Hereditary Factors in Cancer

Study of Two Large Midwestern Kindreds

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MENDELIAN autosomal inheritance patterns have been demonstrated in familial aggregations of polyposis coli, retinoblastoma, xeroderma pigmentosum, neurofibromatosis,[1] Gardner's syndrome[2] and the basal cell nevus syndrome.[3] In addition, an increased familial incidence of carcinoma of the breast,[4] lung,[5] stomach and colon,[6] and prostate,[7] as well as leukemia,[8] multiple myeloma,[9] Waldenström's macroglobulinemia,[10] pheochromocytoma,[11] multiple endocrine tumors,[12] cerebellar hemangioblastoma,[13] and malignant melanoma[14] has been observed. However, the mode of inheritance is not clear in these latter conditions. In appraising these data, it must be kept in mind that only those families showing a high incidence of carcinoma are "selected" for publication. When one considers the high population incidence of carcinoma, ". . . it is bound to occur in excess in some families according to the operation of the laws of probability.[15]"

The purpose of this paper is to present the findings in two large midwestern kindreds in which a high frequency of particular histological types of malignant neoplasms involving a large variety of anatomical sites was found. In one kindred (Nebraska), there was a total of 51 malignant neoplasms of which 31 were confirmed, while in the second (Michigan) kindred, there were 27 carcinomas of which 20 were confirmed.

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Material and Methods

These two large families have been studied in Nebraska and Michigan and shall hereafter be referred to as the "N" (Nebraska) and "M" (Michigan) kindred.

N Family.—The propositus (No. U-11770) was studied at the Omaha Veterans Administration Hospital where he expired at age 44 from adrenal cortical carcinoma. His medical history revealed that many of his immediate relatives had cancer and that they lived over a wide geographic area. A questionnaire was sent to all adult members of the family in order to elicit information regarding a history of carcinoma and to obtain permission to examine surgical and autopsy material for histologic tissue confirmation. Permission forms were included with the questionnaire enabling us to make contact with family physicians, consultants, hospitals, state divisions of vital statistics, and local departments of public welfare. Several field trips were made, and clinic facilities were kindly donated by a private physician who had managed some of the affected members of the family. Complete histories and physical examinations, including pelvic examinations, cervical cytology, and proctosigmoidoscopy, were done on 35 individuals who resided in a contiguous geographic area. When lesions were accessible to surgical biopsy, appropriate tissue was obtained. Blood was obtained for ABO typing, hemoglobin, hematocrit, and cell indices.

M Family.—The propositus (No. 945482) was studied at the University Hospital, Ann Arbor, Michigan, where she expired at age 36 from metastatic carcinoma of the breast. A strong family history of carcinoma had been elicited and similarly questionnaires were sent to members of the family. Histologic confirmation of carcinoma was made through physicians' records and pathology reports from several hospitals. In addition, cytogenetic studies were done on the proband prior to her death. These included karyotype analyses of leukocytes from two peripheral blood cultures, skin from the leg, and the pituitary gland following an ablation procedure.

Whenever possible, slides were personally reviewed from both families. In those cases showing

