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The genetic influences as a factor in carcinogenesis

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BOSTON UNIVERSITY

GRADUATE SCHOOL

THESIS

THE GENETIC INFLUENCES AS A FACTOR IN CARCINOGENESIS

By

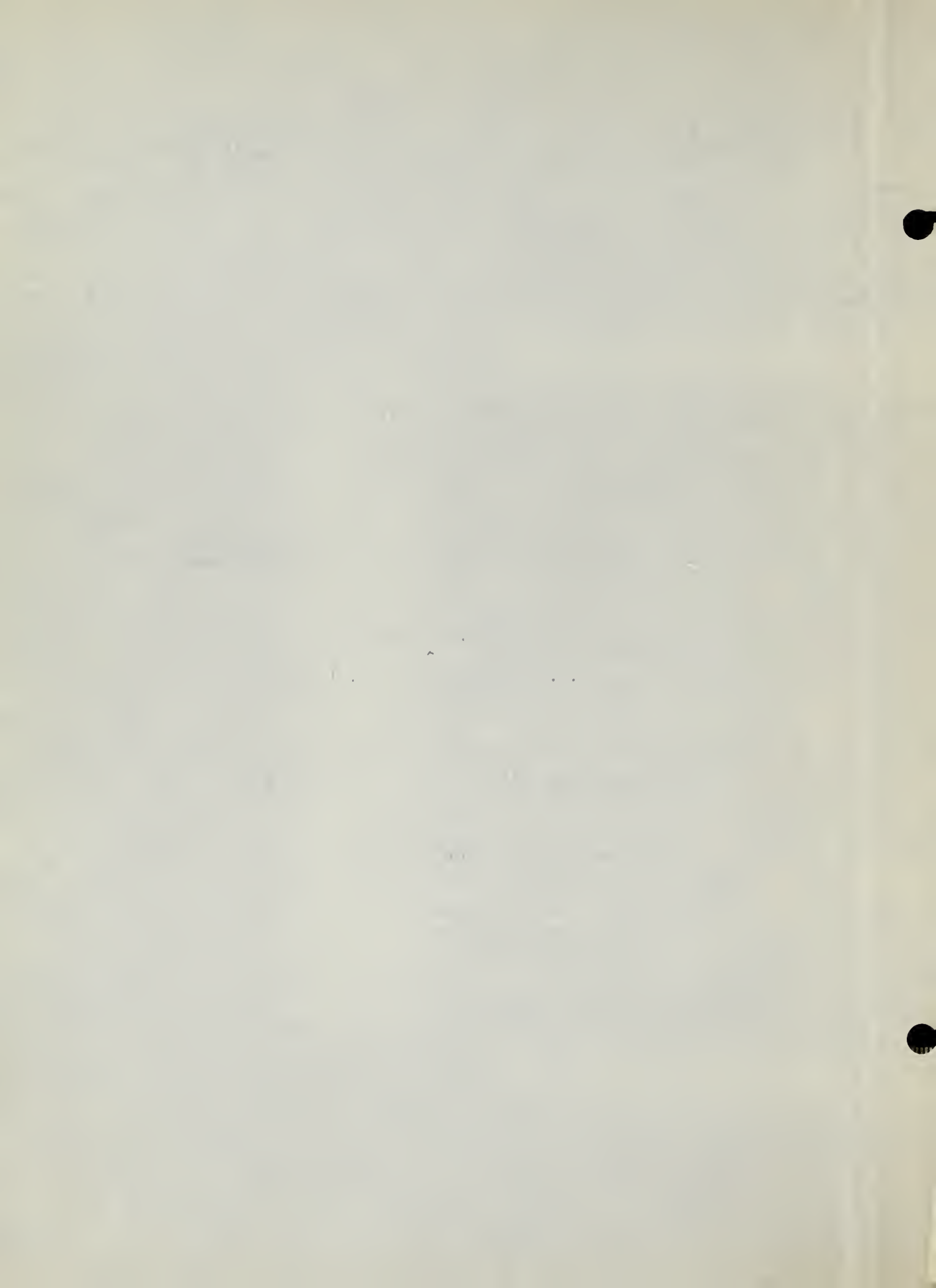
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(A.B., Boston University, 1948)

