A Genetic Study of Carcinoma of The Large Intestine[1]

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INTRODUCTION

IT IS NOW WELL ESTABLISHED that multiple polyposis is a genetic disease, with a dominant mode of inheritance. A review of the subject has been presented by Dukes (1952), and a recent study has been carried out by Reed and Neel (1955). This condition is characterized by the presence of a large number of adenomatous polyps of the colon and rectum. Since the age of onset may be during the first or second decade of life and each polyp appears to be a potentially malignant lesion (Lahey and Swinton, 1952), individuals with the disease often die at an early age from carcinoma of the colon or rectum. Reed and Neel (1955) estimate that in the State of Michigan, the minimum frequency at birth of individuals with the gene for multiple polyposis is about 1 in 8,300. They further estimate that the mutation rate lies somewhere within the range $1\text{–}3 \times 10^{-5}$/gene/generation.

Even though multiple polyposis is a rare disease, the occurrence of a single polyp or a few polyps (occasional discrete polyps) in the colon or rectum is a relatively common condition. Routine sigmoidoscopic examinations carried out in various clinics in the United States have shown that approximately five per cent of all individuals over 35 years of age have one or more polyps of the rectum or sigmoid (Rider, Kirsner, Moeller, and Palmer, 1954; Swinton, 1954). Multiple polyposis is easily distinguished from the latter condition. It is a matter of hundreds or even thousands of polyps versus one or a few.

In 1955, Woolf, Richards, and Gardner presented evidence that in some cases the occurrence of occasional discrete polyps may be influenced by genetic background. Fifty-five adult members belonging to the same generation of a large Utah kindred with a high frequency of carcinoma of the large intestine were given sigmoidoscopic examinations. Twenty-five (45 per cent) were shown to have one or more histologically confirmed polyps. This is a much higher frequency than is expected in the general population. As a further control, similar examinations were given to twenty-one of their spouses. One spouse was shown to possess a questionable polyp, while all other spouses were normal. Twelve to eighteen months after the initial examinations were given, re-examinations were given to some of the members (Richards and Woolf, 1956). Over half the individuals positive for polyps at the first sigmoidoscopic examination were shown to have one or more new polyps at the time of the second examination. Some individuals negative at the first examination were positive at the

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second. The distribution and frequency of positive individuals in the kindred was suggestive of dominant inheritance.

The above observations suggested that carcinoma of the large intestine could have a familial tendency in some cases due to a genetic mechanism other than that associated with multiple polyposis. In order to gain more information on this problem, a propositus study was carried out. The objective was to compare the frequency of deaths due to carcinoma of the large intestine, and to other types of cancer, among the relatives of individuals who died from large bowel cancer not associated with multiple polyposis, with the frequency in a control sample. It was proposed that if another genetic mechanism were operating, such as through the production of occasional discrete polyps, it would be expected that the close relatives would show an increased frequency of deaths due to the disease as compared with an adequate sample taken from the general population.

PROCEDURE AND RESULTS

A diversity of methods has been employed in propositus studies designed to investigate the importance of heredity as an etiological factor in human cancer. Many of these have been reviewed in Jacobsen (1946) and Woolf (1955). The method employed in the present study was used by the present author (Woolf, 1956) in a propositus study on carcinoma of the stomach. The advantages and disadvantages of the method were discussed in that publication, and will not be repeated here.

Propositi for the present study were picked from death certificates for individuals who died in the state of Utah between the years 1931 and 1951. Individuals were selected only when there was substantial evidence on the death certificate, as reported by the attending physician, that carcinoma of the large intestine was actually present. Selection was made for death certificates for white persons born or raised in Utah or in the surrounding intermountain region. Certificates were not included if there was any indication that multiple polyposis had been present.

Upon obtaining the names of a large series of individuals who died from carcinoma of the large intestine, the next step was to take the names to the archives of the Latter-Day Saints (Mormon) Genealogical Society in Salt Lake City, Utah. On file in this office are family group records which are useful for studies of this kind. A survey was made of the records to see if information was available for the families (parents and sibs) of the individuals who died of carcinoma of the large intestine. A family group record was available for approximately one-fourth to one-fifth of the names selected from the death certificates. Upon obtaining the genealogical data the next procedure was to return to the Utah State Division of Vital Statistics. With the aid of the cross index file for death certificates, a careful search was made for the names of the parents and sibs of the individuals who died from carcinoma of the large intestine. Death certificates have been filed in this office since 1905. If a relative died in Utah since that time the certificate was usually found. However, the certificate was not found if the relative died before 1905, had a change in name, died in some other state, or was still alive. The study was concerned only with those relatives who had died in Utah since 1905. As soon as a certificate was located for a relative, notes were made of the cause and date of death and of the age at death.

The study was continued until histories were obtained for 242 families for which at least one death certificate in addition to that of the propositus was seen. One family was not included because the death certificate of one relative of the propositus gave evidence of multiple polyposis.

The control material used for comparison consisted of white individuals of the same sex, who died the same year in the same county and at approximately the same age as each of the deceased relatives of the propositi. Death certificates in Utah are filed by date of death and county, and bound into books. When a death certificate was found for a relative of a propositus, it became a matter of turning the pages of the book until the first qualified control was found. To be considered as approximately the same age as a relative of the propositus a control's age had to be within minus three and plus five years of the relative's age.

The death certificates for 145 fathers, 142 mothers, 309 brothers, and 167 sisters were observed, giving a total of 763. Twenty-six of these had cancer of the large intestine as compared with 8 in the controls. Chi square computed from a 2 x 2 table is equal to 8.7 ($P < .01$). The number of deaths due to large bowel cancer was increased over the controls in all four classes of relatives.