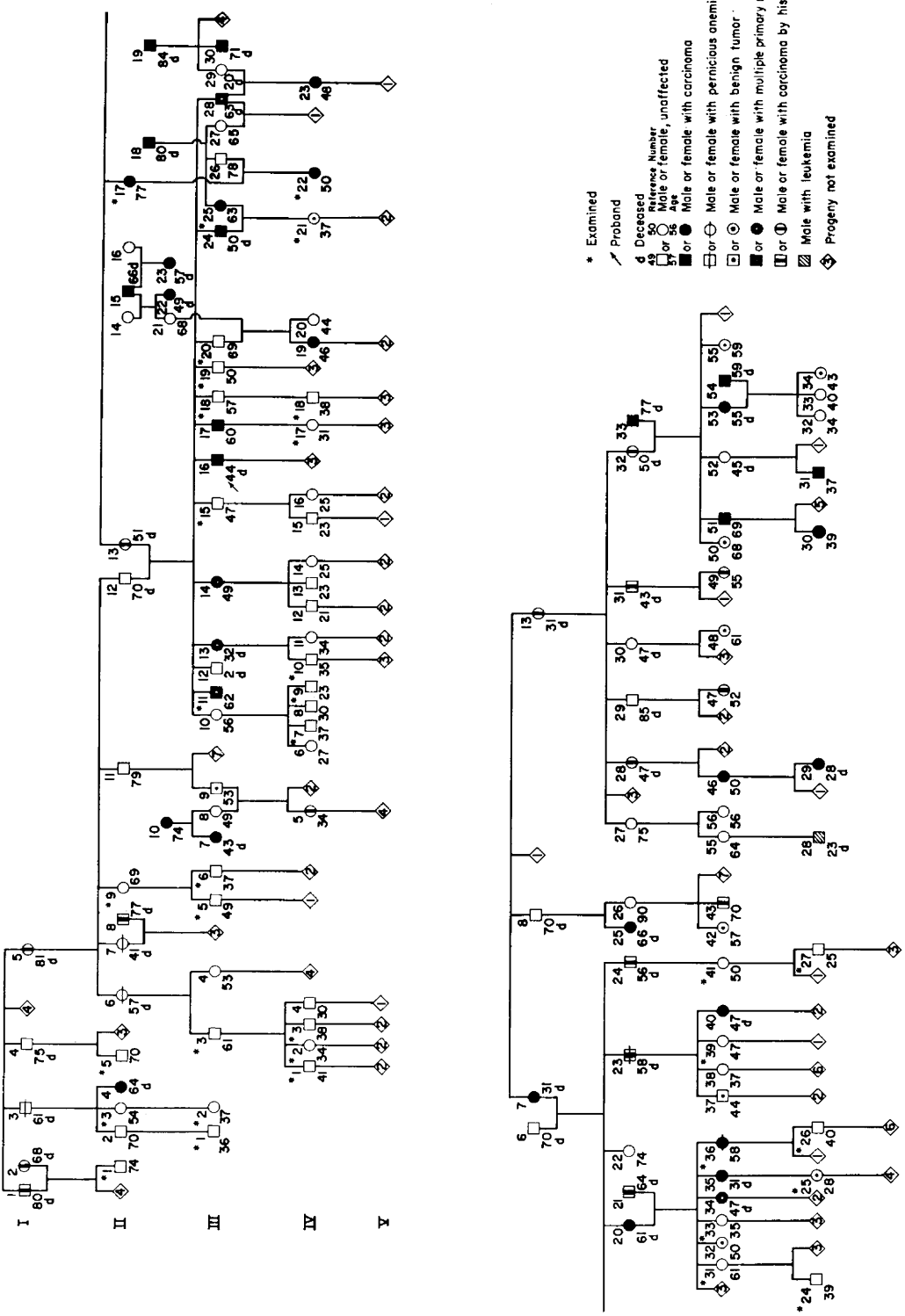

Fig 1.—Pedigree of the N kindred showing the presence of carcinoma in four generations.