Submitted in partial fulfillment of
the requirements for the degree of

Master of Arts

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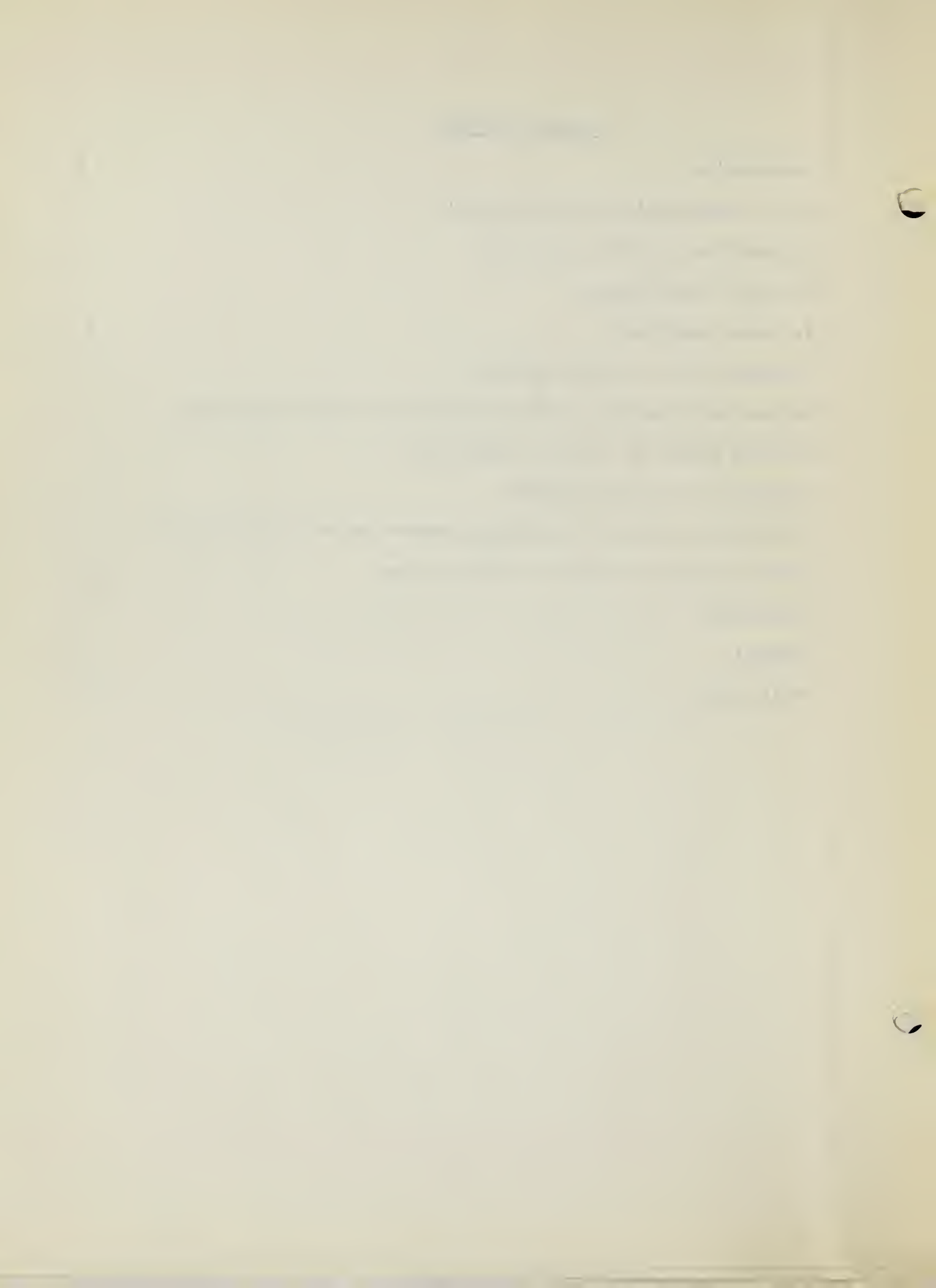
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INTRODUCTION

This paper is written with the prime purpose of presenting an overall review of some of the known factors contributing to the formation of cancer, with special emphasis upon the genetic factors.

