XXV.

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The influence of heredity on cancer.¹⁾

A Study in Eugenics.

By

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(With Plate XI and XII.)

The influence which inheritance exerts on disease is at present under active discussion, but a great deal of confusion exists in the understanding of the term „heredity“ as so applied. The method of determining the existence of an hereditary propensity to a disease consists usually in finding instances of the same or a similar disease among the near relatives of the patient. The fallacies of this method may be illustrated by the following instance: A man previously normal and of normal parentage becomes an alcoholic and as a consequence of alcoholism becomes insane. Some one of his direct descendants also becomes insane. Apparently the inference may be made that the insanity in the second generation was acquired through the influence of heredity. The true cause of the disease, however, was not an hereditary transmission into the germ cell but an intoxication of the latter by the alcohol and its consequent deterioration. It is of great importance to define sharply pathological conditions which are truly „inherited“ or inheritable from those which are „congenital“, i. e. were acquired during foetal life. A foetus, which was infected during its intrauterine life by syphilis or tuberculosis, is not born with an inherited disease, but with one acquired congenitally. The instance of alcoholism shows that even conditions which are transmitted to the germ cell may not be truly inherited, but acquired by the latter. Only when an individual formed from a diseased germ cell, which in its turn develops into

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1) Conducted at the expense of the George Crocker Special Research Fund.

a similarly diseased individual of a next generation. can the disease be said to have been transmitted through inheritance.

Another fallacy must be considered which is inherent in the method of determining the influence of heredity through a simple enumeration of cases in which ancestors were also affected with the disease. The fact that some diseases which occur rarely, as for instance brachydactyly, haemophilia, or night-blindness, affects certain families generation after generation may be an indication in itself that these diseases are hereditary. In diseases, on the other hand, which affect a large percentage of the population, as tuberculosis, or cancer, for instance, the frequency of the occurrence in parents of an affected individual is no indication of the influence of heredity. The same disease may be found just as frequently in the parentage of an individual not affected with the disease. Simple enumeration of the cases of the disease among parents and offspring cannot indicate the influence of inheritance, but the aid of certain laws of regularity in the recurrence must be sought. The Mendelian laws of heredity present such regularity and seem to offer the most promising basis for the study of the influence of heredity in disease. It may be well to present the main outlines of the Mendelian theories before the actual methods employed in the present investigation are stated.

The fundamental laws of the science of modern genetics were discovered by Gregor Mendel in 1865, but they passed unnoticed until they were re-discovered simultaneously by De Vries, Correns and Tschermack, in 1900. Mendel subjected to experimental analysis the commonly known fact that an off-spring may resemble in its different traits of character, one or the other of its parents. He argued that a multi-cellular organism develops, not from a single germ-cell, or gamete, as it is called in genetics, but from a zygote, by which is meant the resultant of the union between the maternal and paternal gametes. In order to learn the fate of parental characteristics in the off-spring, certain simple features have to be selected in each parent and studied in the following generations. These simple features are called unit-characters, and in order to be better able to see the results of breeding, Mendel selected for his studies, pairs of opposite unit-characters. For instance, in his studies on inheritance in edible peas (*Pisum Sativum*), he selected for one parent a tall specimen and for the other a dwarf one. The cross breed of such a union is not a specimen of middle height, but all of the off-spring have the height of the tall parent. Now, the discovery which Mendel made was that in all cases to which his rules applied, when dissimilars meet in one individual, there is, on formation of the germ-cells, a separation between the two characters that came in. This segregation of unit-characters represents the fundamental law of Mendelian inheritance. Of the two opposite cha-

racters, one is called the „dominant“ and the other „recessive“. Upon an examination of a great variety of cases, it was shown that the dominant unit-character indicates the presence of a certain factor in the germ-cell, while the recessive unit-character indicates the absence of the same factor. The importance of this representation of the dominant as due to a factor present in the germ-cell, the recessive, as a condition which results from the absence of that thing, appears distinctly when the unit-characters to be analyzed are conditions of health or disease.

