HEREDITY WITH REFERENCE TO CARCINOMA

AS SHOWN BY THE STUDY OF THE CASES EXAMINED IN THE PATHOLOGICAL LABORATORY OF THE UNIVERSITY OF MICHIGAN, 1895-1913 *

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The statistical study of carcinoma is regarded by many writers as having been carried as far as it can be profitable; and certainly but little that is new has been gained through this method during the last decade. Nevertheless, its possibilities have not been exhausted; and it is highly desirable that the whole neoplasm problem in all of its aspects be attacked again from the statistical standpoint, though in a somewhat different way. Practically all of the old statistical studies of neoplasms, particularly those of carcinoma, were based on mortality reports; or if not on these, on morbidity reports based on clinical diagnoses. In very few instances only has the statistical study been carried out on the basis of the records of a diagnostic pathological laboratory. Statistics of neoplasm from such a source must be of infinitely greater value than those founded on mortality statistics. In the records of the diagnostic laboratory the diagnosis is based on the histological examination, and the percentage of error is reduced to a minimum. In the mortality statistics, on the other hand, the diagnoses are chiefly clinical, and consequently subject to the wide error inherent in the clinical diagnosis of "tumor," neoplasm, "cancer" and the like. Moreover, the material coming to the diagnostic laboratory is usually seen from two to five years earlier than the mortality age. In studies relating to the age-incidence of any form of neoplasm it is evident that the records of the pathological laboratory for that neoplasm will be much more trustworthy than the mortality statistics. It is also possible many times in the diagnostic laboratory to follow the course of a neoplasm over a definite period, so that important practical knowledge may be gained as to rate of growth, recurrence, healing, metastases, etc.

The following study of the influence of heredity on carcinoma is taken from the records of the pathological laboratory of the University of Michigan during the years of my service from 1895 to 1913. During this period 3,600 cases of neoplasm of all varieties have been studied, either in material taken for practical diagnosis or obtained by necropsy. Of these 3,600 cases, some 1,600 were cases of carcinoma, as was shown by the microscopic diagnosis. Practically every variety of carcinoma

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described in the literature, and a few others, as well, are to be found in this material; and the same is true of the other forms of neoplasm. While carcinomas of the breast, uterus and lip form the greater part of the cases examined, all other localizations are represented. Another great advantage is that about 90 per cent. of the material was derived from the general population of the state of Michigan. The fact that the university hospital is a state hospital and not a charity institution, gives it a much more representative population than would be found in the charity hospitals of the greater cities.

The difficulty of obtaining a family history from patients in charity hospitals is well known. Few of them know the cause of death in their grandparents or in other members of that generation. The same thing is true, though to a less extent, of the patients from whom the material used in this study was obtained. Therefore what worth this study may have must be positive; the negative findings cannot be taken as absolute. In about six hundred cases of carcinoma no family history was obtainable; in the majority of those in which a family history was obtainable the details are meager. In spite of these handicaps, in a surprisingly large number of cases a family history of carcinoma is given — about 15 per cent. of all in which the family history is obtainable.

The existence of a family susceptibility to carcinoma, denied by many writers, affirmed by others, has again become, as a result of the studies of endemic carcinoma in mice, a question exciting lively interest. These investigations appear to show that certain family strains in mice do not develop spontaneous tumors, and that, further, such strains are resistant to tumor transplantation from other mice. Other family strains show a high frequency of spontaneous tumors, and in such strains transplantation may be successfully carried out. It would appear then, that the latter strains possess a familial predisposition or susceptibility to the development of neoplasm, and that intrinsic or inherited factors play some part in the development of neoplasms. Bashford denies this, and Tyzzer, who carried out breeding experiments with animals representing different strains, was unable to find that the transmission of the predisposition to neoplasm followed the laws of heredity.