A thorough, but by no means all-inclusive survey of the literature in the field of modes of transmission of inherited carcinoma in animals is reviewed. Evidence that Mendelian laws of inheritance hold true--as far as carcinoma is concerned--in man as well as in the lower mammals, is presented. However, these Mendelian laws in man are made far more complex than in other animals by other factors, such as hormonal, virus and environmental, as reported by Little (1933).

Space is devoted to a review of the theories behind the formation of cancer. These theories, together with the possible preventive measures that may be taken to minimize the manifestation of this disease in persons with a family history of a high cancer incidence, are considered.

Although preventive medicine in itself cannot remove existing cancer, it can in some cases keep the disease under control. According to Farber (1949) it must be remembered that today the only methods available to the physician in the treatment of cancer are surgery and radiation; and it is possible that if the populace at large can be made more acutely aware of cancer--more cancer conscious--perhaps then the



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physician will be able to use these known tools earlier and with more success.



FACTORS CONTRIBUTING TO CARCINOGENESIS

Little (1941) presented convincing evidence that the chromosomes contained in the fertilized egg play a part in determining whether or not the resultant organism will have a tumor. However, the extent of the importance of heredity in determining the appearance of cancer in the life of the organism is also greatly influenced by other very important factors. According to Pittner (1937), one of these extra-chromosomal factors is a virus-like factor found in the milk of a strain of mice with a high incidence of mammary gland cancer.

Another extra-chromosomal factor which must be considered in the development of the breast cancer of mice is oestrogen. Bonser , Strickland and Connal (1937) were able to induce cancer in a strain of mice where Bittner's milk factor is normally absent. It would seem that the oestrogen alone was able to stimulate the development of cancer in the absence of the milk factor.

Strong (1935) used a large number of mice (C B A strain), of known immunity to cancer. Nevertheless, four tumor formations, an incidence of 4.8 per cent, spontaneously appeared in a normally long lifetime in these "Immune" mice; they occurred at the end of eighty, ninety-one, one-hundred five and one hundred fourteen weeks.

Bonser, et al (1937), working with the same strain, developed five tumors in mice treated with a combination of oestrone and prolactin, and with oestrone alone. A control group developed no tumors. The percentage of tumor incidence of this group was 15.6 per cent. These tumors also occurred earlier than in Strong's mice (fifty-five, eighty, eighty-one,

eighty-three and one hundred three weeks). Bonser also reported that forty-one mice reached tumor age and did not develop any signs of tumor. These results are significant in that if chance alone determined the formation of the tumor, it would have occurred only .2 times per one hundred.

Lathrop and Loeb (1916) found that the effect of non-breeding on cancer-susceptible strains tended to lower the tumor incidence and lengthen the age at which tumor developed. These facts tend to support further the contention that the oestrone and prolactin treatments alone had determined the development of the tumors reported by Bonser.

A most important question to be asked is whether this factor, together with the genic factor, is similarly involved in the growth of breast cancer in other species, particularly in man. Different opinions are found in the literature on this matter.

Wasler (1932) and Wassink (1935) presented favorable statistical data based upon population frequencies in the Scandinavian countries indicating that these two factors are involved in man. However, Passey (1942) declared that after careful study of cancer "trees" in England, such evidence cannot be definitely borne out, for in six hundred cases of cancer of the breast, he was unable to find three daughter generations with breast cancer, e.g. grandmother and mother and daughter.

The relationship between genic and environmental factors in lower animals was investigated by Pybus and Miller (1935) who reported the results of breeding experiments with Strain Edinburg mice exhibiting a low mammary cancer incidence, mated to a high incidence strain (Simpson).

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The F_1 produced no mice with mammary cancer; the F_2 produced two cancerous mice and one hundred fifty-eight non-cancerous mice. This was interpreted as demonstrating a simple recessive mode of transmission. However in 1944 they repeated this experiment using an Edinburg male and a Simpson female. These matings produced an all-cancerous F_1 . A back cross with an hybrid female and its father showed a high percentage of cancerous offspring. Another cross of a male hybrid mated to an Edinburg female showed no cancerous offspring. Thus was demonstrated the presence of a milk factor, which had been unknown to the authors in their first experiment. This milk factor was obviously responsible for the high incidence of cancer in the F_1 of the first and second parts of the second experiment (1944). The absence of this factor accounted for the absence of cancer in the first experiment (1935). Also, this factor is not carried by the male of either strain; this is obvious since the progeny of the cancerous hybrid male mated to the low incidence strain female showed no mammary cancer. Similar results were noted from the earlier experiment.