The off-spring of two parents with opposite characters, the first hybrid generation (F^1), according to Mendelian writings, shows apparently only the dominant character. When this off-spring is inbred, a complete segregation of characters shows itself in the next generation of hybrids (F^2). Not all the off-spring find the same dominant unit-character, but only 75 % show the dominant character and 25 % the recessive. Now, if the entire F^2 off-spring should be divided into two parts, of which three show the dominant character and one the recessive, and when the different members should be inbred, the results will show that the recessive quarter would always give only a recessive off-spring. One third of the dominant off-spring will also present a dominant characteristic, while the remaining two-thirds of the entire F^2 off-spring, on inbreeding, will be crossbred and will result again in $\frac{3}{4}$ ths dominant and $\frac{1}{4}$ th recessive.

These Mendelian laws of inheritance were demonstrated to be true for a great number of characteristics in plants and animals. But it must be understood that in more complicated conditions, the arithmetical relation cannot be shown always to be mathematically exact. Still, a unit-character must, in the next generation, accord closely numerically with Mendelian expectations, or, to use Mendelian phraseology, must be a „true mutation“, in order to be considered of importance. Otherwise, it would be considered a simple variation and as such would have no direct influence upon the formation of the off-spring. It is extremely difficult to demonstrate the truth of these laws of heredity in human pathology; nevertheless, a great deal has already been done to indicate that certain pathological conditions like brachydactyly, haemophilia, and color blindness are not only inherited, but closely follow the Mendelian laws.

The question presents itself as to whether it is feasible to suppose a priori that the occurrence of cancer may also be influenced by heredity. Adherents of Cohnheim's and similar hypotheses of the genesis of cancer consider the factor of heredity of great importance in the disease, while those who attribute a great value to the possibility of the parasitic origin of the disease, believe that inheritance exerts no influence on it.

Let us consider to what extent it may be true that inheritance exerts no influence even on infectious diseases. The fact that tuberculosis may

affect several members in the same family of the same, or different generations, is indeed no proof of any hereditary influence, since it is quite apparent that the conditions there are very favorable for infection. However, there exists a great deal of evidence of the fact that members of the same community, subjected to the same conditions of life, the same opportunities for infection, remain immune against a certain infectious disease, while other members of the same community, or even the same family, suffer from it. During periods of the severest epidemics, there are individuals who remain exempt from the disease, though they come in the closest contact with affected individuals. The only possible explanation of this phenomenon is that certain organisms are more susceptible to infection or intoxication than others.

Racial immunity against certain diseases is another indication that different individuals of the same species of animals or men may have different intrinsic constitutions and therefore react differently to noxious agents. Such a peculiar susceptibility in one individual and resistance in another against a certain disease may be logically considered an innate unit-character and as such be transmitted through inheritance.

An analysis of all the available data of the pathogenesis of cancer tends to show that the disease is caused by a combination of three factors. A direct cause — the nature of which is as yet unknown, and which may be a group of cells changed biologically so that it has become capable of unlimited proliferation —, plus a mediate cause, which may be an injury or a changed mode of living or any other environmental condition, — and plus an intrinsic constitutional susceptibility. We have not sufficient knowledge to analyze the first factor in the causation of cancer. The mediate causes are changeable and consequently can not be transmitted to subsequent generations in accordance with the present conceptions of heredity. But it should be feasible to presume that the specific susceptibility to development of cancer of one organism and the resistance of another, may be inherited. Thus it seems clear a priori that it may be advantageous, for the general study of the genesis of cancer, to investigate into the possibility of the influence of inheritance on this disease.

The problem of inheritance in cancer has been occupying the minds of investigators for a long time, but in view of the fallacies inherent in the methods employed thus far, the results obtained are entirely unsatisfactory.