On the other hand, a family predisposition in the human species to certain forms of neoplasm has long been recognized, particularly in the case of certain benign neoplasms (fibroma, lipoma, chondroma, osteoma, angioma, leiomyofibroma, glioma, neurofibroma, papilloma, adenoma and cyst-adenoma), and to a less marked degree in the case of certain forms of sarcoma and carcinoma. While the existence of such a predisposition is generally accepted by text-books on pathology, no good statistical studies exist of the hereditary occurrence of these neoplasms.

Cancer surveys of living patients, as conducted in Germany some years ago, have given little information concerning the family occurrence of neoplasms, chiefly for the reason that it is practically impossible to trace the members of a given family through more than one or two generations, and unless all of the members of the family for several generations can be considered, no accurate conclusions can be drawn. The difficulties attendant on such a statistical study are very great; and except in rare cases complete family records of cancer incidence are not found in the literature. One of the most striking is Broca's case,[1] also quoted by Levin, who criticizes the method of investigation, because no comparison was made between the number of the affected and unaffected members in each generation. If the total number of ascendants is not considered, and only those affected by carcinoma picked out, a family may appear to be a cancer family when in reality the proportion of cancerous to non-cancerous members is very small. As Levin states, Broca's family might give very different results if studied from the standpoint of the history of all its members.

Levin, to my knowledge, is the only one who has attempted a statistical study of heredity in cancer from the standpoint of an entire family history. He collected data[2] from five families, in two families fairly complete and in three fragmentary. In the families studied he noted that they were characterized on the whole by the occurrence of cancer of the intestines in the males, and cancer of the breast in the females. His charts show that the incidence of cancer in these families is not greater numerically than would be found in the population as a whole, but that the occurrence of "cancerous fraternities" (a fraternity in which one or more members suffer from cancer, with a history of cancer either on the maternal or paternal side, or both) speaks for some influence of heredity on cancer. In other words, a cancerous fraternity must mean the union of two germ-plasms, each of which is characterized by the presence of germ-cells that are non-resistant to cancer.

In my material of 3,600 cases of neoplasm examined pathologically, there were 1,600 cases of carcinoma. About one thousand of these gave fairly good family histories with the ages of the members. A smaller number (30 per cent.) gave detailed histories. From this number are taken the families which show multiple occurrence of carcinoma. In many of these all of the members of the family for three generations are given; in others, the records are incomplete. Four families give complete records of the descendants of the cancerous grandparent. The incidence of cancer in these families is so striking that it can be interpreted as showing an inherited susceptibility to cancer.

1. Broca: Quoted by Wolf, Die Lehre von den Krebskrankheiten, Jena, 1907; Williams, p. 369.
2. Levin: Ztschr. f. Krebsforsch., 1912, ix, S. A., p. 5.

CANCER FAMILIES

FAMILY G. (Chart 1).—In this family a fairly complete survey was made of the two generations derived from a cancerous grandfather with a traditionary history of cancer in his line and a grandmother with a normal family history. From these there were ten children, five males and five females. Two of the daughters died of cancer of the uterus at 55 and 40 years, while two sons died at 42 of cancer of the stomach, and a third one at 45 of cancer of the abdomen. All five of these individuals were married to normal partners without a family history of cancer, and all had issue, as follows: Oldest daughter who died at 55 of cancer of the uterus, had ten children: one daughter operated on at 42 for "cancer" of the uterus and still living; another daughter operated on at 22 for uterine tumor and bilateral dermoids of ovary, and still living. The remaining eight children are all living and well, only two being over 40 years of age. The second daughter, who died at 40 of cancer of the uterus, had four children, two sons and two