To explain the relationships of the genic and environmental factors in humans is a more complex undertaking. Little (1941) suggested certain experiments to be undertaken in order to clarify these complex relationships. His program included at least five definite experiments. These were:

I. A determination of the incidence of breast carcinoma in a population of women who were:

A. Nursed by mothers known to have died from breast cancer at a comparatively early age.

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B. Nursed by mothers known to have died in old age without mammary cancer.

C. Bottle fed.

II. Studies among brother and sister incidence of cancer, involving records of number of children in each family and order of births.

III. Studies among Negro and white crossings, with special attention to incidences of skin carcinoma.

IV. Studies of relationship between testicular carcinoma and mammary cancer in males.

V. Studies of the incidence of cancer in ovariectomized women.

In 1945, a study was made by Duffield based on statistical data taken from the United States Census of 1940. Although the data could not be broken down in as many subdivisions as Little might have preferred, some pertinent statements were obtained:

1. "It is true that cancer mortality bears some relation, direct or indirect, to marital status."

When classifying cancer deaths according to the locus of the tumor on the body, further significant conclusions were obtained:

2. "The frequency of mortality from cancer of the breast and genital organs (other than the uterus) among married females is greater than in spinsters."

3. "On the other hand, spinsters appear to have lower mortality from cancer of the uterus and of the stomach."

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Age significance was also noted. Married young women had less cancer than their unmarried sisters. This has been attributed to two causes, namely:

1. That married women are under closer medical supervision than spinsters.

2. That spinsters may undergo endocrine disturbances due to leading an "abnormal" life.

Further work along lines suggested by Little seems to be desirable.

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INTRODUCTION TO GENETIC INFLUENCES

According to Blank (1944) it has been generally agreed that a predisposition toward cancer can be inherited, but that other factors exist which are inherited independently and which govern the localization of the disease.

Wright (1934) suggested that one of the ultimate aims of all genetic analyses is to break down the characteristics into terms of genes, for the genes will behave in accordance with Mendelian Laws of heredity, whether they are in a highly inbred or in a heterozygous population, and regardless of whether they be color genes or those influencing cancer development. The following example will serve to illustrate why it is necessary to understand Mendelian theory in terms of genes rather than in terms of characters.

According to the Mendelian law of segregation, when a homozygous black mouse, BB, is mated to a homozygous brown mouse, bb, the F_1 offspring, Bb, is a heterozygous hybrid, since it receives a dominant single gene from one parent, and a recessive single gene from the other parent. When the F_1 generation is mated, the 1:2:1 ratio (1 BB to 2 Bb to 1 bb, or 1 black homozygous, 2 black heterozygous and 1 brown homozygous) is obtained. However, in this case both the genotype and the phenotype can be recognized, by means of back cross studies. Contrasting this method to the one about to be described, where Mendel's law in terms of the character alone rather than in terms of genotype and phenotype is stressed, it appears that character and gene are more significant for progeny prediction.

A black mouse of unknown genotype, mated with a brown mouse, results

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in an all black F_1 generation, which when interbred, results in an F_2 of 3:1 or three blacks to one brown. This is not always true. It is possible for the black mouse to carry such genes as those influencing albinism, and either parent or both may also carry other recessive genes. The resultant offspring could conceivably be white, or even dilute, depending entirely upon the genotypes of the parents, which are not known in this case.

In the same way, unless the exact genotype of the mouse carrying the cancer gene is known, we cannot predict with assurance the resultant offspring. It is this possibility that has often been overlooked when results have been tabulated, for not only must the cancer gene be known, but the "background" genes must be determined, e.g. recessive epistasis, etc.

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THE ROLE OF ENVIRONMENT

Another important group which must be taken into consideration is that of environmental factors. The importance of environmental factors may be drawn from the experiments of Iljin (1930) whose work on the temperature effects on the color of the Siamese cat furnishes a classic example.

