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Among the many unsolved problems in medicine, that of the etiology of cancer is one that probably remains most obscure. Closely associated with this problem is the question: "Is cancer hereditary?"

For a great many years it has been noticed that neoplastic diseases in certain instances have seemed to occur more often in certain families than the law of chance would ordinarily allow. Napoleon Bonaparte died of carcinoma of the stomach and three sisters, one brother, his father and grandfather were all supposed to have died of gastric carcinoma. Blank (1) cites the instance of two famous physicians, Broca and his father-in-law, Lugol, who, in 1856, made record of information concerning a family (which may well have been their own) which included three members of the medical profession. Wolff in 1907 published their figures. There was a total of 16 cases. Ten were cancer of the breast and four were malignancy of the liver. Single examples such as these are sufficient to raise the logical question concerning the hereditary aspects of cancer - a question that has been and will be asked many times of every practicing physician.

A great deal of work has been done in experimentation with laboratory animals and there is little or no doubt that a genetic factor has been shown to exist in the etiology of neoplasms in the animals. Although the

results obtained from such animal experimentation cannot always be applied to human beings in every respect, the idea should not be maintained that such information obtained from lower animals is of no value in the oncology of man. As Weller (2) puts it, "The problems of neoplasia are biological problems and the processes of life are so fundamentally similar throughout the Vertebrata and particularly in the Mammalia that we cannot afford to disregard knowledge which comes from animal experimentation." This writing, in dealing with the genetic aspects of human cancer is concerned primarily with such information, which has been obtained through studies limited to man himself.

In the search for the answer to the hereditary factors in human neoplasia many investigators have turned to the study of so-called "cancer families". Hauser and Weller (3) made follow-up studies on the cancer family of Warthin. At the time of the first report made by Warthin in 1913, of the 48 traced descendants of a cancerous grandfather, 15 had developed cancer and in two others neoplasms had appeared which had not been proved to be malignant. The more complete report made by Warthin in 1925 showed an incidence of 28 neoplasms in a total of 146 individuals, but of these only 88 had reached adult life. At the time of the follow-up report made by Hauser and Weller the family presented 43 carcinomata in 41 individuals from a total population of 305. Since only 174 had attained an age of 25 years, this gives a cancer incidence of 23.6 per

cent in those reaching that age. In two branches of the family cancer has never appeared. They found the anatomical location of the primary lesion to be more significant in this family than the total incidence, 26 carcinomata having occurred in the gastro-intestinal tract and 15 in the endometrium. The authors make no conclusions as to the mendelian implications but the family provides strong presumptive evidence for an inheritable organ-specific predisposition to carcinoma.

Finney (4) in a report on a cancer family states that there was a mother, 4 daughters and 3 nieces, all but one of these having had cancer of the breast. Three of the daughters had a second carcinoma in the other breast and one of these later had a third cancer of the stomach. This report, although covering only 8 individuals in two generations, also points toward an organ-specificity.

Retinoblastoma affords demonstrations of two closely linked tendencies - organ-specificity and familial concentration. Oliver (5) states that the neoplasm has a dominant inherited tendency according to most investigators and that familial records indicate that the hereditary tendency for this cancer is transmitted directly from parent to child but the gene does not always become manifested. Oliver also mentions the report of Fall which mentioned one pair of twins both of whom were affected and two other pairs of twins in which this also held true. Weller (2) states that retinoblastoma has an incidence of

0.01 per cent, not in the total population but in those having diseases of the eyes and in pointing out the familial concentration of this disorder mentions the report of Newton which states that 10 out of 16 children were involved, the article by Thompson which shows 5 out of 14 children involved, and Wilson's writing which reports 8 out of 8 children with the neoplasm. Berrisford (6) reports the case of Thomas G. who survived enucleation of his left eye when 5 months old. From his son, Frank, one eye was removed at 5 months of age. Beatrice, a daughter of Thomas G., was apparently normal; but of her 8 children, 3 required bilateral and one unilateral exenteration for retinoblastoma.

Familial concentration and organ-specificity can be exemplified by the report of Macklin (7) which states that in 60 cases of retinal angioma (the total number of cases up to 1930), 6 cases were in one family and there were two families with 3 cases each. This is important in the genetic study of neoplasms as this serves as an example of a type of tumor that is so rare that the probability of its chance occurrence more than once within the same family is very small.