TABLE 1.—*Registry of Malignant Neoplasms in Family N* *

Pedigree Index No.	Age	Sex	Stomach	Colon	Skin	Ovary	Uterus	Cervix	Renal	Unknown
I 5	D81	F	...	...	...	...	...	...	...	—
I 7	D31	F	...	...	...	...	...	...	...	—
I 13	D31	F	...	...	—	...	—	...	...	...
										+
										64
II 4	D64	F	...	...	...	...	...	....	...	Sarcoma
II 13	D51	F	...	...	...	...	...	...	...	—
							+			—
II 17	77	F	...	...	...	...	55	...	...	77
				+						
II 20	D61	F	...	61	...	...	...	...	...	...
II 21	D64	M	...	...	...	...	...	...	...	—
II 23	D58	M	—	...	...	...	...	...	...	...
II 24	D56	M	...	...	...	...	...	...	...	—
			+							
II 25	D66	F	66	...	...	...	...	...	...	...
							—			
II 28	D47	F	...	...	...	...	47	...	...	...
II 31	D43	M	...	...	...	...	...	...	...	—
							—			
II 32	D50	F	...	...	...	...	50	...	...	...
				+	+					
III 11	62	M	...	55	50	...	...	...	...	...
				—		+	+			
III 13	D32	F	...	32	...	27	31	...	...	...
				++++				+		
III 14	49	F	...	48	...	...	...	41	...	...
									+	
III 17	60	M	...	...	...	...	...	...	60	...
			+	+						
III 28	D63	M	63	45	...	...	...	...	...	...
				+			+			
III 34	D47	F	...	42	...	...	45	...	...	...
III 35	D31	F	...	...	...	...	...	...	...	+
					+					
III 36	58	F	...	...	54	...	...	...	...	...
							+			
III 46	50	F	...	...	...	...	38	...	...	...
							—			
III 49	50	F	...	...	...	...	55	...	...	...
					+					
III 51	69	M	...	...	66	...	...	...	...	...
							+			
III 53	D55	F	...	...	...	...	47	...	...	...
					—					
IV 5	34	F	...	...	34	...	...	...	...	...
				+						
IV 19	46	F	...	46	...	...	...	...	...	...
							+			
IV 22	50	F	...	...	...	...	36	...	...	...
							+			
IV 23	58	F	...	...	...	...	46	...	...	...
				+						
IV 29	D28	F	...	26	...	...	...	...	...	...
						+				
IV 30	39	F	...	...	...	37	...	...	...	...
					+					
IV 31	37	M	...	...	35	...	...	...	...	...
			Additional Malignancies							
I 1	D80	M	Carcinoma of larynx				—			
							+			
III 16	↗D44	M	Adrenal cortical carcinoma				43			
							+			
III 24	D50	M	Cancer of lip				26			
							+			
III 40	D47	F	Malignant melanoma				40			
							—			
III 43	70	M	Carcinoma of prostate				69			
							—			
III 47	52	F	Hodgkins disease				48			
							—			
IV 28	D23	M	Leukemia				23			

+ = tissue confirmation, — = no tissue confirmation; ↗ =proband.

Numbers set below + and — signs indicate the age at which lesion was discovered.

* Since this paper was submitted for publication, the following members of the "N" kindred have received confirmed diagnoses of carcinoma: III 42, adenocarcinoma of the endometrium at age 56; IV 22, a second primary, undifferentiated carcinoma of the colon at age 51; II 17, a second primary, adenocarcinoma of the colon at age 77, died, age 78; II 26, adenocarcinoma of the right breast at age 90; III 49 and 43-year-old sister, 1 carcinoma of endometrium.