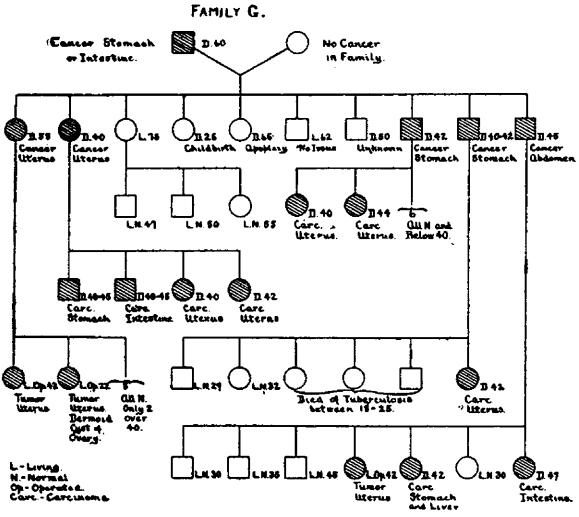

Chart 1

daughters all dying of cancer, the two sons of cancer of the stomach and intestine, and the two daughters of carcinoma of the uterus. The third daughter, living and well at the age of 75, has three normal children living at the ages of 47, 50 and 55. Four children had no living issue. The eighth child, a son, died at 42 of cancer of the stomach. His wife was of normal family history. They had eight children, of whom two daughters have died of cancer of the uterus at 40 and 44 years, while the remaining six are all living and well below the age of 40. The ninth child, a son, died of cancer of the stomach when between 40 and 42 years of age. He left six children from a marriage contracted with a woman of non-cancerous family history. One daughter died at 42 of cancer of the uterus, three children died of tuberculosis between the ages of 18 and 25 years, while two others are living and well at the ages of 32 and 29 years. The tenth son died at 45 of cancer of the abdomen, most probably primary in the stomach. He left, from a marriage contracted with a woman of non-cancerous family, seven children, of whom one died at 42 of cancer of the stomach and liver, another at 47 of cancer of the intestine, while a third was operated on at 42 for tumor ("cancer") of the uterus, and still lives in apparent good health. Four others are living and normal at the ages of 45, 35, 30 and 30.

Of the forty-eight descendants of the cancerous grandfather seventeen have died or been operated on for "cancer." The preponderance of carcinoma of the uterus (ten cases) and of the stomach (seven cases) is very striking in the family history.

FAMILY F. (Chart 2).—In this family the maternal grandmother died of tumor. Her non-cancerous brother had two children, both of whom died of "cancer." Her only son died at 61 of dropsy. He married a woman who had two brothers who died of cancer of the stomach. She herself died of Bright's disease at 75. Her

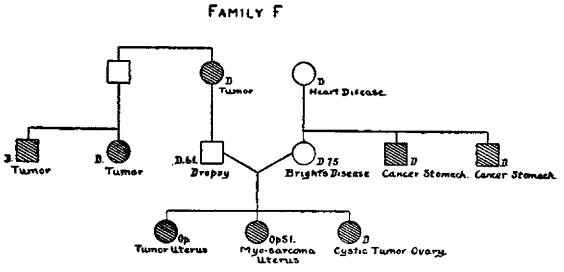

Chart 2

mother died of heart disease. The three daughters of this pair who show a double family history of susceptibility to cancer all had neoplasms; the oldest was operated on for tumor ("cancer") of the uterus and is still living; the second was operated on at 51 for myosarcoma of uterus, while the third daughter died of cystic tumor of the ovary. In this family history the preponderance of stomach and uterine neoplasms is also shown.

FAMILY P. (Chart 3).—The paternal grandfather had a nephew who died of cancer of the lip. In the first filial generation there was one daughter who died at 35 of cancer of the lip and a son who died at 86 of cancer of the scalp and cervical lymph-nodes. This son married a non-cancerous woman whose only sister

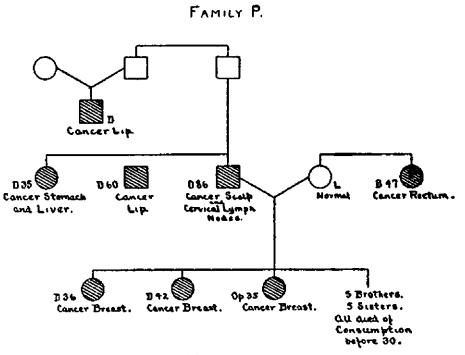

Chart 3

had died at 47 of cancer of the rectum. From this union thirteen children, ten of whom (five brothers and five sisters) all died of pulmonary tuberculosis before the age of 30, while three remaining daughters had carcinoma of the breast, two dying at the ages of 36 and 42, and one operated on at 35.