The genetic factor of neoplasia as well as a tendency toward familial concentration are well brought out in certain precancerous conditions that are inherited. Blank (8) lists neurofibromatosis and tuberous sclerosis as appearing as family traits and lead often to the formation of cancer. Intestinal polyposis has also been established

as a frequent basis for development of malignant growths in members of families affected by this condition. In addition to the above, Blank states that xeroderma pigmentosum which is transmitted as an incomplete sex-linked recessive invariably leads to formation of cancer in the skin of all members of a family who have inherited the disease.

Bauer (9) reviewed several reports on cancer families relating a particularly interesting history of a family compiled by Gardner and Frazier covering five generations and including 217 members, 38 of which suffered from deafness of both ears. Seven of them were diagnosed by physical and neurological examination as having bilateral tumors of the acusticus; in two others it was established through autopsy; and several became blind through choked disc. The authors thought that this strange disease behaved as a dominant. Bauer also refers to the incidence of certain rare neoplasms in many families, the conspicuous frequency with which cancer of the same kind, afflicting the same organ or system of organs, occurs in numerous families and in general agrees with Hauser and Weller (3) that in some families there undoubtedly occurs both an inheritable tendency to certain neoplasms and a tendency to development of cancer in specific organs.

A report made by Macklin (10) gives the history of 3 sisters in England who simultaneously discovered that they had rectal cancer and serves to substantiate the idea of organ specificity. These sisters were 32, 34, and 35 years

of age, respectively, at the time of discovery of the rectal neoplasm. It is interesting to note that that year there were 21 deaths from rectal cancer in the British Isles.

Another approach made by several investigators in the study of the genetic aspect of cancer is the study of family histories of cancer patients. Bargen, Mayo, and Griffin (11) conducted such a study which dealt with 438 individuals and their families. They followed 176 patients with proved cancer of the large intestine in whose families the incidence of cancer was marked. The cases were studied not with reference specifically to the presence of gastro-intestinal cancer in the family but for the presence in relatives of cancer of any part of the body, including cases of cancers of unspecified site. They attempted to standardize the findings in this group by comparison with two equally uncontrolled groups of patients. Three groups of patients and relatives that were observed at the Mayo Clinic were studied. Group A consisted of 176 patients treated on the enterologic services for proved cancer of the large intestine. Group B was a control group consisting of 176 patients observed in the years 1931 to 1936 inclusive for whom the diagnosis of hypertrophic arthritis was made but in whom cancer was not found. Group C comprised 86 patients with proved cancer of the kidney that were observed in the years 1910-1939 inclusive for whom a history of cancer of other members of the family could be elicited. The relatives of the

three groups were then divided into two groups: 1) those in whom cancer was affirmed to have been present; and 2) those for whom no information of its presence was at hand. Those relatives in whom cancer was affirmed to have been present were further divided into three groups, dependent on the alleged site of cancer: 1) cancer of stomach or large intestine; 2) cancer of specified site elsewhere; and 3) cancer of unspecified site. If there was any doubt in the statement of the informant as to the actual existence of cancer in other members of the family, these were classed in the group without cancer. If there existed any doubt as to the site, it was classed as unspecified site.

The following table summarizes the results in the group of relatives with affirmed presence of cancer:

Group	Total Relatives With Cancer	Per Cent Distribution		
		GI Tract	Other Than GI	Unspecified
A	290	42	36	22
B	57	25	50	25
C	104	29	48	23

The number of relatives with cancer of unspecified site is roughly one-fourth for all three groups. In the two control groups B and C, cancer of the gastro-intestinal tract and cancer of specified site other than gastro-intestinal tract occurs roughly in proportion of 1 to 2. Group A shows a behavior tendency of gastro-intestinal cancer which serves to substantiate Bauer's idea of an organ-susceptibility.

From the above information Bargen, Mayo and Griffin make the conclusion that a definite tendency is indicated in the behavior of familial cancer of the colon and rectum and that when multiple cancers occur in any family and one cancer at least is localized in the colon or rectum, there is an appreciably greater chance that cancers in other members of the family will be localized in the colon, rectum and also in the stomach than occurs in cancerous families in which colonic and rectal cancer is not known to exist.

They further make a comparison of Groups A, B, and C with respect to the total number of relatives more than 40 years of age with and without cancer, the total relatives with cancer and the per centage of relatives with cancer. These results are in their table:

Group	Total Relatives More Than 40 Years of Age - With and Without Cancer	Total Relatives With Cancer	Per Cent With Cancer
A	1108	290	26
B	1033	57	6
C	471	104	22

This table illustrates a greater incidence of cancer in families of patients having cancer of the intestine than of those having hypertrophic arthritis, (B), also a greater incidence of cancer in families of patients with renal cancer than of those in Group B.