Two methods have been employed for the study of the subject. Either a statistical enumeration has been made of those hospital cases of cancer in which the occurrence of the same disease in some other member of the family was mentioned, or else a count has been made of the number

of cancer cases occurring in a so-called cancer family. The most complete case of such a family is the one published by Broca, a full chart of which is shown below.

Chart of Broca's cancer family.

(After Wolf: Die Lehre von den Krebskrankheiten. Jena 1907.)

1st Generation.

Mrs. L. died 60 yrs old of Carcinoma of the breast, had four daughters — A, B, C and D.

2nd Generation.

A died of Cancer of liver 62 yrs old.
B died of Cancer of liver 43 yrs old.
C died of Cancer of breast 51 yrs old.
D died of Cancer of breast 54 yrs old.

3rd & 4th Generations.

A had 3 daughters, all were unmarried and lived at Broca's time, 68, 72 and 78 yrs respectively. None had Cancer.

B had 5 daughters and 2 sons. First son 28 yrs old — no Cancer. Second son 64 yrs — Cancer of stomach. One daughter died of Cancer of breast. Second and third daughter also died of Cancer of breast. Fourth daughter died of Cancer of Liver. Fifth died 68 yrs old — No Cancer.

C had 5 daughters and 2 sons. One son died a soldier—had no Cancer. Second son died 72 yrs old — had no Cancer. The latter 2 children had no Cancer.

1st daughter of C died 34 yrs old of Cancer of breast. She had 2 sons and 3 daughters. First son died 58 yrs old — no Cancer. Second son and 2 daughters had no Cancer. The third daughter died of Cancer of the breast.

2nd daughter of C died of Cancer of breast. Her son had no Cancer.

3rd daughter of C died of Cancer of Uterus.

4th daughter of C died of Cancer of breast. Her 2 sons had no Cancer.

5th daughter of C died of Cancer of the liver.

D had one son who had no Cancer.

The error in both methods of investigation is identical and is due to the fact that no comparison is made between the number of the affected and unaffected members in each generation. It is possible that a family may appear to be greatly affected with cancer because it consists of a

large number of membres, while the relative number of the affected and unaffected individuals may be normal. The analysis of Broca's family may have given different results if the investigation would have covered the off-spring of all the brothers and sisters of the original patient.

In order to present the true condition, the study of inheritance in cancer must consist of an analysis of all the members of the family which is under investigation. Furthermore as stated above certain mathematical laws of regularity must be sought and the application of Mendelian principles to the analysis of the material seems to be of greatest promise.

The study of heredity on human subjects by the aid of a special mathematical method of analysis developed recently into a new science of eugenics. The English Beometrical School of eugenics applies to the study of the subject a method different from the Mendelian. This school analyses the material in conformity with Galton's law of heredity. This law of Ancestral Heredity established by Francis Galton in 1897, i. e. four years before the Mendelian laws were rediscovered, consists in the following. An individual in his composition represents the sum of contributions of all this ancestors. The two parents contribute the half of the total or each $\frac{1}{4}$, the four grandparents contribute one $\frac{1}{4}$ of the total or each one sixteenth and so on. According to this law the series $\frac{1}{2} + \frac{1}{4} + \frac{1}{8} + \frac{1}{16}$ equal 1, i. e. it equals the total inheritance. This law was developed by Galton through a statistical study of the different colour characteristics of a large number of Basset Hounds. It does not take in consideration the fundamental principles of Mendelism, of segregation and dominance and represents rather the result of certain effects in a given generation than an analysis of these effects. Nor is this law antagonistic to Mendel's law of heredity as it was thought at first, but it apparently expresses in a less satisfactory manner the same phenomena. The numerical relationship between the recessive and dominant characters in hybrid generations as indicated by the Mendelian laws accords frequently with Galton's formula. But the latter fits only a restricted series of cases and is not based on as truly scientific deductions as the Mendelian principles. The latter are consequently more promising for the study of heredity in human Pathology.