FAMILY S. (Chart 4).—The paternal great-grandfather died at about 70 of cancer of the stomach. His only son died at about 60 of cancer of the stomach, having married a woman who died at about 50 of cancer of the breast. They had six children, all of whom died of cancer; two daughters died at 80 and 60 of cancer of the breast, and another at 60 of multiple carcinoma of the breast, bladder and

rectum. Two sons died of cancer of the stomach at the ages of 75 and 40, the third son dying of cancer of some internal organ, most probably the stomach. Only one son had issue, by marriage with a normal line. The only child died at 36 of cancer of the uterus. Of the eight descendants of the cancerous great-grandfather all died of cancer. As in Family P., the occurrence of carcinoma in both paternal and maternal lines apparently strengthens the susceptibility, both families becoming extinct.

CANCEROUS FRATERNITIES

These are of much more frequent occurrence in the case-histories of carcinoma (Charts 5, 6, 7, 8, 9) than the striking family histories given above show. The reasons for this are obvious: Few individuals of the

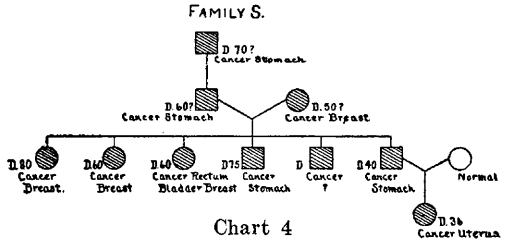

Chart 4

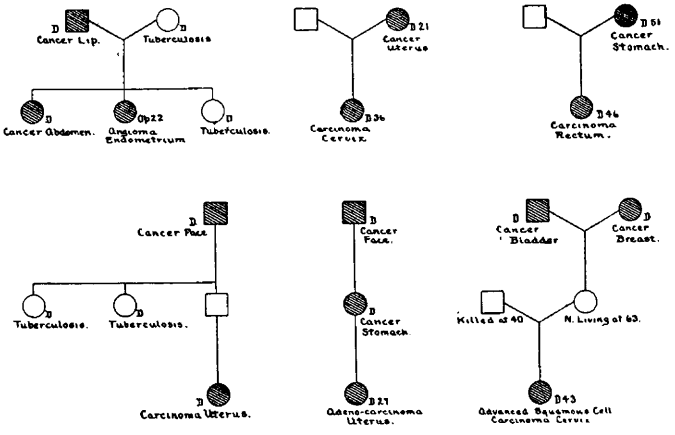

Chart 5

general run of the American population know anything about their family history except for the immediate members. By far the majority do not know the cause of death of their grandparents. Twenty-nine cancerous fraternities are selected as representative of our case-histories. Two generations only are represented in the majority, but in some of them three generations, and in one instance, four generations are shown. The normal members of the second and third generations are also given, so that the proportion of cancerous to non-cancerous individuals in two generations is exact. The majority of the cancerous fraternities occur in small families, and in many cases the patient from whom the material

examined came represented the end of the family line. In several instances all the members of the small family are cancerous. The charts explain themselves. The most striking thing shown, aside from the susceptibility of the family group, is the great prominence of tuberculosis