Crabtree (12) obtained data of 1029 cancer patients which included 522 white females and 507 white males. The females include 294 with cancer of the breast, 152 with

cancer of the uterine cervix and 76 with cancer of the exposed areas of the skin. Males included 256 persons with cancer of exposed sites of skin, 131 with cancer of the lower lip and 120 with cancer of the lung. He proposes the following observations in his study: The incidence of fatal cancer in parents and siblings of white females with skin cancer is nearly twice that which would be expected on a basis of normal experience; for patients with cancer of the breast and cancer of the cervix, the familial incidence is more than 1½ times the normal; for males with cancer of the skin excessive familial incidence is noted only for those persons whose skin cancer developed at a relatively early age; for patients with cancer of the lip the familial incidence is only slightly in excess of normal; and for those with lung cancer it is considerably below normal. He notes further that where an excessive familial incidence is found it is almost always limited to the parents and siblings of those patients whose cancer developed early in life. This he found especially true in the cases of patients with cancer of the cervix, of the female breast and males with cancer of the skin - the familial incidence being from 1 3/4 to 2 1/2 times the normal, but for these same clinical groups whose cancer occurred relatively late in life, the familial incidence is altogether normal. Crabtree's interpretation of these observations is that the familial factors when involved in the genesis of cancer tend to express themselves relatively early in the life of

the individual, while cancer of any of these specific sites which develops relatively late in life can more reasonably be ascribed to environmental factors. He states further that an excessive familial incidence of cancer does not necessarily imply the presence of hereditary or genetic factors in the genesis of the disease; e.g. - taking both male and female patients with cancer of the skin - there was a familial incidence of 126 cancer deaths, the expected number being 90.6, 32 of these 126 deaths stated to be due to skin cancer. He argues that it is conceivable that the excessive mortality from skin cancer in parents and siblings may be due to certain environmental factors common to both patients and members of their families and thus in no way related to innate conditions of heredity. On the other hand, cancer of the female breast and cervix are much less likely to have origins from environmental factors which would be common to both patients and members of their families. Hence, an excessive familial incidence of the disease in such cases may be assumed to be somewhat more probably of hereditary origin. He gives a normal familial incidence in patients with cancer of the lip, cancer of the lung as presumptive evidence of the absence of heredity as a predominant element in the genesis of these two forms of the disease and therefore suggests for these two sites a relatively greater importance of environmental factors.

Gross and Matte (13) interviewed 19 patients with leukemia, 10 of them had a family history of either tumors

or leukemia, a percentage of 53%. Two families were revealed in which more than one member developed leukemia. Their control group consisted of patients suffering from conditions other than tumors and leukemia. 301 patients suffering from various conditions were interviewed and no more than 12% of these patients revealed history of tumors among members of their families.

Smithers (14) analyzed the family histories of 459 patients with cancer of the breast and found that the patient questioned had to the best of her knowledge no evidence of a family history of cancer in 292 cases and reported family cancer in 167 instances. Of these 167, 76 were said to have had cancer of the breast. In 54 cases a history of cancer in more than one member of the family was obtained.

The 167 patients with a known family history of cancer stated that they knew of this on their mother's side only in 88 instances and on their father's side only in 34, amongst brothers and sisters in 33 and on both paternal and maternal sides in 12 cases. This gives a maternal side history of 100 cases to a paternal of 46. Of 459 mothers, 66 were known to have died of cancer, and of these, 25 had cancer of the breast. Of 459 fathers, 30 were known to have died of cancer, none had breast cancer. There were 1008 sisters, 288 of whom had died, 59 in infancy and another 200 of causes believed to have been other than cancer. Of the 29 known to have died of cancer, 11 had cancer of the breast. There were also 11 sisters living

who had received treatment for breast cancer. There were 1059 brothers, 425 of whom had died, 75 in infancy and another 332 of causes believed to have been other than cancer, 18 had died of cancer, none with cancer of the breast. Smithers' preliminary analysis of the above data suggests that there is a significantly high death rate from cancer of the breast in families of patients with that disease, but no higher death rate from other forms of cancer than would be expected in the general population.

Penrose, MacKenzie, and Karn (15) also made a genetical study of human mammary cancer and analyzed 510 such cases. The mothers of 408 of the patients had died and in 25 of these death was due to mammary cancer. Other types of malignancy accounted for 51 deaths. The number of deaths due to mammary cancer if the women had been subject to the mortality in the general population was estimated to be 11.17. For other types of malignancy the mortality among the mothers showed no significant increase above the expected total, i.e. - 51 observed as compared with 48.76 expected. There were 102 mothers still living, 6 of these were under treatment for mammary cancer and 4 had some other type of malignancy.