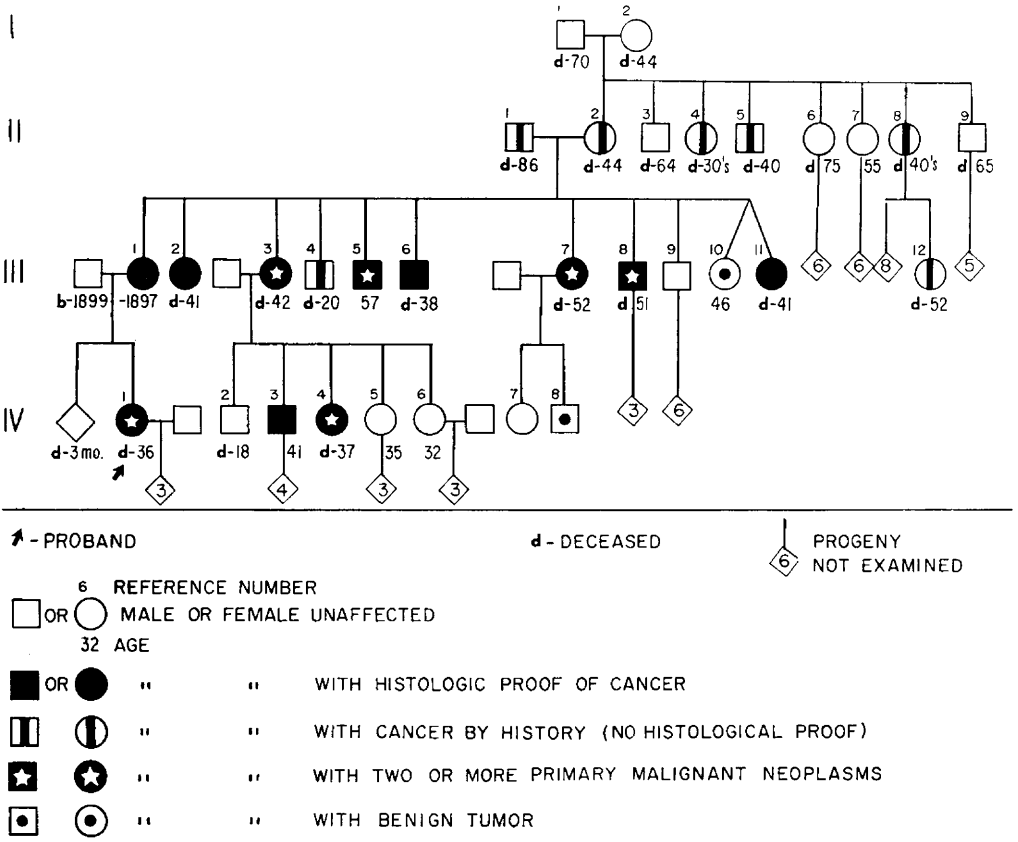

Fig 2.—Pedigree of the M kindred showing the presence of carcinoma in three generations.

multiple primary malignant neoplasms, other pathologists also reviewed the slides.

Results

Kindred N.—The proband (Fig 1, III-16) expired at age 44 from carcinoma of the adrenal cortex. Analysis of the pedigree showed 40 cases of carcinoma occurring over four generations. The proband had twelve siblings and, of these, six have had diagnoses of carcinoma (Fig 1, III-11, III-13, III-14, III-17, III-24, III-28) with four of these six affected individuals showing multiple separate primary malignant neoplasms (III-11, III-13, III-14, III-28). The histologic types of carcinoma in his siblings included the following: carcinoma of the lip, stomach, colon, endometrium, and kidney.

Of the four showing multiple primary carcinomas, the combinations included the following: colon and skin (Fig 1, III-11), stomach and colon (Fig 1, III-28), uterus and ovary (Fig 1, III-13), carcinoma of the cervix and four primary colon carcinomas (Fig 1, III-14). The proband's mother (Fig 1, II-13) expired at age 51 from carcinoma (unconfirmed) and his maternal grandmother (Fig 1, I-7) expired at age 31 from metastatic carcinoma (unconfirmed). His father (Fig 1, II-12) expired at age 70 and was not known to have had cancer. However, his paternal grandmother (Fig 1, I-5) expired at age 81 from carcinoma of the larynx (unconfirmed). A maternal first cousin of the proband (Fig 1, III-34) had two primary carcinomas (colon and endometrium). Her mother expired at age 61 from carcinoma of the colon. She had two siblings with carcinoma. One of these expired at age 31 from carcinoma with the primary presumed to be liver; the second is still alive but has had a diagnosis of squamous cell carcinoma of the skin and is under treatment for pernicious anemia (Fig 1, III-35, III-36). A registry of the tumors found in this kindred is given in Table 1.

There has been a suggestive increase, primarily by history, of diabetes mellitus, hypertension, obesity, arthritis, and pernicious anemia.