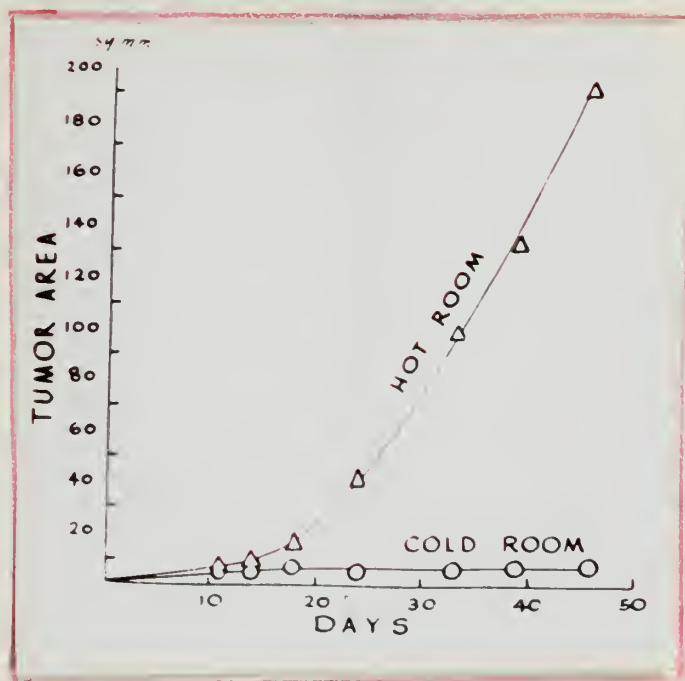
It is a well known fact that the colors of animals are heritable characters. However, the genetic factor determining melanism can produce melanism only under strictly fixed external conditions. The experiment consisted of keeping two pure bred Siamese cats in a room with a comparatively low temperature which averaged 15°C . After two and one half months their color had become gradually but continually darker. These changes of color must be considered the result of the influence of low temperature, since control animals were kept in an identical environment save for the temperature, which was 30°C . To prove further that the low temperature alone was the factor determining the change of color, certain other tests were performed. Part of the animal was shaved; wadding was laid on the shaven skin; and this was covered by a cotton bandage tied to the shoulders to prevent heat loss. A thermo-couple placed under the bandage showed this temperature to be raised to 36°C . Two weeks later the bandage was removed, and the new hair that had grown in was white. Thus it is clear that at a low temperature, the hair becomes intensely pigmented, while at a higher temperature, the pigmentation is decreased. When the bandage was removed and room temperature restored the appearance of the hair changed back to the dark. It was also found that various other parts of the cat's body

were more and less susceptible to this color change brought about by temperature. The different parts of the bodies of the Siamese cats, therefore, had a varying sensitivity to low temperature. Thus he concluded that there were relative thresholds of irritation in the various body parts, and that the color of the Siamese cat is under a double control: the genetic or innate physiological factor, and the external temperature which constitutes the environmental factor.

Wallace (1942) and his associates found that under carefully controlled conditions which involved a constant tropical environment (92°F), subcutaneous methylcholanthrene-induced tumors appeared earlier in strain C₃H mice than in litter mates which were kept in a constant temperate environment (65°F). The impetus for this research was a series of conclusions submitted in a statistical report by Gover and Collins (1940) which apparently revealed a higher rate of skin cancer in our southern states than in our northern climes. The striking results of Wallace's experiment are demonstrated graphically by the following illustration from his report.

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SUBCUTANEOUS-INJECTION EXPERIMENT



* A GRAPHIC ILLUSTRATION OF THE INFLUENCE OF A PHYSICAL FACTOR, i. e. HEAT, UPON THE GROWTH OF CANCER. THE AREA OF CANCEROUS TISSUE INCREASES DIRECTLY WITH THE INCREASED LENGTH OF EXPOSURE TO A TEMPERATURE OF 92° FARENHEIT.

*From Wallace, E. W., Wallace, H. M. and Mills, C. A. 1942. Effects of climatic environment upon the genesis of subcutaneous tumors, induced by methylcholanthrene in mice. J. Nat. Cancer Inst. 3:107.