Histories of these 510 cases of mammary cancer disclose a total of 1255 sisters, 365 of whom had died, the cause being unknown in 58 cases. Of the remaining 307 deaths, calculation of the expected number of deaths due to breast cancer gave a value of 6.98. Actually 23 had died of this condition. Only 19 had died of other types of

malignancy against the expected number of 25.21. Among the 890 sisters still living, 24 were known to have been under treatment for breast cancer and 7 for other types of malignancy. These three investigators bring out another interesting correlation which concerns the sites affected in pairs of sisters and other relatives. Laterality of initial lesions showed a strong tendency to similarity in sisters as shown in their table:

	Mothers				
Propositae	Right	Both	Left	Unknown	Total
Right Side	7	1	7	1	16
Left Side	2	-	10	3	15
Total	9	1	17	4	31
	Sisters				
Right Side	12	-	10	3	25
Left Side	4	1	16	1	22
Total	16	1	26	4	47

Information on fathers and brothers was analyzed also and one case of male mammary cancer was found which was regarded as exceptional in so few families.

Penrose, MacKenzie, and Karn indicate that the above analysis strongly suggests that the transmission of a specific factor is a major cause of mammary cancer. The hypothesis of inheritance of special organic disposition suggested by Bauer is supported by the homolateral familial findings. There was no increase in the incidence of cancer generally, which might have suggested a general hereditary predisposition to malignancy of any type. The familial

incidence among siblings was not high enough to suggest any mendelian explanation of the inheritance.

Deelman (16) conducted a study of relatives of cancer patients by using questionnaires and balancing a non-cancer case of the same age and sex against each case of cancer. He found cancer to be more than twice as frequent among the parents and three times as frequent among the siblings of cancerous individuals as in the families of the non-cancerous. This excess of cancer in families of cancer patients occurred in relatively few families. With these cancer families eliminated, there was left a large group of cancer patients in whose families cancer was absolutely not more frequent than agrees with the normal chance of dying of cancer.

The evidence presented by Hunter (17) in his review of family histories is somewhat contradictory to the evidence given in aforementioned studies. He reviewed the family histories from insurance applications of those who subsequently died of cancer, in comparison with those of insured persons dying from other causes and found no significant difference between the two groups.

There are several elements encountered in the study of family histories of cancer patients which contribute more or less to the inaccuracy of such investigations. These elements cannot be entirely eliminated in spite of the most diligent efforts on the part of those conducting the studies. Lack of accurate knowledge of other members of the family serves as an example of such difficulties as

well as the fact that there is a reluctance on the part of some people to admit deaths from cancer within the family. Wrongly diagnosed cases may also constitute a source of error.

If heredity is a factor in the etiology of neoplasms, the study of the occurrence of tumors in identical twins should be an aid in shedding some light on the question. Macklin (18) believes that if tumors are dependent wholly or in part upon hereditary factors, identical twins should resemble each other with respect to presence or absence of tumor more often than they differ in this regard and they should exhibit the same type of tumor far more often than they show diverse types of tumor and that they should be much more alike in these two respects than are dizygous twins. In her analysis of tumors in monozygous and dizygous twins, Macklin collected from the literature 53 pairs of monozygous twins and 35 pairs of dizygous twins in whom tumors had occurred in either one or both twins. As the result of an appeal she collected 14 more cases and to this list added three personal cases.

An initial analysis was made of these 17 "new" cases consisting of 9 identical twin pairs and 8 fraternal twin pairs. In the identical twin cases both twins were affected in 6 cases - 66.6%. In the fraternal twin series both were affected in 3 cases, or 37.5%. In the identical twin series both were affected with the same type of tumor in the same site in 5 cases, or 55.5%, while in the fraternal twin series both were so affected in 3 cases - 37.5%. Age

of onset was more nearly similar in the identical twins than in the fraternal. In the 6 identical twin pairs in which both twins were affected the average difference in age of onset was 0.6 years while in the fraternal twin pairs with both twins affected, the average difference was 2.9 years.