The present investigation of the influence of heredity in cancer consisted of the collection of material and of analysis of the collected data in accordance with the Mendelian laws of eugenics, and to the knowledge of the writer, presents the first attempt of its kind. The main difficulty in the pursuance of these investigations consists in the frequent lack of opportunity to ascertain all the facts relating to all the members of a

certain family. This requires a great deal of tact and resourcefulness on the part of the investigators, who are called the Field-workers in eugenics. But even given the willingness of the members of the family to supply the known data and given the necessary persistence of the field-workers in obtaining them, it frequently occurs that after several months of work and study, a family history must be declared valueless because further and complete data cannot be obtained. The different members of the family may be scattered so far that it would require an immense outlay of money and labor to collect the data, or else certain facts cannot be verified. Verification of such facts whenever possible, must be done by both the aid of witnesses, other members of the family, and records of vital statistics.

When the collection of data is completed, the analysis of the cancer family in relation to the influence which inheritance exerted on the occurrence of the disease is pursued in the following way: In the first place, an examination is made as to the number of brothers and sisters of the individual affected with cancer, the respective ages of the surviving members, and the cause of death of those who died. The result shows the percentage of the individuals of this so-called primary fraternity, who reached the cancer age and were resistant to the disease, as well as the percentage of those who suffered from the disease.

It may be well to define here the two expressions used in eugenics, i. e. „fraternity“ and „generation“. A fraternity means the whole number of brothers and sisters of an individual. All members of a fraternity belong to the same generation, but a generation within one family consists of several fraternities. The members of one fraternity in a generation are first cousins to members of the other fraternity, i. e. the former are children of a brother or sister of the parents of the members of the other fraternity. Following the primary fraternity the investigation is continued to the parents of the first individual and the former's sisters and brothers, who together present a former fraternity, according to the conceptions of eugenics and further, to the parents' parents and their brothers and sisters, who again will represent another fraternity. As a rule, no reliable results can be obtained further back than the grandparents, so they will represent the first generation, the parents the second generation, the fraternity of the individual with whom the investigation started will represent the third generation, his children and his sisters' and brothers' children will represent the fourth generation, and so on. After such a genealogical table is completed, giving the ages, cause of death, presence or absence of cancer of all the individual members of the family, an analysis may be made which will give the true numerical relationship between the number of the

susceptible and resistant members in each fraternity and the influence of the paternal and maternal germplasm, or in other words, the influence of heredity.

The present investigation was conducted only for a few months, and the results are of necessity but fragmentary. Still the analysis of the data indicates that the work has a great value and it is consequently presented in order to interest other institutions of research to pursue the study simultaneously. The material was collected by Misses E. P. Moore and M. M. Sturgis. Both of these field-workers obtained their training at the Eugenic Record Office at Cold Spring Harbor, Long Island, N. Y., under direct supervision of Prof. C. B. Davenport. The writer takes great pleasure in expressing here his feeling of gratitude to Dr. Davenport, both for furnishing the best available assistance for the collection of the data, as well as for the general interest which he has taken in the work. The writer also acknowledges his indebtedness to Dr. William Taylor, of Philadelphia, Dr. Arpad G. Gerster, of New York, Dr. Thomas H. Fenton, Dr. G. E. Pfahler, and Dr. David F. Weeks, Superintendent of the New Jersey State Village for Epileptics at Skillman, for their kind assistance in offering cancerous families for investigation.

In all, data were collected from five families. Three families are as yet in too fragmentary a state to be available for complete analysis. The other two families are fairly complete.

The charts A and B show graphically the method of the work. The George Crocker Special Research Fund of Columbia University is in possession of all the original data, where they will be accessible to future students. In the charts the names of the different members of the families are omitted and the following symbols are used. Each individual member is represented by a Roman numerical followed by an Arabic and then again a Roman. The first Roman numerical indicates the generation to which the individual belongs, the Arabic shows the consecutive number within the generation and the second Roman indicates the section in the chart where the individual is placed (see Explanation to Charts A and B).