Eighty-one deaths from cancer other than of the large intestine were observed

TABLE 1. COMPARISON OF THE NUMBER OF DEATHS DUE TO CANCER OF THE LARGE INTESTINE AND OTHER TYPES OF CANCER IN THE FAMILIES OF THE PROPOSITI AND AMONG THE CONTROLS

Relation	Death Certificates Observed	Deaths Due to Cancer of the Large Intestine		Deaths Due to Other Types of Cancer	
		Families of the Propositi	Controls	Families of the Propositi	Controls
Father	145	4	1	12	11
Mother	142	6	0	8	20
Brother	309	9	6	45	33
Sister	167	7	1	16	19
Total	763	26	8	81	83
		$\chi^2 = 8.7$*		$\chi^2 = 0.007$*	
		$P < .01$		$.90 < P < .95$	

* Chi square based on totals (one degree of freedom).

TABLE 2. COMPARISON OF THE NUMBER OF DEATHS DUE TO CANCER IN THE FAMILIES OF THE PROPOSITI AND AMONG THE CONTROLS

Type of Cancer	Relatives of the Propositi	Controls
Large Intestine	26	8
Stomach	26	33
Breast	2	6
Small Intestine	0	1
Uterus or Ovaries	8	5
Liver or Pancreas, or Gall Bladder	9	9
Prostate	9	6
Lung	3	3
Other Types	24	19

TABLE 3. DISTRIBUTION OF DEATHS DUE TO CANCER OF THE LARGE INTESTINE IN THE FAMILIES OF THE PROPOSITI

Number of deaths due to Cancer of the Large Intestine	Observed Number of Families
0	221
1	17
2	3
3	1
4 or more	0
Total	242

among the relatives and 83 among the controls. The difference is clearly not significant ($.90 < P < .95$). The results are summarized in table 1.

The different types of cancer deaths occurring among the relatives of the propositi and controls are shown in table 2. It is observed that with the exception of cancer of the large intestine, there is good agreement between the relatives and controls concerning the frequency of the various types of cancer deaths.

The distribution of deaths due to cancer of the large intestine in the families of the propositi is shown in table 3.

DISCUSSION

Even though an attempt was made to select propositi who were free of multiple polyposis, due to the inherent nature of death certificates, there is no certainty that this was achieved in all cases. Therefore, it is important to consider whether the occurrence of this disease in some of the families could be contributing to the significant difference in the frequency of deaths due to carcinoma of the large intestine between the relatives and controls. This possibility was investigated by examining all available evidence from the records of autopsies, operations, x-rays, and sigmoidoscopic examinations of the 26 relatives who died of cancer of the large bowel and of the propositi to whom they were related.

Medical records definitely excluding multiple polyposis were available for eight of the 26 relatives. For the remaining 18 relatives, medical records were either missing or else incomplete with regard to the predisposing condition of the bowel. Seven of these 18 relatives were removed from the possible multiple polyposis group because of the conclusive evidence that the related propositi did not have the disease; thus it was concluded that the gene for multiple polyposis was not segregating in these families. This leaves 11 relatives for whom information was not available. The ages at time of death for these ranged from 60 to 82 years with a mean of 70.7 years. The ages at time of death for the related propositi of these 11 individuals ranged from 63 to 80 years with a mean of 72.4 years. These ages at death are much higher than expected for patients with multiple polyposis. The average age at death in a large series studied by Dukes (1952) in England was 41.6 years, while in the general population of England and Wales, the average age at death from rectal cancer is 67 years, This age difference has also been reported by Reed and Neel (1955) for data collected in Michigan. The above evidence suggests strongly that the results of this

study are not attributable to the segregation of the gene for multiple polyposis in some of the families. Hence the data are compatible with the hypothesis that a genetic mechanism exists for carcinoma of the large intestine which is independent of the one associated with multiple polyposis.

On the basis of experimental work with mice, Heston (1952) has suggested that cancer occurs in mice when the combined action of genetic and non-genetic components, which are probably additive in nature, surpasses a certain physiological threshold. It seems likely that a similar situation exists for human cancer, although at present little is known of the nature and relative importance of these genetic and non-genetic components. Even though, in the present study, the number of deaths, among the relatives of the propositi, due to cancer of the large bowel is significantly greater than the number among the controls, it is not large enough to suggest that heredity is of greater etiological importance than some other unknown non-genetic factors. Therefore the genetic component encountered here appears to have about the same magnitude of importance as has been shown for carcinoma of the stomach and breast (see Woolf, 1955, 1956).

Of interest is the observation that with the exception of carcinoma of the large intestine, the number of deaths due to other types of cancer among the relatives of the propositi was not increased over that in the controls. This organ-specificity of the genetic component is similar to that observed for stomach cancer (Videbaek and Mosbech, 1954; Woolf, 1955, 1956) and breast cancer (Penrose, MacKenzie, and Karn, 1948; Woolf, 1955). These observations illustrate further the independence of the genetic mechanisms leading to the occurrence of neoplasia.

On the basis of the observations of Woolf, Richards and Gardner (1955), and Richards and Woolf (1956), it is speculated, as noted earlier, that one possible method by which the genetic component encountered in this study predisposes to the malignant condition is by the production of occasional discrete polyps in the colon or rectum. Genetic factors predisposing to these polyps in some families could account for the findings of this study.

SUMMARY

A propositus study was carried out to test the hypothesis that a genetic component, independent of the one associated with the familial disease, multiple polyposis, exists for cancer of the large intestine. The results of this study are compatible with this hypothesis.

Propositi were obtained from death certificates for the state of Utah and family histories from the records of the Latter-Day Saints Genealogical Society in Salt Lake City, Utah. Causes of death for the relatives (sibs and parents) were determined from death certificates for the state of Utah. The control material was also obtained from death certificates.

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