

Cancer of the Lower Digestive Tract in One Family Group¹

ELDON J. GARDNER AND FAYETTE E. STEPHENS

Laboratory of Human Genetics, University of Utah, Salt Lake City 1, Utah

INTRODUCTION

NINE cases of carcinoma of the lower digestive tract have been detected among the descendants of one couple. A total of 45 members are included in the group. The primary site in eight of these cases was localized in the bowel or rectum. Both sides of the family have been traced as far as possible. No cancer has been detected in the father's side. The mother died with cancer of the bowel. One of her brothers likely had cancer of the digestive tract but died in an accident. Another brother had cancer of the lip. A half sister had tumors (probably cancerous) removed from her breasts. Four of her more distant relatives died from cancer of the digestive tract. One relative has had rectal tumors removed, one has had breast tumors removed and another has had abdominal tumors removed. The evidence indicates an inherited tendency favoring carcinoma of the lower digestive tract coming through the mother's side of the family.

The data have been obtained from personal interviews with members of the immediate family concerned and members of other related families. The neighbors and close associates were also interviewed. The information obtained from these interviews was verified as far as possible from medical records and death certificates. Detailed clinical information concerning some of the more recent cases has been obtained from the doctors who have treated and who are now treating the members of the group. Unfortunately most of those who have had the symptoms are dead and several of the doctors are no longer available. Arrangements are now in progress to provide complete medical examinations for all members of this family group now living, along with the members of other families having a history of cancer of the lower digestive tract. The objective of this examination project is twofold: to secure further information for the genetic analysis of cancer of the lower digestive tract and to provide early diagnosis for polyposis and precancerous conditions for the good of the people concerned. One case of polyposis has recently been detected in this group by a private physician and will undergo surgery in the very near future. Throughout the study attention is being given to the advisability of early diagnosis and careful clinical follow-up of relatives of patients with proven cancer of the lower digestive tract.

Received January 11, 1950.

¹ This research was supported by a grant from the United States Public Health Service.

This family group is a part of one of twenty-five kindreds now being investigated for the incidence of cancer. Some of the kindreds in the larger study were suggested by doctors, some were selected from the sampling of death certificates and some were chosen because they are large kindreds well represented in Utah and readily available for study. This particular one (Kindred 109) was first suggested by a medical student who was interested in the possible inheritance of cancer in a family which had come to his attention. Another lead to the same group came from the sampling of death certificates. Several other families showing a history of polyposis and cancer of the lower digestive tract are included in the larger study. The pedigree reported here is the most extreme case encountered so far, but a comparable pattern is observed in other kindreds, suggesting a simple dominant mechanism of inheritance. The data available for the different members of the family group with the source of these data are given below. Since the methods of diagnosis and treatment for cancer of the lower digestive tract have changed considerably in recent years the dates are given with the case histories to facilitate proper orientation.

HISTORY OF THE FAMILY GROUP AND INCIDENCE OF CANCER

The members of the entire kindred (Kindred 109 in the Laboratory of Human Genetics, University of Utah) are shown diagrammatically in figures 1 and 2. The concentric rings represent generations and the individuals are numbered from right to left in order of birth in each sibship. The kindred has descended from one man and his two wives. The four children (*II-1* to *4*) of the first wife and their descendants are symbolized in figure 1. The eight children (*II-5* to *12*) of the second wife and their descendants are represented in the right hand side of figure 2 (family *A*). The only daughter (*II-7*)² of the second wife, died in 1909, at the age of 53. The death certificate lists the cause of her death as "cancer of the bowel." The doctor who treated her is not available. The nurse who cared for her is now past 80 years of age but seems mentally alert. She describes clearly and consistently the symptoms and prolonged suffering of *II-7*. The description fits well a case of cancer of the bowel. The relatives and neighbors who were present at the home of the patient during the period of her illness and death tell a similar story. Although no pathological examination was made and no medical records are available the evidence favoring "cancer of the bowel" as stated in the death certificate is convincing. Her husband (*II-15*) was killed in an accident at the age of 34. His three brothers (*II-13*, *14*, *16*) died at the ages of 95, 77, and 80 respectively from causes incident to advanced age. *II-13* and *II-16* had no children. *II-14* had nine sons and daughters (*III-71* to *79*) who now have a number of descendants (*III-227* to *259*). No cancer has been detected in this family (family *B*, figure 2). No other relatives of *II-15* have been located.

