82	11.25	1.43
Present study and Dukes, 1952	Males and females	45	91	40.21	11.77	1.23

* See Table 4 for further description.

TABLE 6.—CALCULATION OF THE RELATIVE REPRODUCTIVE SPAN (RRS). SEE TEXT FOR SYMBOLS

x, i (Age interval)	p_x	d_i	$1 - \sum_0^{x-1} d_i$ *
0–14	.000	.016	.992
15–19	.063	.027	.970
20–24	.250	.0555	.929
25–29	.275	.0935	.855
30–34	.200	.138	.739
35–39	.125	.162	.589
40–44	.060	.167	.425
45–49	.019	.138	.272
50–54	.006	.099	.153
55+	.002	.104	.052
Total	1.000	1.000	—

* $\sum_0^{x-1} d_i$ as used here represents the proportion of deaths up to the mid-value of each age interval.

$$RRS = \sum_0^{100} p_x \left(1 - \sum_0^{x-1} d_i\right) = 0.78$$

plaints but will steadily decline from that time, the above assumption involves an error of a year or so. A method based on this assumption will overestimate the true value by a few percent. It is not possible to say whether these two biases will cancel out. The relative fitness at the present may be higher than the calculated value since this value depends on deaths with a mean around 1935. Better diagnosis and greater use of radical surgical procedures in the future treatment of multiple polyposis may be expected to increase the life expectancy of affected individuals and so raise the relative fitness.

CALCULATION OF THE MUTATION RATE ESTIMATE

Because of the late appearance of polyps, and symptoms subsequent to polyps, in some individuals (e.g., Dukes (1952) studied an individual who at 38 was normal to sigmoidoscopy but at 44 had polyps and at 56 developed carcinoma of the colon; in the present study III-5 in Kindred 1826 first had intestinal complaints at age 57; polyposis was diagnosed at 58), it is not possible, at present, to be certain that any individual will not later develop polyposis, although it seems quite unlikely that polyps will first appear after age 50. Therefore, it is not feasible to calculate a direct estimate of the mutation rate. Only one kindred (1963) of the present study presents a reasonable case for mutation. The propositus of this kindred has 9 sibs whose ages range from 25 to 40 and both parents are living at age 69; all are reported free of significant intestinal complaint. Several other kindreds may demonstrate mutation but again no proof can be offered. At present we are forced to rely on an indirect calculation of the mutation rate.

If the mutation rate/gene/generation is m and the population is in equilibrium with respect to production and loss of genes for polyposis, the following customary equation applies:

$$m = \frac{f(1 - W)}{2}.$$

The estimate of W from the relative reproductive span is more reliable and will be used here. Substitution of the values for f and W gives

$$m = \frac{1.21 \times 10^{-4}(1 - .78)}{2} = 1.3 \times 10^{-5}$$

Since f is probably an underestimate, the value of m may, perhaps, actually be up to twice this value. The probable bias of W is not known. Considering the bias of f, it seems unlikely that the true value of W would be such that m would be less than about three-fourths of the calculated value. m probably lies within the range $1\text{–}3 \times 10^{-5}$.

DISCUSSION

The present study is one of a series of investigations on mutation rates carried out by this Clinic. Some of the problems inherent in such investigations, as they have impressed themselves on us, have been discussed elsewhere (Neel, 1952; Neel and Schull, 1954; see also Haldane, 1949, Nachtsheim, 1954; and Vogel, 1954). In addition to certain methodological questions which are common to all mutation rate studies, each trait selected for study has raised particular difficulties more or less unique to that trait. Thus, in the case of multiple polyposis, we are confronted with the fact that it is very difficult to demonstrate that any particular "sporadic" case is due to mutation. As a consequence, no use can be made of the "direct" method of estimating mutation rate (i.e., from the observed frequency of sporadic cases). Both the necessity of performing sigmoidoscopic and X-ray studies on the parents of affected persons and the late appearance of polyps and symptoms in some individuals

preclude even an approximate direct determination of mutation rate. In passing, we may note that although we recognized the unpleasant nature of these diagnostic studies, we were unprepared for the lack of cooperation sometimes encountered, especially since the studies were so obviously to the advantage of the person being investigated.