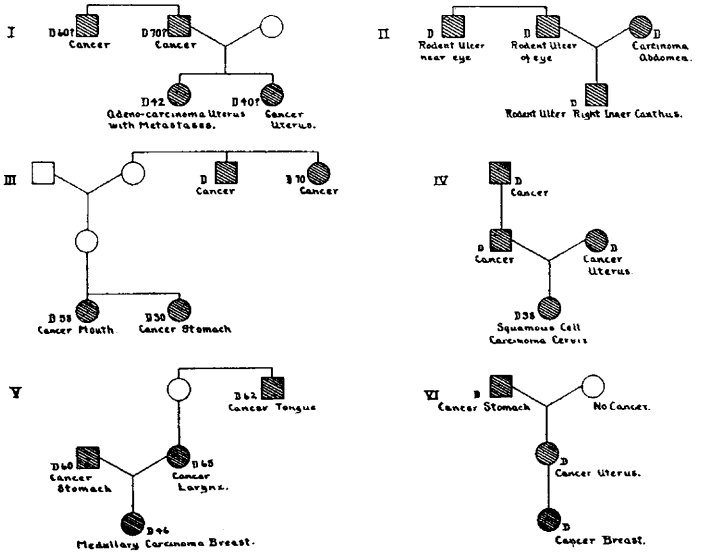

Chart 6

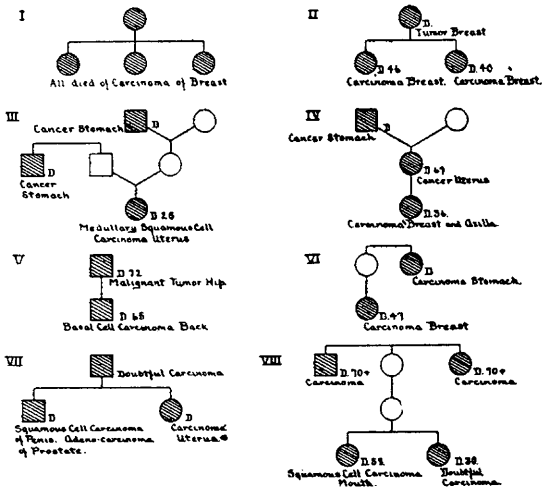

Chart 7

as the most commonly associated disease of the cancer stock. The two susceptibilities seem to run together, at least, in so far as our family histories are concerned. A tuberculous ancestry is not infrequently found in families where there is no family history of cancer back of the present

generation. Next to tuberculosis the diseases most commonly associated with carcinoma are cardiac and renal disease.

It will be noted that the uterus, breast, gastro-intestinal tract and mouth are the parts of the body most frequently involved in the case of these family cancers. Cancer of the lip and rodent ulcer of the face show also a tendency to family occurrence.

The study of a large number of cases of carcinoma yields isolated but striking examples of a marked family occurrence through several generations; and a much more frequent family group or "cancerous fraternity" occurrence. From such histories it is hardly possible to draw any other conclusion than that a definite cancer susceptibility exists in certain families. The great frequency of the association of cancer with tubercu-

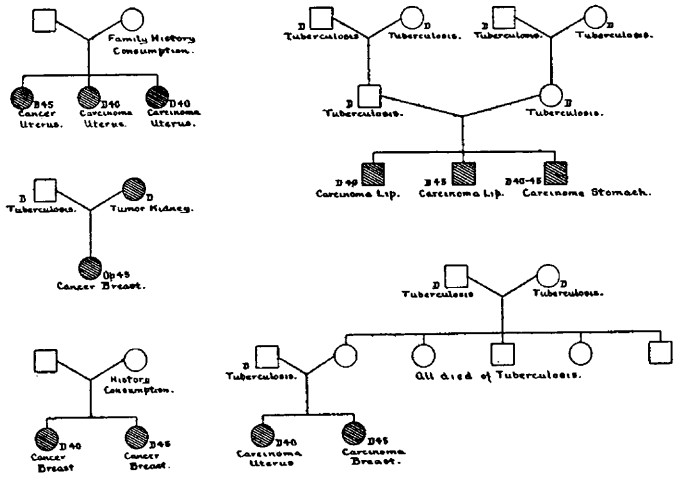

Chart 8

losis might be taken as an evidence of a general weakened resistance on the part of the family lines; and this conclusion is supported by the extinction of many of these lines through a lessened fertility.

In the study of all of our neoplasm material a family susceptibility is occasionally shown in the case of angioma, lymphangioma, fibroma, neurofibroma, lipoma, myofibroma of uterus, adenoma of breast and adenoma of thyroid; but extremely rarely in the case of sarcoma.