All four of the children of *II-7* and *II-15* very likely had cancer of the bowel or rectum at the time of their death. *III-67* had an operation on the lower digestive tract in 1934 at the age of 57 and died eight months later, at the age of 58. According to the death certificate he died with "carcinoma of the rectum." An intimate friend with whom *III-67* had lived and worked most of his life took care of him during his illness. The friend describes graphically the symptoms and intense suffering of *III-67* before and after the operation. He tells of

² *II-7* and *II-15* have been moved away from their proper places in their respective families for convenience in making the chart.

going to the nearby pasture and cutting sections of moist sod with a shovel and bringing it into the house to use for cold packs on the abdomen of *III-67* to relieve the pain. Relatives who were present in the home tell the same story. There is a striking similarity between the symptoms experienced by *III-67* and his mother *II-7*. The evidence strongly supports the cause of death as recorded on the death certificate. *III-68* died in 1921 at the age of 41. "Carcinoma of the bowel" was the cause of death according to the death certificate.

III-69 was living in a different community at some distance from the family home at the time of her illness and death. She died in 1916 at the age of 33. The death certificate lists "carcinoma of the rectum" as the cause of death. She was treated by a doctor not acquainted with other members of the family. The case history strongly supports the cause of death listed on the death certificate. *III-70* was living in another state at the time of his illness and death. He had an operation for carcinoma of the lower digestive tract in 1942 at the age of 56 and died a few months after the operation. The cause of death was reported as accidental, but the letters received by other members of the family, immediately preceding his death, and the conditions surrounding his death, indicate that he took his own life. He wrote his niece (*IV-214*) to the effect that the "curse of the family" had returned, following the operation. He told other family members that he had cancer like his sister and brothers who were dead. His wife was dead and he was very much discouraged.

In the next generation, four have died with cancer of the digestive tract. They were living in widely separated areas at the time of their illness and death. Three of these cases (*IV-208*, *215*, and *216*) were described in the death certificates as "carcinoma of the rectum" and one (*IV-222*) was described, following the autopsy, as "adenocarcinoma of the stomach and metastases." *IV-208* had an operation on the lower digestive tract on February 5, 1937 and died on February 12 of the same year with "carcinoma of the rectum." She was 34 years old at the time of her death. Her infant son (*V-162*) died on May 9, 1936 at the age of two months. The cause of death was reported by the attending physician on the death certificate as "pyloric stenosis and peritonitis." *IV-208* was ill with cancer at the time the child was born. Her daughter (*V-163*) is now 18 years of age and apparently in good health. The eldest living member of this family group (*IV-209*) is now 44 years old. At present, he has two large tumors on the jaw and face. He is a farmer who works hard and is apparently in good health. He has not yet had an examination of the lower digestive tract. *IV-210* died at the age of 22. The cause of his death was listed in the death certificate as "intestinal flu." *IV-211* is now living. He has not yet been examined. *IV-212* was killed in an accident when 11 years old and *IV-213* died with cerebrospinal meningitis when only one month old.

In the family of *III-68*, two sons (*IV-215* and *216*) both died, according to the death certificates, with "carcinoma of the rectum." *IV-215* died in 1940 at the age of 35 following an earlier operation. He had trouble with his digestive system for several years preceding his death. In his earlier life he had surface tumors removed from his forehead and back. His oldest daughter (*V-168*) now 19 years old has had a lump removed from her head and another still remains. His son (*V-170*) now 12 years old has surface lumps on his body. In a superficial examination one of the writers observed seven lumps, six in the head, neck and back region and one on the lower arm, ranging from the size of a quarter to that of a small hen's egg. These are subcutaneous swellings which are likely not related to the cancer of the lower digestive tract. This group will be given a careful examination in the near future.