Since the direct method was not feasible, we have employed the indirect approach, based on estimates of frequency and relative fitness. The estimation of the relative fitness of affected individuals proved to be difficult, partly because it approaches that of the general population. The observed relative fitness of about 0.8 is appreciably higher than that of most other dominant traits for which mutation rate estimates exist. The most critical assumption underlying the use of the indirect method, in this and other studies, is that genetic equilibrium obtains, i.e., that the loss of genes (for the trait in question) in each generation is balanced by the appearance of new genes through mutation. While there are on record a number of kindreds highly suggestive of the occurrence of mutation with respect to the gene for multiple polyposis (e.g., our Kindred 1963; families 12 and 21, Dukes, 1952; 1 kindred, Gardner and Woolf, 1952), the assumption that the polyposis locus is in genetic equilibrium because of mutation from the normal allele to the gene for multiple polyposis is less tenable here than in the case of some other dominant traits which have been utilized in mutation rate studies. On the other hand, the proportion of propositi whose disease is not clearly inherited in both this study and that of Dukes (1952), while obviously an overestimate of the true proportion of sporadic cases, is in keeping with the hypothesis that each generation about one-quarter of the polyposis genes must arise through mutation if genetic equilibrium exists.

A few general remarks concerning the philosophy of this Clinic with regard to mutation rate studies are perhaps appropriate at this point. Almost every mutation rate estimate advanced to date—not excluding our own—can be subjected to severe criticism. It seems not only possible but probable that many of the existing estimates err by a factor of two or even more. At this stage in our developing appreciation of the problem, this does not seem to us a serious deterrent to such studies. The present challenge is to fix the order of magnitude of the phenomenon in a relatively long-lived animal, by a series of studies on as many traits as possible. Later, as techniques improve and the outlines of the problem become clearer, greater accuracy will be possible, as will a comparison of human mutation rates with those of other forms. The present estimate of $1\text{–}3 \times 10^{-5}$ mutations/gene/generation falls well within the range of other available estimates, all of which, of course, assume that only a single locus is involved. The dangers inherent in attempting to generalize at the present time from this and the other existing estimates to *all* genes have been discussed elsewhere (Neel and Schull, 1954). On the other hand, each new estimate strengthens the foundation of fact from which generalizations may someday be possible.

CONCLUSIONS AND SUMMARY

In a study of the genetics of multiple polyposis of the colon, a rare dominant trait, special emphasis has been given to the estimation of the frequency and relative fitness of individuals bearing the gene, and of the mutation rate of the gene. The

material of this study consists of 23 kindreds, including 70 certainly and 13 probably affected persons. Fourteen of the 23 kindreds contain two or more affected members. The mean age at death from cancer of the colon or rectum subsequent to polyposis, in 91 very probably or certainly affected individuals in the present study and in that of Dukes (1952), was 40.21 ± 1.23 years. From a survey of the University of Michigan Hospital records between 1935 and 1944, the proportion of individuals, among persons dying before age 40 from cancer of the colon or rectum who also had multiple polyposis, was estimated. This estimate, which is minimal, is 0.103 ± 0.040. From these facts and the known distribution of age at death from cancer of the colon and rectum in Michigan, an estimate of the minimum frequency at birth of individuals with the gene for multiple polyposis was obtained: $(1.21 \pm 0.49) \times 10^{-4}$ or 1 in 8,300.

Two estimates of the relative fitness of individuals with the gene have been derived, the more reliable being that of the "relative reproductive span." This is a weighted measure of the survival, to and through the reproductive period, of persons with the gene relative to that of persons lacking the gene. This estimate is 0.78. Using these estimates for frequency and relative fitness, and considering the known biases involved, the mutation rate is estimated to be $1\text{–}3 \times 10^{-5}$/gene/generation.