In the chart A there is noticed a male member of the family, VI—45—III, who died of cancer at the age of 25 yrs. He had been injured on the chest (broke two ribs) in a foot ball game, Nov. 1904. An abcess followed which never healed and led to a growth of sarcoma which was operated in Nov. 1905 at a hospital and death ensued December 1905. The man's mother, III—9—III, died at 47 years of age of cancer of the Uterus, and her father had a sister, II—13—XIV, who likewise died at 77 years of age of cancer of the Uterus. The foot-ball youth belonged to a generation that is still young. His mother was one of six women who reached the cancer age. Three of these women are still living at 75 or over. The history of

this family is not complete, but it seems probable that not more than a quarter of the grown sisters will die from cancer. This proposition would accord with the hypothesis that resistance to cancer is a positive trait and liability to cancer results from its absence. It is interesting to note here in this connection that Levin and Sittenfield (Proceedings of the New York Pathological Society, Oct. 1910) found in recent studies on the influence of heredity in cancer of the white rat, the same fact, namely, that resistance to the growth of an inoculable cancer in these animals behaves in the manner of a Mendelian dominant unit-character.

Another strain of the same family indicated on the Chart A is instructive. A female, IV—256—XV, who had four children, died at the age of 36 of cancer of the uterus. Besides the patient, there were seven in her fraternity who had reached the cancer age. In the maternal side of this fraternity, we find the mother, III—76—XIV, is living at 84 years after a paralytic stroke. Though she has resisted cancer, one of her three sisters, III—67—XIII, who had reached the cancer age, died of cancer of the uterus at 63. Of her five brothers that passed mature life, one III—59—IX died of cancer of the lip; thus about one $\frac{1}{4}$ of the nature persons of this fraternity died of cancer.

Going back to the parents of this cancerous fraternity, we find the mother, II—13—XIV, whose grand nephew died of cancer after a foot-ball accident, as described above, and who herself died of cancer of the uterus at 77, had a niece, III—11—III, who at 77 has cancer of the omentum and another niece, III—9—II, who died at 47 of cancer the uterus.

Let us take up now the paternal side of the fraternity to which IV—256—XV belonged. The father, III—66—XIV, died at 66 years of age from an accident. He had three sisters over 75 years old of whom one died of paralysis and two still survive. He had three brothers who reached the cancer age, One, III—56—VIII, had cancer at 76 at the side of the head near the ear. The father of III—66—XIV died at 72 of cancer on the side of the head near the eye. One notes in this family, represented by Chart A, an organ specificity in the susceptibility to growth of cancer. All the affected women are attacked in the uterus, except one in the omentum, and father and son are affected in the face near the ear.

Let us turn now to an analysis of the family represented by Chart B. We start with a male individual, III—17—II, who died in 1893 of cancer of the intestines. He had married III—18—II and the off-spring were a child who died in infancy, a son now 47 and an unmarried daughter of 43. III—17—II had an elder brother, III—10—II, who passed mature life and died of empyema. This brother married III—9—II, in whose family was a tendency to cancer. They had one daughter, IV—26—I, who is now 52 and has cancer of the breast. They have also one son living at 46 years

and another son, IV—23—I, who died of cancer of the intestines. His eldest surviving daughter, V—25—I, now 33, has cancer of both breasts. The father of III—17—II, II—13—II died of cancer of the stomach. He also had another brother, II—17—III, who died at 58 of cancer of the stomach, and a sister, II—16—III, who has cancer of the breast. The mother of III—17—II had a brother, II—7—II, of whose three daughters one, III—13—II, died of cancer of the breast.

This complex of families is thus characterized on the whole by cancer of the intestines in the males and by cancer of the breast in the females.