IV-216 died on July 31, 1936 at the age of 29 from "recurrent carcinoma of the rectum," following an operation on the lower digestive tract performed on December 20, 1935. He had a tumor removed from his jaw about six months before the operation on the lower digestive tract. *IV-219* has had a surface tumor removed from his back. A recent illness brought him to his family doctor who discovered a condition of polyposis in the colon. He

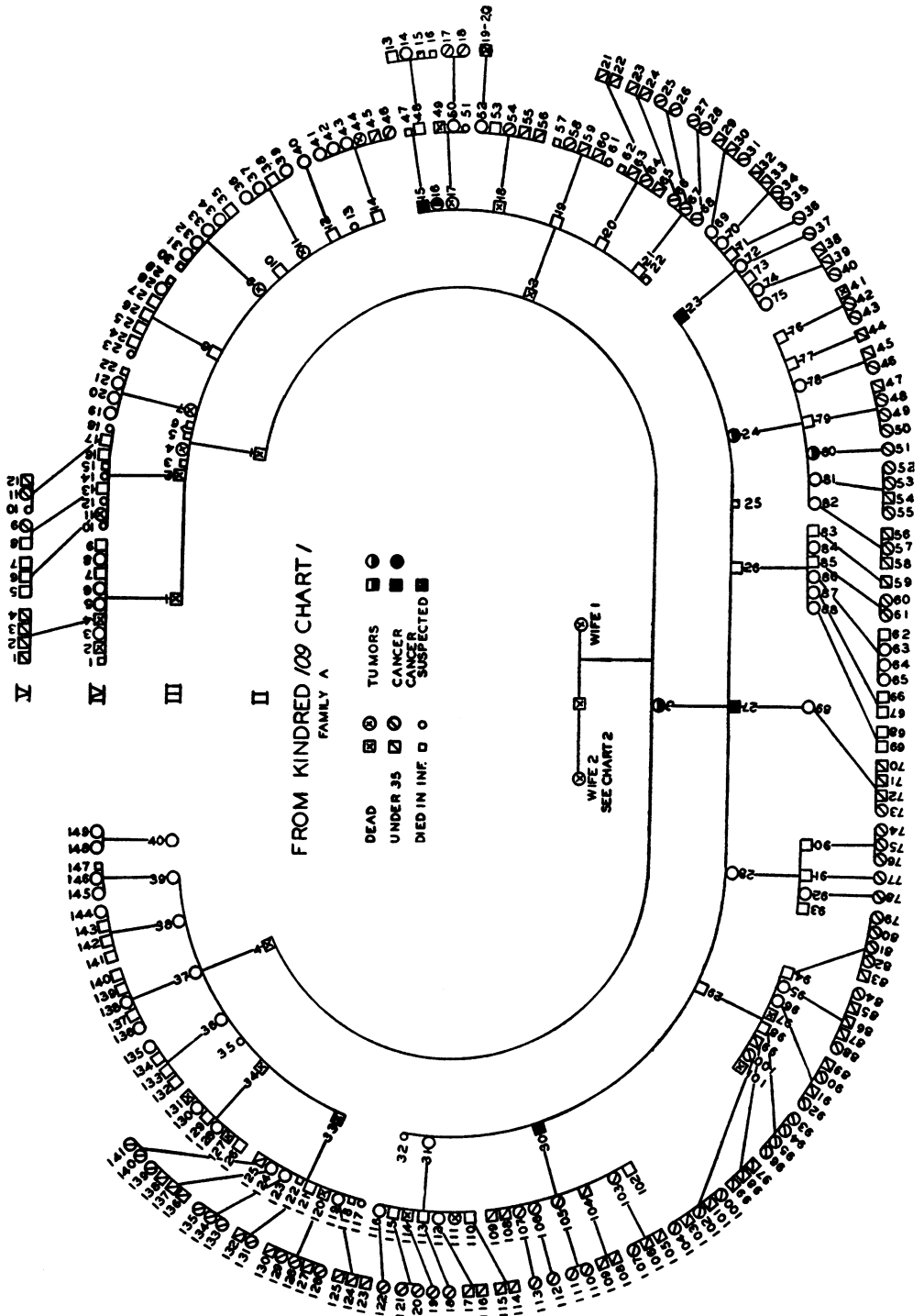


FIG. 1. Pedigree of Kindred 109, showing descendants of I-2's first wife.