TABLE 2.—*Registry of Malignant Neoplasms in Family M*

Pedigree Index No.	Age	Sex	Lip	Duodenum	Colon	Pancreas	Uterus	Ovary	Stomach	Breast	Unknown
II 1	D86	M	—	...	...	...	...	...	...	...	...
II 2	D44	F	...	...	—	...	...	...	...	...	...
II 4	D30	F	...	...	—	...	...	...	...	...	...
II 5	D40	M	...	...	—	...	...	...	...	...	...
II 8	D40	F	...	...	—	...	...	...	...	...	...
							+				
III 1	68	F	...	...	...	...	52	...	...	...	...
									+		
III 2	D41	F	...	...	...	...	...	...	39	...	...
					+		+	+			
III 3	D42	F	...	...	41	...	42	39	...	...	...
											—
III 4	D20	M	...	...	...	...	...	..	...	...	20
					+++						
III 5	57	M	...	...	42 45 56	...	...	...	...	...	...
				+							
III 6	D38	M	...	38	...	...	...	...	...	...	...
						+	+				
III 7	D52	F	...	...	...	52	45	...	...	...	...
			+		+						
III 8	D51	M	50	...	36	...	...	...	...	...	...
							+				
III 11	D41	F	...	...	...	...	38	...	...	...	...
III 12	D52	F	...	...	...	...	...	...	...	...	—
										++	
IV 1	↗ D36	F	...	...	...	...	...	...	...	33 35	...
					+						
IV 3	41	M	...	...	32	...	...	...	...	...	...
					+		+	+			
IV 4	D37	F	...	...	37	...	28	28	...	...	...

↗ = proband; + = tissue confirmation; — = no tissue confirmation.
Numbers set below + and — signs indicate the age at which the lesion was discovered.

Thirteen of the 35 examined had blood group A and, of the five with a history of a malignant neoplasm, all had blood group A. Two of these five had multiple primary tumors. There was no evidence of consanguinity in this family.

Kindred M.—The propositus expired at age 36 from metastatic carcinoma of the breast. She had had a primary adenocarcinoma of each breast, the one on the right being poorly differentiated while the one on the left was well differentiated. Karyotype analyses of leukocytes, skin, and pituitary were normal. Pedigree analysis (Fig 2) showed that malignant neoplasms were present in 18 individuals and were transmitted through two and possibly three generations (Fig 2, II-1, carcinoma of the skin; II-2, carcinoma of the "bowels," unconfirmed). The proband's mother (Fig 2, III-1) had carcinoma of the endometrium. She had ten siblings and, of these, seven had histologic confirmation of carcinoma and one other had a diagnosis of "intestinal cancer" by history and expired at age 20. Four of these had multiple primary cancers which included the following combinations: carcinoma of the colon, uterus, and ovary (Fig 2, III-3), three primary colon carcinomas (Fig 2, III-5), carcinoma of the pancreas and uterus (Fig 2, III-7), and carcinoma of the lip and colon (Fig 2, III-8). (Refer to Table 2 for the specific lesions in the rest of the family.) Again, there was a large variety of malignant neoplasms in this family which included adenocarcinoma of the breast, carcinoma of the lip, antrum, duodenum, colon, pancreas, endometrium, and ovary. In addition, there was an increase by family history of diabetes mellitus, hypertension, obesity, and rheumatoid arthritis in affected as well as nonaffected members of the kindred. A history of consanguinity could not be elicited.

Comment

Hereditary factors are clear in only several of the mentioned types of malignancies. However, for most malignancies there is no simple genetic interpretation. Studies do show that the frequency of the type of tumors in close relatives of the propositi is higher than that found in the general popu-

lation. Contrariwise, the frequency of tumors other than the type found in the propositi is not higher than that found in the general population. On the basis of these observations Stern [16] concludes that while genetic factors may play a role in the origin of tumors, "such genotypes are specific for different types of tumors. No genotypes seem to lead to 'cancer in general.'"

Warthin [17,18] reported several families with a high frequency of carcinoma. In one of these families, gastric and colonic neoplasms predominated in the males, genital neoplasms in the females, and multiple primary malignant tumors occurred in some individuals. This family was similar in many respects to the two families described in this paper. Warthin referred to this as the "cancer family" and "cancer fraternity"; subsequent investigators have substantiated the validity of his concept.[1-9]

Twin studies [1] have shown concordance for cancer in both monozygotic and dizygotic twins with higher concordance among monozygotic twins who also had a higher tendency for malignant tumor to occur at identical anatomical sites. Nevertheless, there was also some discordance among monozygotic twins suggesting that environmental factors are important.

Studies of the ABO blood groups in cancer patients have suggested a correlation between blood group A and gastric carcinoma,[19] carcinoma of the genital tract in females,[20] tumors of salivary gland tissue in general,[21] and of mucinous secreting tumors in particular.[22] Blood group A was similarly correlated in a population of patients with multiple primary neoplasms.[23] An increased incidence of blood group A was found in those members with malignancies in the N kindred. Blood groups were not performed in the M kindred with the exception of the propositus who was also blood group A.