A general analysis of the charts A and B shows that the incidence of cancer in these families is not greater numerically than would be found among the population of the community as a whole. But there are several points in the analysis, which indicate that cancer may be influenced by heredity. A cancerous fraternity, i. e. a fraternity, in which one or more members suffer from cancer, usually shows in a previous generation a cancerous member either on the paternal or maternal side or both. In other words, a cancerous fraternity is usually derived from the union of two germ-plasms, each of which is characterized by the presence of germ cells that are non-resistant to cancer.

Chart C.

Name of fraternity	Primary Fraternity				Paternal side			Maternal side		
	Total number of members	Number of cancer age	Number having cancer	pCt. of members having cancer	F	FF	FM	M	MF	MM
A	5	4	1	25	C	?	C	—	—	?
B	4	3	1	33	—	—	—	C	—	—
C	8	7	2	28	—	—	—	C	?	?
D	8	4	1	25	—	C	—	C	C	?
E	9	7	1	14	C	?	?	—	—	—
F	15	6	1	17	—	—	—	C	—	C
G	13	10	1	10	—	?	?	C	—	—
H	10	7	1	14	—	C	—	—	—	C
Total	72	48	9	19						

Explanation of Chart C.

The capital letters in the first column are symbols used instead of the names of the different cancerous fraternities. F = means father, FF = father's father, FM = father's mother, M = mother, MF = mother's father, MM = mother's mother. C = in the last six columns indicates a member who had cancer, — = a member who has had no cancer. ? = a member whose cause of death could not be ascertained.

The chart C presents a number of cancerous fraternities selected at random from the families studied in the present investigation with their respective paternal generations showing the incidence of cancer in the

parentage of the cancerous fraternities. Furthermore the percentage of the cancerous members in each cancerous fraternity corresponds very closely to the Mendelian percentage of members with recessive unit-characters in a hybrid generation.

The general conclusion thus may be drawn from the analysis of chart C that resistance to cancer is a dominant character whose absence creates the susceptibility to cancer. Another general inference may be made from the present investigation that the susceptibility is specific in different families for different organs. The family represented by chart A indicates a preponderance of the cancer of the uterus in the female members, while the family of chart B is characterized by cancer of the breast. W. Roger Williams (*The Natural History of Cancer*, 1908) and other writers have noticed previously this organ specificity in the inherited susceptibility to cancer.

The conclusions arrived at this time cannot be considered in any way final, but it is possible that further study may show that the conclusion to which the writer came at a previous investigation (*Annals of Surgery*, 1910, LI, 769) of the general clinical statistics of cancer, that hereditary disposition has no influence on cancer, may have to be revised in the future.

The most important result of the present investigation thus far consists in the fact that it shows the importance of the presence of an inherited resistance to cancer growth. It may be of the greatest benefit for the future study of the subject of cancer to bear in mind not the fact that one out of ten persons who reach the cancer age one suffers from the disease, but that 9 out of 10 remain immune. It indicates further the necessity and importance of further experimental study of resistance or immunity against cancer in lower animals.

Explanation to charts A and B.

The roman numerals on the margin of the charts indicate the different generations.

The roman numerals on the top of the charts indicate the several sections.

The charts are divided by vertical red lines into several sections to facilitate the finding of the various members of the family.

□ Square indicates a male member.

○ Circle indicates a female member.

The black horizontal lines join all the members of a fraternity.

The black vertical lines joining a square or a circle with an upper horizontal line indicate the fraternity to which the individual belongs.

The black horizontal lines joining a square with a circle indicate man and wife.

The black vertical lines joining man and wife with a lower fraternity line join parents with off-spring.

The arabic numerals over the horizontal lines indicate successively the number of individuals in a generation.

The red lines under a square or circle indicate an individual who reached the cancer age and was alive during the time of the investigation.

Red cross under a square or circle indicates an individual who died at cancer age from causes other than cancer.

Red C inside of a square or circle indicates an individual who had cancer.