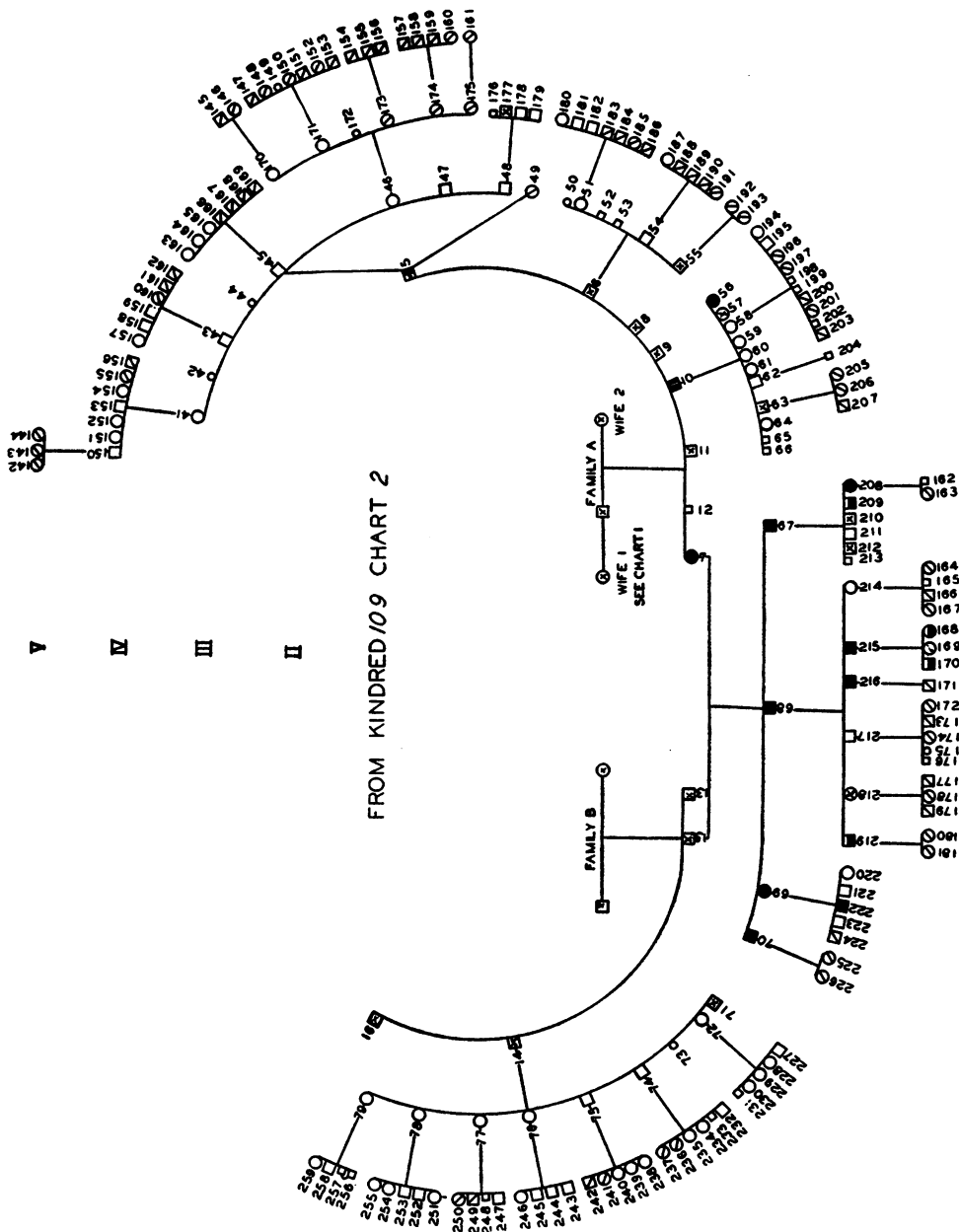


FIG. 2. Pedigree of Kindred 109, showing descendents of I-2's second wife and Family "B", connected by marriage to Kindred 109.