While a familial incidence of carcinoma may be exceedingly high, it is essential that in addition to a consideration of genetic factors environmental factors which might influence such "cancer susceptible genotypes" [24] be investigated.

The N and M families are of interest from the standpoints of (1) the wide distribution of anatomical sites of the malignant neoplasms, (2) the finding of five individuals with multiple primary carcinomas in the N kindred (four of these were siblings of the proband) and five individuals with multiple primary malignant tumors in the M kindred (four of these were in one sibship), (3) the high incidence of endometrial carcinoma in both families in the face of the lesser frequency of this lesion in the population when compared to carcinoma of the cervix, (4) the transmission of malignant disease through four generations in the N kindred and through three generations in the M kindred, and (5) similar ethnic stock in both families (Scotch, Irish, and English) as well as similar geographic residence. With respect to the latter point, it is possible that there is a common ancestor in these two families. Genealogic evidence places members of both families in the same communities in Owen, Campbell, and Madison Counties in Kentucky and later in Park and Vigo Counties in Indiana. These families were found later in St. Charles and Gentry Counties in Missouri. In one case, a paternal great aunt of generation I in the M kindred may have married a paternal uncle of generation I in the N kindred in 1834.

The pedigrees of both families are compatible with autosomal dominant inheritance. However, multifactorial inheritance cannot be excluded. Autosomal recessive inheritance and chromosomal aberration are unlikely explanations. "Cytoplasmic inheritance" [25] must be considered. In both of the kindreds, there is a predominance of female *transmission* as well as an unusually intense concentration of lesions in the sibship of generation III in the N kindred, where seven of 13 siblings were affected (Fig 1) and that of generation III of M kindred, where nine of 11 siblings were affected (Fig 2). If cytoplasmic inheritance were the case, increased transmission through the affected female would be expected on theoretical grounds since the sperm is predominately nuclear.

Finally, the possibility of a viral agent must be considered. Such a virus could be

cytoplasmic and/or *nuclear*. The high incidence of multiple primary tumors in the N and M kindreds is not unlike that found in several animal strains which have been infected with the polyoma virus. In such animals, a wide range of tumors is found including multiple primary malignant neoplasms.[26] Animal strains may vary with respect to oncongenicity to the polyoma virus ranging from high susceptibility to marked resistance. This phenomenon appears to be determined by a single autosomal gene showing incomplete dominance in the case of mice.[27] It is possible that a similar "human polyoma" infection could be present in our two kindreds. Such an agent could act in concert with "cancer-susceptible genotypes" in these kindreds. Many of the individuals in these kindreds who do not at this time show clinical evidence of carcinoma nevertheless by virtue of their young ages remain at risk. Some have benign tumors and some have pernicious anemia.

Although monomeric inheritance in the N and M kindreds cannot be conclusively demonstrated, it seems likely that the respective members represent "carcinoma-susceptible genotypes." The major investigative value of these family studies is that it has opened the way to future epidemiologic studies in quest of possible carcinogens. Although innocuous to the "wild-type," ie, "carcinoma-resistant genotypes," such carcinogens might serve in these families as a potent stimulus for genes inducing carcinoma in selective organ sites.

Summary

Study of two large midwestern kindred which are possibly related has revealed an unusually high incidence of carcinoma in each. This has included a wide spectrum of malignant neoplasms including multiple primary carcinomas in members of each family. The variety of anatomic sites of malignancies as well as the transmission was also strikingly similar.

Possibilities for the inheritance of neoplasms in these families have been discussed. While autosomal dominant inheritance most likely explains the pedigree findings, the role of cytoplasmic and/or viral factors must also be considered. Intensive studies of "cancer families" such as these may lead to new clues to the etiology of carcinoma.

Miss Rose Reynolds prepared the medical illustrations and Mrs. Betty Fraser supplied genealogic assistance.

John Forgrave, MD, permitted the study of his patients and made available his private clinical facilities for investigative purposes.

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