CONCLUSIONS

1. A marked susceptibility to carcinoma exists in the case of certain family generations and family groups.

2. This susceptibility is frequently associated with a marked susceptibility to tuberculosis, and also with reduced fertility.[3]

3. The striking association of tuberculosis with cancer in certain families has also been noted by Kuthy and Williams, "The Natural History of Cancer," p. 371.

3. The multiple occurrence of carcinoma in a family generation practically always means its occurrence in a preceding generation.

4. The family tendency is usually more marked when carcinoma occurs in both maternal and paternal lines.

5. Family susceptibility to carcinoma is shown particularly in the case of carcinoma of the mouth, lip, breast, stomach, intestines and uterus.

6. In a family showing the occurrence of carcinoma in several generations there is a decided tendency for the neoplasm to develop at an earlier age in the members of the youngest generations. In this case the neoplasm often shows an increased malignancy.

7. Because of the difficulty of obtaining complete family records, the laws of inheritance of carcinoma susceptibility cannot be determined

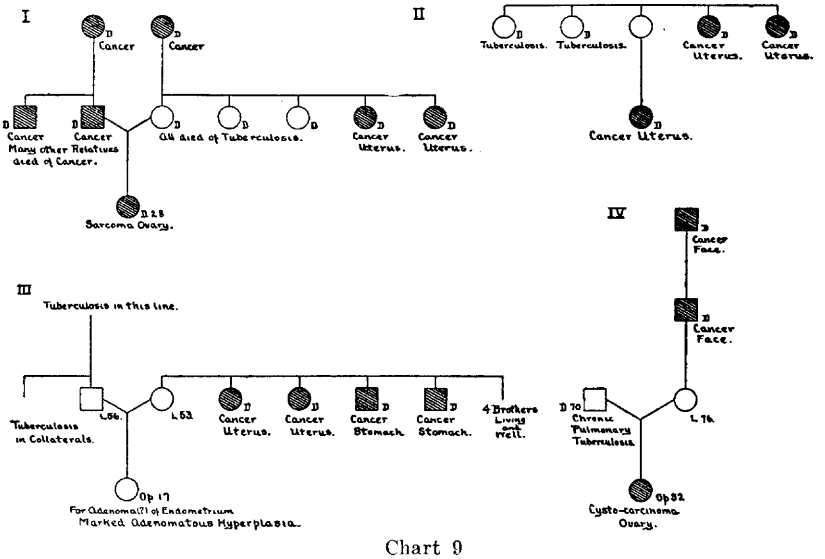

Chart 9

accurately, and it is highly desirable that investigations of large family records should be made relative to the occurrence of carcinoma susceptibility. In Levin's study of cancerous fraternities in connection with the whole family history the percentage of cancerous members in each cancerous fraternity corresponds very closely to the Mendelian percentage of members with recessive unit-characters in a hybrid generation. The same conclusion might be drawn from my cases in certain instances, but it does not seem to me that the data are sufficient for such conclusions. He himself does not consider this conclusion as final. Levin also concludes that resistance to cancer is a dominant character whose absence creates a susceptibility to cancer. While some of my cases show a family history suggesting this, others would indicate a progressive degenerative

inheritance — the running-out of a family line through the gradual development of an inferior stock, particularly as far as resistance to tuberculosis and cancer is concerned.

Levin, as well as Williams,[3] noted the family tendency to specific localization of the cancer, particularly of the uterus in the women, and of the gastro-intestinal tract in the men. This is well shown in my family histories and in some of the cancerous fraternities. Levin concludes that the most important result of his investigation is the fact that it shows the presence of an inherited resistance to cancer growth. I would put it in just the opposite way and say that my observations are important in that they show in certain families an inherited susceptibility to cancer. If the majority of the human race do not show this susceptibility, resistance to cancer is a normal trait of the species. An increased susceptibility becomes, therefore, the abnormal character of importance, and our investigations should be carried along the line of attempting to determine just what lies back of this susceptibility.

3. Williams: The Natural History of Cancer, 1908, p. 364.