has been referred to a surgeon and will undergo surgery in the very near future. He is now 35 years of age. IV-218 was killed in an accident at the age of 29. The other two members of the family (IV-214 and 217) are apparently in good health. All of the grandchildren of III-68 are under 35 years of age. One son of III-69 (IV-222) died in 1941 at the age of 31

with adenocarcinoma of the stomach with extensive metastases in different parts of the body including the region of the lower digestive tract. The cause of death was confirmed by autopsy. All of the other children of *III-69* are under 45 years of age. The youngest is less than 35. The two children of *III-70* are also under 35.

Among the descendants of *II-7* and *II-15*, 5 died in infancy, 8 are now over 35 years of age and 19 are under 35 years of age. Nine members of the family have died with cancer of the digestive tract and only four have died from causes other than cancer. Three of these deaths were accidental and one was attributed to intestinal flu.

Evidence for Polyposis and Cancer Among the Relatives of II-7

In the family (family *A*, figure 2) of the mother (*II-7*) of the family group described above several cases have been detected and others are suspected. Her brother (*II-10*, figure 2) died in an accident at the age of 70. He was ill at the time of his death and cancer of the digestive tract was strongly suspected but not confirmed. His oldest daughter (*III-56*) died in 1945 following an operation for carcinoma of the lower digestive tract at the age of 54. Generalized metastases were observed in the operation. She had undergone an operation for "carcinoma of the breast" ten years earlier. The oldest full brother (*II-5*) of *II-7* had cancer of the lip. Her half sister (*II-3*, chart I) had tumors (probably cancerous) removed from her breasts in 1921. She was in poor health for several years before her death. Cancer of the digestive tract was suspected by her relatives but she did not submit to surgical exploration. She died in 1931 at 77 years of age. The cause of death was listed on the death certificate as "apoplexy."

Among the more distant relatives of *II-7*, *III-15* had an operation a few months ago (1949) for cancer of the lower digestive tract. He is living but not well. *III-16* had a cancer removed from her face several years ago and has recovered. *III-23* had an operation on the digestive tract at the age of 63 and died following the operation. The cause of death as listed on the death certificate was "carcinoma of the stomach." *III-24* had a radical resection for breast tumors in middle life. She died in 1942 at 70 years of age. According to the death certificate the cause of death was "cirrhosis of the liver." *III-27* had trouble with his digestive tract for several years before his death. According to the death certificate he died in 1943 from "carcinoma of the stomach" at the age of 65. *III-30* died in 1937 at the age of 51 from "carcinoma of the stomach" following a gastric resection. *IV-80* had rectal tumors removed at the age of 50 and *IV-82* has recently had rectal tumors removed. In the entire kindred (109 or figure 1 and family *A*, figure 2) 49 died in infancy, 195 are now over 35 years of age, 14 have had cancer of the digestive tract and 39 have died from causes other than cancer. About 26 percent of those who have died after reaching maturity, in the entire kindred, have had cancer of the digestive tract. The evidence suggests that the predisposing factor (polyposis) for the cancer of the lower digestive tract is inherited and may have come to the family under discussion through the line of the mother (*II-7*).

No evidence of cancer of the lower digestive tract or polyposis has been detected in the families of *II-1*, *II-4*, *II-5* or *II-6*. Evidence suggesting the presence of this character has been indicated in the families of *II-2*, *II-3*, *II-7* and *II-10*. Three (*II-3*, *II-7* and *II-10*) of these latter four individuals very likely had the condition themselves. *II-2* died at the age of 60 with organic heart disease and it is not known whether or not he had polyposis at the time of his death. These data are in keeping with Mendelian principles of heredity and can be explained on the basis of a simple dominant mechanism of inheritance. The families of both wives of the original man show some expression of the trait.