Macklin's study of the cases from the literature showed that of the 53 pairs of monozygous twins both twins showed tumors in 32 cases, 60.4%, and in 31 pairs the tumors were the same. In one pair the tumors were different. This gave a concordance in type of tumor in 97.0%. There were 21 pairs with only one twin affected and one pair in whom the type of tumor was different, giving a concordance of 58.5% in the entire series. Of the 35 pairs of dizygous twins there were 12 pairs, 34.3%, with both affected. One pair of twins with both members affected had the second twin showing a tumor dissimilar to that which appeared in the first twin and 3 years later a tumor similar to that of the first twin. This pair was counted twice. In the 12 pairs with both twins affected 5 pairs, 41.7%, showed similar tumors and 8 pairs, 66.6%, showed dissimilar tumors. If all 35 pairs are considered, there is concordance in 14.3%, discordance in 88.5%.

Macklin here raises the possible objection that the reason for the high degree of concordance in monozygous twins in the type of tumor as compared with the dizygous pairs is that half of the dizygous twin pairs are apt to

be of different sex. If the female shows breast or uterine cancer the male cannot show the same type. To overcome that objection she compared pairs of dizygous twins both of the same sex and both affected with one-egg twins where both were affected. There were 27 pairs of like-sexed dizygous twins with 12 instances, 44.4%, in which both were affected. Seven of these had similar and seven had dissimilar tumors - this was due to the fact that there were 2 pairs of twins with both similarly affected and one twin with a second dissimilar tumor. Thus, in the like-sexed dizygous twins there was concordance in which both twins were affected in 58.3% as compared with 94.7% in monozygous twins with both affected. Concordance was determined for the whole series and the twins were alike in 26% of the like-sexed dizygous twins and in 58% in the monozygous twins. The difference in age of onset was 9.5 years for like-sexed dizygous twins and 1.2 years for the monozygous twins.

In the 32 pairs of monozygous twins with both affected Macklin found the average difference in age of onset to be 1.5 years and the corresponding value for the dizygous twins to be 7.8 years.

Macklin concludes from her comparison of monozygous and dizygous twins that if one member of an identical twin pair is affected with cancer, the second twin is more liable to be affected with the same tumor in the same site than if the twins belong to a fraternal twin pair since her figures showed that concordance, both with respect to both twins being affected and to the same type

of tumor occurring in both twins, was more frequent in monozygous twins than in dizygous twins. Her second conclusion is that identical twins resemble each other much more closely with respect to time of onset than do fraternal twins.

Bauer (9) states that on a genetic basis, identical twins should both suffer from tumor or cancer with especially great frequency and reviewed several individual reports showing both twins in identical pairs having been afflicted with tumors. It is his belief that it does not follow without exception that they must both be afflicted, because exogenous influences also play a certain role in cancer incidence.

Hammett (19) in his correlation of genetics, chemistry and cancer states that the present group of chemical elements is the product of inorganic evolution and although transformations may occur, these either are produced by highly artificial means or the rate of natural occurrence is so slow that we may neglect them. He brings out along the same line that the present constellation of genetic elements is the product of organic evolution and here, too, change can apparently be induced by artificial means and natural saltations may occur - these latter events being too rare to be pertinent. This occasional mutability of chemical and genetic elements does not detract from the belief that a high degree of fixation has been arrived at insofar as our particular time range of observation is concerned and therefore, according to

Hammett the chemical law of conservation and the genetic law that like begets like are expressions of true succession and continuance.

Hammett brings out that the essence of the law of chemical conservation is that regardless of multiplicity or kind of chemical combinations entered into or departed from by any chemical element, the identity, integrity, and transmissibility of the element as an entity remains unchanged. He reviews, too, the law that like begets like which states that regardless of multiplicity or kind of genetic combinations entered into or departed from by any genetic element, the identity, integrity and transmissibility of the element as an entity remains unchanged and states that this common characteristic of persistence suggests a relation between the two laws. The author states that there could be no inheritance in living things if the constituent chemical elements and the properties inherited therein did not persist as such and that inheritance in living things depends upon this property of chemical persistence - perhaps it even takes origin therefrom. He postulates that when chemical elements go from the non-living to the living state they seem to express other potentialities and properties than those they show in non-living substance and states that the law that like begets like may be conceived as an expression in living things of the law of conservation of chemical integrity.

Hammett has formulated the Law of Continuance which

he states may apply to both the living and non-living: "The elements of all substance and their inherent properties and functions tend to persist and hold on in uninterrupted succession throughout their transmigrations." He reasons that chemical elements are thus the building tools of heredity and heredity can be considered the dominating force for continuance in the inorganic world as it is in that of living organisms.