An appendix derives equations for the estimation of relative reproductive span.

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APPENDIX

DERIVATION OF EQUATIONS FOR ESTIMATING THE RELATIVE REPRODUCTIVE SPAN (*RRS*)

The direct estimation of the relative fitness of individuals with a disease like multiple polyposis, from their observed reproductive performance, may be unsatisfactory because of the late onset of the disease in some individuals. In such a situation an indirect estimate may be necessary. If reliable data are available on the age at death due to the disease and the assumption is justified that early death from the disease is the only factor lowering the relative fitness of such individuals, it is possible to obtain an indirect estimate which may be more reliable than the direct.

Consider two cohorts, C_1 and C_2, each containing N new-born individuals (N being large). The cohorts differ only because all members of C_1 have the gene for polyposis and all members of C_2 lack it. If the cohorts are enumerated each year from birth ($x = 0$) to death, and births to cohort members at each year x are noted, we may define the following terms:

$$f_x = \text{age-specific fertility} = \frac{\text{number of births to a cohort in the year } x}{\text{number of individuals of the cohort alive at the beginning of year } x},$$

l_x = proportion of C_1 surviving to age x,

L_x = proportion of C_2 surviving to age x.

f_x is postulated to be equal for the two cohorts, i.e., as long as an individual with the gene is living he is assumed to be as fertile as individuals lacking the gene. (The small bias introduced by this assumption is discussed in the text.)

Our observed data on births and deaths are not in terms of cohorts but are obtained from a population composed of all ages. It is therefore pertinent to note that for a normal population in equilibrium the age-distribution will be that of a "life table population" (Dublin, Lotka, and Spiegelman, 1949), i.e., L_x is the proportion of persons who are age x. We shall make use of this equivalence below. In terms of the observed population data we may define two further terms:

p_x = the proportion of births, among all births, which occur to parents of age x (mean of values of paternal and maternal age distributions),

d_i = the proportion of deaths, among all deaths, from cancer secondary to polyposis which occur at age i.

The mean number of children (live-born) ever born to the N members of C_1 is

$\sum_x l_x f_x$, the summation extending to the longest life span. The corresponding mean for the N members of C_2 is $\sum_x L_x f_x$. Therefore,

$$W = \text{relative fitness} = \frac{\sum_x l_x f_x}{\sum_x L_x f_x}.$$

But, for any age j

$$f_j = \frac{N p_j \sum_x L_x f_x}{N L_j}, = \frac{p_j \sum_x L_x f_x}{L_j},$$

so that

$$W = \sum_x p_x \left(\frac{l_x}{L_x}\right),$$

under the above assumptions, summation again extending to the longest life span.

If the assumption stated above, i.e., that early death is the only effect of the gene on fitness, does not hold, $\sum_x p_x \left(\frac{l_x}{L_x}\right)$ will not equal W. We may define $\sum_x p_x \left(\frac{l_x}{L_x}\right)$ as the *relative reproductive span* (RRS). Its usefulness for the present study as a means of estimating W, requires the above assumption, but, for other traits where a direct estimate of W is available, it may be helpful in testing the validity of this assumption.

Let

q_x = probability that a person with the gene for polyposis who reaches his xth birthday will die from cancer secondary to polyposis before his $x + 1$th birthday,

r_x = probability that a person lacking the gene for polyposis who reaches his xth birthday will die before his $x + 1$th birthday.