DISCUSSION

Nine members of one family have died with cancer of the digestive tract. In eight of these nine cases the primary site has been localized in the bowel or rectum. Six were definitely established in the rectum and two were described more generally in the bowel. Only four members of the family who reached maturity have died from causes other than cancer. Three of these met accidental deaths at an early age. The incidence of cancer, and particularly cancer of the lower digestive tract, is much greater in this family than that of the general population of the state (Utah State Department of Public Health Morbidity and Mortality Report, 1946). In Utah, the death rate from cancer of all types was 79.37, 79.68, 83.92, 76.30, and 76.30 per 100,000 population for the five years from 1942 to 1946, respectively. In the family group under discussion, nine of a total of 45 members have died with cancer. The death rate calculated from these figures would be 20,000 per 100,000. Only about 4 percent of the cancer deaths in Utah in 1946 were attributed to cancer of the rectum. Six of the nine, or about 66 percent of the cancer deaths among members of this family were established as cancer of the rectum. Figures are not available to compare the cases localized in the colon, with the general population of Utah. However, all nine of these cases were localized in the digestive tract and the case histories have a good deal in common.

Obviously, this family group does not represent a random sample of the population of Utah. The comparison with the incidence of cancer of this type in the population is given merely to indicate the degree of concentration of cancer of the lower digestive tract in one family group. On the basis of this single pedigree, a simple dominant mode of inheritance is postulated for the predisposing factor (polyposis) involved. If this hypothesis is correct half of the children of a parent showing the trait would be expected to inherit the gene and, if penetrance is complete, express the character. No expression would be expected in families where neither parent carried the gene. Whether the family was picked at random or selected, this pattern would be expected to follow, if the hypothesis is correct. The objective of the study is to test the hypothesis by following this family and others showing a history of cancer of the lower digestive tract with careful and accurate clinical data.

The results of a study made by Jüngling and cited by Habs (1938-39) indicate that polyposis of the large intestine in which frequently a carcinoma develops is inherited as a simple dominant trait. Macklin (1932) has cited several cases of rectal polyps associated with carcinoma in family groups. Wassink (1935) has made extensive statistical studies of the families of cancer patients and has found that among the relatives of persons affected by cancer of the rectum and of the stomach, the mortality from cancer is considerably

higher than that of the average population. Several Members of the family described here have had tumors in various parts of the body including the lower digestive tract. Some who are now living and apparently in good health have tumors. These people will be provided regular medical examinations as a diagnostic measure for the benefit of the family concerned and as a means of obtaining more complete and reliable data concerning the onset of cancer, relationship between tumors and cancer, as well as the hereditary pattern in the family.

No environmental factor has been suggested to account for the high incidence of cancer of the lower digestive tract in this family. The family home is in a farming community and most of the older members of the family have lived all of their lives in the same community. Several people now living in the community have associated intimately, lived and worked, with the members of this family who have since died with cancer. No cases of the same type of cancer have been known to occur among other people of the community. Several of the younger members of the family left the family home while young and some of these, while living in widely separated parts of the United States, have died with cancer of the rectum. This suggests that an hereditary mechanism is a primary factor in the predisposition for this type of cancer.

SUMMARY

Nine cases of cancer of the digestive tract have been identified in one family group made up of a total of 45 individuals. The primary site for eight of the nine cases was established in the region of the bowel and rectum. Among those who have reached maturity, nine members of the family have died with cancer of the digestive tract and four members have died from causes other than cancer. No cancer has been detected on the father's side of the family. About 26 percent of the entire kindred from which the mother has come, who died after having reached maturity, have had cancer of the digestive tract. A simple dominant inheritance is suggested as a hypothesis to explain the inheritance of the predisposing factor (polyposis) for cancer of the lower digestive tract in this family. It is proposed to test this hypothesis by providing regular medical examinations for the younger members of the family and the members of other related families over a period of years.

REFERENCES

- HABS, H. 1938-39. Krebs und Vererbung. *Zschr. klin. Med.* 135: 676-691.
MACKLIN, M. T. 1932. The hereditary factors in human neoplasms. *Q. Rev. Biol.* 7: 255-281.
UTAH STATE DEPARTMENT OF HEALTH. *Morbidity and Mortality Report*, 1946.
WASSINK, W. F. 1935. Cancer et hérédité. *Genetica*, Gravenh. 17: 103-144.