Hammett brings out that the peculair properties of the particular elements suitable for the substance, reaction basis and form of living not only make possible the exercise of the potentialities of heredity in organisms, they also set the limits thereto. The ability of all cells to select those particular chemical groups which by their association act to characterize the cell type is an endowment of heredity. The ordered production of a species-true organism is the property of heredity and thus the species specificity in chemical composition and the superimposed specificity in organ and tissue composition are determined through heredity. Heredity selects the characterizing chemical building materials of the developing organism. In his correlation between cancer and the Law of Continuance, the author states that cancer is an increasing mass of self-reproducing cells for which the Law of Continuance is a determinant, i.e. - the course of development and distinctive chemical nature of cancer cells is set by heredity. He refers here to the heredity of cancer cells themselves and is not referring to heredity

in the host. The fact that cancer cells proliferate true to type and form other cancer cells Hammett uses as evidence for the above correlation.

Many theories have been formulated with respect to the role of genetics in the etiology of human neoplasia, a few of these theories are recorded here. Bauer (9) believes that there exists an inheritable tendency to cancer, specifically to cancer in a certain organ or system of organs and that in addition to this there exists a general blastoma tendency, the general blastoma tendency part of the theory being based on reports of one or more neoplasms within the same individual. He has set up the following formula showing nine genotypically fundamentally different types of individuals with reference to an existing or non-existing constitutional tendency to cancer:

1. NgNg.N1N1	4. NgCg.N1N1	7. CgCg.N1N1
2. NgNg.N1C1	5. NgCg.N1C1	8. CgCg.N1C1
3. NgNg.C1C1	6. NgCg.C1C1	9. CgCg.C1C1

N - Non-Cancer
C - Cancer
g - general neoplastic dispostion
1 - Localization factor ($1_1, 1_2, 1_3, \ldots 1_n$)

The impregnated ovum from which the individual will grow which is later going to be afflicted with cancer contains an abnormal gene or an abnormal gene complex called C. Cancer immune individuals possess, instead of C, the normal gene N. N and C are allelomorphs. A new individual receives one allelomorph from each of his parents and may have the genetic formula NN, NC, or CC. If the abnormal gene C is recessive only the homozygotous individual with the genetic formula CC would have the

tendency to cancer, but if C is dominant of N, the heterozygous individual NC would also inherit the tendency to cancer.

In order to produce cancer in an individual, the two abnormal genetic factors Cg and Cl must be present and Bauer pictures the general blastoma tendency as expressed by the allelomorphs Ng and Cg, the specific organ susceptibility by the allelomorphs Nl and Cl, or Nl, or Cl, etc. He states that he cannot state conclusively whether Cg is dominant over Ng or recessive, and likewise whether Cl , Cl , etc., have recessive or dominant character with respect to Nl, , Nl_2, etc.

If both abnormal genetic factors are recessive only the last of these nine genetic formulae, viz., Cg.Cg.ClCl, would indicate a constitutional cancer candidate. If only one of the factors were dominant, e.g. Cg over Ng, and if the other abnormal factor were recessive, two of the nine individuals, 6 and 9, would be potentially cancerous. If both abnormal factors are dominant over the normal factors, four of the nine individuals, 5, 6, 8 and 9, would be constitutional cancer candidates.

Following along the general theoretical vein dealing with more or less strict mendelian ratios, Slye (20), as a result of her experiments on mice, has arrived at two conclusions: 1) the genetic difference between susceptibility and insusceptibility to cancer involves one gene, that is, they are unit characters; 2) the susceptibility to cancer behaves like a recessive, while insusceptibility behaves like a dominant character.

Many workers, although firmly convinced that genetics plays a very important part in the etiology of neoplasia, are of the opinion that other factor or factors are involved in the formation of cancer. Weller (2) states that the cause of disease is never a single factor - two elements always enter into the etiology: one is inherent in the germ plasm of the individual and the other is brought to bear upon the organism from beyond the confines of the germinal elements from which it has developed - the intrinsic and extrinsic factors. These two ingredients may be combined in every possible proportion. He states that intrinsic factors are operating whether there be direct transmission of a predisposition to neoplasia or whether the inheritable condition is a somatic structural or functional variation which makes the affected individual more vulnerable to the cancerogenic effect of extrinsic factors. In contrast with Bauer's formula, Weller states that neither a gene for "cancer" nor a "cancer-resisting" gene is essential for exemplification of intrinsic factors in the etiology of neoplasms - broad conceptions of the transmission of certain qualities must be entertained. In support of his theory, Weller brings in a very appropriate quotation made by Baur: "We have likewise reason to expect that hereditary transmission in accordance with other laws than mendelian will occur in the case of all social differences which are based, not upon peculairities of the chromosomes, but on those of some other part of the idioplasm. Differences in the structure of the remainder

of the thread equipment of the cell nucleus, in the structure of the chromosomes, etc., must certainly produce differences in the finished organism..... Very numerous observations on plants combine to show that hereditary differences in their vitality are transmitted in accordance with other laws than the mendelian. The mendelian laws of separation do not prevail universally, and .... in the case of man, no less than in that of other organisms, we are likely to encounter phenomena of hereditary transmission which do not occur in accordance with these laws."