Since persons with the gene for polyposis, before onset of symptoms, are assumed not to differ from persons without the gene, and, if after onset of symptoms they are considered to be still subject to all the other causes of death from which persons without the gene die, the probability that such a person will die within the year following his xth birthday is $q_x + r_x - q_x r_x$ (very nearly; shorter time intervals would make this more exact). Since $q_x r_x$ for ages of interest to us, i.e., up to the end of the reproductive period, is small compared to q_x and r_x, we may neglect this term and write

$$l_x = 1 - \sum_0^{x-1} l_i(q_i + r_i)$$

and

$$L_x = 1 - \sum_0^{x-1} L_i r_i.$$

Neglecting products of the form $q_i r_j$, etc. we may write

$$L_1 = l_1 + l_0 q_0 ,$$

$$L_2 = l_2 + l_1 q_1 + l_0 q_0 ,$$

and, in general,

$$L_x = l_x + \sum_0^{x-1} l_i q_i .$$

Therefore

$$L_i r_i = l_i r_i + r_i \sum_0^{i-1} l_j q_j$$

and

$$\frac{l_x}{L_x} = \frac{1 - \sum_0^{x-1} l_i (q_i + r_i)}{1 - \sum_0^{x-1} l_i r_i - \sum_0^{x-1} \left[r_i \sum_0^{i-1} l_j q_i \right]}.$$

Let

$$K_x = \sum_0^{x-1} \left[r_i \sum_0^{i-1} l_j q_i \right].$$

Then

$$\frac{l_x}{L_x} = 1 - \frac{\sum_0^{x-1} l_i q_i - K_x}{1 - \sum_0^{x-1} l_i r_i - K_x}$$

Since, nearly,

$$\sum_0^{100} l_i q_i + \sum_0^{x-1} l_i r_i + \sum_x^{100} l_i r_i = 1,$$

and putting

$$\sum_0^{100} l_i q_i = P$$

where P is the proportion of persons born with the gene for polyposis who die from cancer secondary to polyposis, and noting that, by definition,

$$\sum_0^{x-1} d_i = \frac{\sum_0^{x-1} l_i q_i}{\sum_0^{100} l_i q_i} = \frac{\sum_0^{x-1} l_i q_i}{P},$$

then

$$\frac{l_x}{L_x} = 1 - \frac{\sum_0^{x-1} d_i - \frac{K_x}{P}}{1 + \frac{\sum_x^{100} l_i r_i}{P} - \frac{K_x}{P}}.$$

Since only $\sum_0^{x-1} d_i$ is known, it is necessary to consider the appropriateness of estimating l_x/L_x by $1 - \sum_0^{x-1} d_i$. The magnitude of P is not known with certainty but study of kindreds in which the gene for polyposis is segregating yields information since we find (in this study and in Dukes, 1952) that the observed proportion of cases of polyposis among adult offspring of an affected parent approaches the expected 0.5 and that large bowel cancer usually follows before age 50 is reached, although there are several instances of later onset. It seems unlikely that during the present century any large proportion of individuals born with the gene fails to manifest multiple polyps and subsequent cancer. Such cancer, until recently, must usually have proved fatal. The 1940 American life table indicates that about 83 per cent of live-born individuals will be alive at age 50 and, therefore, persons with the gene are likely to survive to the age where cancer from malignant degeneration of polyps is prevalent. With these considerations, the value of P would be expected to be at least of the order of 70 per cent. For low values of x, e.g., in the case of multiple polyposis under 25 years of age, the expression for l_x/L_x is seen to reduce to $1 - \frac{\sum_0^{x-1} d_i}{1 + \frac{1-P}{P}}$, so that if $\sum_0^{x-1} d_i = 0.1$ and $P = 0.7$, $l_x/L_x = 0.93$, while the approximation $1 - \sum_0^{x-1} d_i$ gives 0.90. A higher value for P, of course, makes this approximation better. The approximation should be of this order in the middle-aged range and, for high x, should be better yet.

If we introduce this approximation to l_x/L_x into our previous formula for *RRS*, we have

$$RRS = \sum_x p_x \left(1 - \sum_0^{x-1} d_i\right),$$

the relation to be derived. This estimate should slightly underestimate the true value of *RRS*.