In further substantiation of his theory, Weller utilizes a quotation from MacDowell: "It is highly regrettable that, outside the immediate circle of geneticists, there seems to be an impression that the gene is self-sufficient and is either dominant or recessive. Especially as applied to neoplasia this misunderstanding has led to erroneous conclusions both on the part of hostile critics and ardent believers. Dominance is only a special case at the end of a continuous series of interrelations between pairs of genes. No gene can produce its effect without the cooperation of many other genes.... And genes and extrinsic conditions cooperate in all cases."

Macklin (10) illustrates her theory of causes other than heredity entering into the causation of neoplasms by the equation that heredity plus extrinsic factors produces cancer. She states that this equation is flexible

so that as one of these variables become large the other may be permitted to be correspondingly small. When both heredity and extrinsic factors are potent we should expect malignant changes early, when both are minimal we should expect an individual to be relatively cancer resistant. As further explanation of her equation, Macklin states that one factor may be so powerful as to render the other negligible - e.g., retinoblastoma occurring shortly after birth exhibits little ground for believing external factors to be operative, while the X-ray skin cancers of unprotected workers are an example of the other extreme.

Blank (8) concludes that cancer is not a unit disease as far as genetic behavior is concerned - tumors of different types and sites differ in genetic behavior and thus it is unlikely that a heritable condition of cancer exists as such. He believes there exists a general inherited disposition, whether of susceptibility or refractoriness, to formation of tumor and that in certain persons, exist factors, probably inherited independently of a general dispostion, which govern the localization of the disease. He includes environmental factors in his theory, indicating that an inherited favorable internal environment may exist and this, combined with general susceptibility may lead to formation of cancer in certain tissues. In essence he agrees, too, with the equation stated by Macklin when he states that when general susceptibility is great in an individual

even relatively slight irritation by agents of many kinds may lead to formation of cancer while on the other hand there are purely external cancerogenic agents which are strong enough to lead to formation of cancer in certain tissues, even in persons in whom an inherited predisposition is not distinct or perhaps too weak to be detected by methods used at present in testing hereditary traits. He suggests, too, that the predisposition to cancer may not have been inherited but rather acquired under conditions the nature of which is not yet known.

Burdette (21) emphasizes environmental influences in his statement that the visible expression of a gene, the phenotype, depends on the conditions existing during the period of gene action and that the effects of a gene may vary with environmental conditions. He agrees with Hammett when he states that the gene itself passes from generation to generation unchanged. He concludes that the end result of gene action in an organism does not necessarily indicate the presence or absence of the gene on the chromosome, and, applying this to cancer, the susceptibility to cancer must be studied and the presence or absence of cancer must not be regarded as necessarily indicating the presence or absence of these genetic factors for susceptibility.

SUMMARY

In the consideration of the hereditary element in human oncology, three principal approaches to the question have been discussed: 1) The study of "cancer families"; 2) The family histories of cancer patients, and; 3) The study of tumor incidence in identical twins, including a comparison of such incidence in monozygous and dizygous twins.

Analyses of the histories of cancer families have brought out three important general points:

1. Neoplastic processes have occurred in certain families more frequently than would be expected according to the "normal" cancer incidence.

2. The anatomical location of primary lesions in many instances is just as important, if not more so, than the incidence of such lesions. For the most part, the studies show a rather marked organ-specificity tendency.

3. It has been definitely shown that several conditions, known to be pre-cancerous, are hereditary.

Studies of family histories of cancer have demonstrated, in certain instances, a tendency toward organ-specificity, and have generally indicated a greater incidence of cancer of various types in families of cancer patients than in families of patients without cancer. However, every investigation along this line has not demonstrated the above tendencies.

Statistics derived from an analysis of tumors in twins point out the following general characteristics:

1) Tumors affect both members of monozygous twin pairs more often than they do both members of dizygous twin pairs; 2) The occurrence of tumors of the same type in the same organ takes place more often in both members of identical twins than it does in both members of fraternal twins; 3) The age of onset of neoplasms is more nearly identical in monozygous twins than in dizygous twins.

Hammett (19) has drawn a relationship between the law of chemical conservation and the law of genetics and has formulated the "law of continuance." He has applied this law to cancer cells stating that the course of development and distinctive chemical nature of cancer cells are set by heredity.

CONCLUSIONS

The increase in incidence of cancer in certain families over what would ordinarily be expected and the tendency in many cases in those families toward organ-specificity in such incidence furnishes strongly presumptive evidence that a genetic factor or genetic factors are present in the etiology of neoplasms in man. Such presumptive evidence is offered also by the greater incidence of cancer in families of cancer patients and the apparent tendency toward organ-specificity in these groups. The studies of tumors in identical twins further serves to substantiate the evidence of presence of hereditary factors in the causation of neoplastic processes.

In certain conditions, known to be pre-cancerous, there is no doubt that hereditary factors are involved.

Several theories have been advanced with reference to the method of inheritance but the exact mechanism of transmission has not as yet been established.

DISCUSSION

What is the practical value of presumptive evidence of hereditary factors being involved in the etiology of cancer? The information so far obtained strongly indicates that genetic factors are present in greater or less degree and although such information, strictly speaking, can be classed only as circumstantial evidence, a great deal can be accomplished in the eradication of this scourge if sufficient effort is put forth. Careful histories of every patient can be taken, especially familial histories. Individuals can be forewarned to some degree if their families show a tendency toward either cancer of a particular organ or cancer in general. These people can have more frequent examinations, making possible very early diagnosis in many cases should cancer occur.

BIBLIOGRAPHY

1. Blank, F.: Genetic Aspects of the Cancer Problem, Arch. Surg. 49:301-315 (Nov.) 1944.

2. Weller, C. V.: Intrinsic Factors in the Etiology of Neoplasms, Am. J. Cancer 30:39-46, 1937.

3. Hauser, I. J., and Weller, C. V.: A Further Report on the Cancer Family of Warthin, Am. J. Cancer 27:434-449, 1936.

4. Finney, W. P.: A Cancer Family, Proc. Staff Meet. Mayo Clin. 7:383-384, 1932

5. Oliver, C. P.: The Use of Genetics in Cancer Research, Texas Rep. Biol. M. 8:2, 183-206, Summer, 1950.

6. Berrisford, P. O.: Statistical Notes on Glioma Retinae, With a Report of Forty-one Cases, Royal Lond. Ophth. Hosp. Reps. 20:296, 1916.

7. Macklin, M. T.: Heredity in Cancer and Its Value as an Aid in Early Diagnosis, Edinburgh M. J. 42:49-67, 1935

8. Blank, F.: Genetic Aspects of the Cancer Problem, Arch. Surg. 49:301-315 (Nov.) 1944.

9. Bauer, J.: Genetics in Cancer, Middleton Goldsmith Lecture New York Pathological Society, October 12, 1932, Lancaster Press, Inc. 1934.

10. Macklin, M. T.: Inheritance and Human Cancer, Ohio State M. J. 43:836-840 (Aug.) 1947.

11. Bargen, J. A., Mayo, C. W., and Griffin, L. A.: Familial Trends in Human Cancer, J. Hered. 32:7-10 (Jan.) 1941.

12. Crabtree, J. A.: Observations on the Familial Incidence of Cancer, Am. J. Pub. Health 31:49-56 (Jan.) 1941.

13. Gross, L., and Matte, M. L.: New York State J. Med. 48:1283-1284 (June) 1948.

14. Smithers, D. W.: Family Histories of 459 Patients with Cancer of the Breast, Brit. J. Cancer 2:163-167, 1948.

15. Penrose, L. S., MacKenzie, H. J., and Karn, M. N.: A genetical Study of Human Mammary Cancer, Brit. J. Cancer 2:168-176, 1948.

16. Deelman, H. T.: Heredity and Cancer, Ann. Surg. 93:30, 1931.

17. Hunter, A.: The Inheritance of Cancer in Mankind, Am. J. Cancer 19:79, 1933

18. Macklin, M. T.: An Analysis of Tumors in Monozygous and Dizygous Twins, J. Hered. 31:277-290 (June) 1940.

19. Hammett, F. S.: Genetics, Chemistry and Cancer, J. Hered. 31:511-513 (Dec.) 1940.

20. Slye, M.: Heredity as Determining the Types and Site of Cancer and the Age at Which it Occurs, Am. J. Path. 17:655-665 (Sept.) 1941.

21. Burdette, W. J.: Genetics and Cancer, New Orleans M. and S. J. 101:124-129 (Sept.) 1948.