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Therefore, an important fact concerning cancer inheritance which must not be overlooked is that this disease will manifest itself usually in conjunction with external or environmental factors. This theory was first set forth by Loeb (1916) who stated it in a concise formula: $HS = C$. H stands for the heritable gene, S for the external environment or stimulation, and C represents the cancer.

To show just how closely related the environmental factors are to the genetic background, the experiments conducted by Andrevont and Dunn (1948) reveal significant data. Although these experiments were performed for another purpose, namely to determine the presence of a mammary tumor agent in a C strain of mice, they serve as well to demonstrate the relationship between environmental and genetic background. Strain C₃H mice known for its high incidence of mammary tumor was inbred and when parturition was imminent, the pregnant mice were operated upon to remove the young. These were then suckled by strain C 57 mothers (resistant to mammary gland cancer). Thus was established a strain which was susceptible to mammary tumor, yet free from the agent which caused it (milk virus). Any introduction of the agent would cause the individual or its progeny to have observable tumors. When the new strain, designated CH₃- was mated to strain C, the resultant offspring should have been either tumorous, due to the virus agent present, or non-tumorous due to the lack of the agent. However, in these experiments, the virus factor was not found in the strain C. Nevertheless, the experiment served to demonstrate how very closely linked are heredity and environment.

The Bittner's milk factor and the oestrogen factor are further ex

amples of the importance of environmental factors, as mentioned previously. These environmental factors themselves are divided into two classes: the internal and the external. The external factor has been illustrated by Iljin's experiments (1930) and the internal factors are those such as have been shown by Russell and Green (1943), who have described the skeletal development as affected by intra-uterine factors. They cross-bred a strain of mice having the normal number of sacral vertebrae (five) with an inbred strain having an atypical number of vertebrae (six). The number of vertebrae of the F_1 hybrids more closely approached the number of vertebrae of the maternal rather than the paternal parent, regardless of which parent had the atypical number. Furthermore, when fertilized ova from pure five-vertebrae strain matings were transferred to the uteri of six-vertebrae strain foster mothers, and completed their development there, the vertebral number of the resulting embryo resembled that of the foster mother more than that of their true mother's strain. This indicates the importance of the intra-uterine environment.

The internal environment may also be influenced by genetic factors, as was demonstrated by Bittner (1936), who showed that the milk factor varies in effectivity in relation to the strain in which it is found. In one mouse it may produce tumors at an early age, while in another strain it may be present but inactive. The milk factor, therefore, is an environmental one, however its effectiveness may be determined by genetic forces within the strain.

A more recent experiment demonstrating how the internal environment, influenced by genetic factors, in turn influences the cancer incidence, is that of Bittner and Huseby (1946). They observed tumor development in two

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strains of mice, A and Z, which were genetically similar with respect to susceptibility to cancer and presence of milk agent, as far as was possible to determine. In virgin females reported, a higher incidence of cancer developed in strain A than in strain A. The authors attributed this phenomenon to an "inherited hormonal influence" as determined physiologically by the appearance of the adrenal glands; strain Z glands were larger and showed greater secretion.

It is of the utmost importance when considering environmental factors in relation to cancer genesis to consider also nutrition. Since adequate nutrition is so essential for normal growth and maintenance, it follows logically that some relationship should exist between nutrition and abnormal or cancerous growth.

In the past ten or twelve years, much research has been carried on in the search for more knowledge about the effects of nutrition and malnutrition on carcinogenesis. For example, White and Edwards (1942) performed an experiment involving the feeding of a group of rats a cystine-supplemented diet. During the feeding, a carcinogen, p-dimethylaminoazobenzene was administered orally. A similar group was fed this agent without the benefit of the cystine-supplemented diet. At the end of two hundred days, the supplemented diet rats developed only fifteen per cent hepatic tumors. Ninety-six per cent of the normal dieted rats had this type of cancer. However, these results are not as significant as they at first appear, for after four hundred days, seventy per cent of the cystine-supplemented rats developed hepatomas. It was concluded that cystine does not prevent tumor formation, but that it merely increases induction time.

The following is a summary of the findings of the study. The results indicate that the majority of respondents are satisfied with the current state of affairs. However, there are several areas where improvement is needed. The most significant findings are as follows:

- 75% of respondents are satisfied with the quality of service.
- 60% of respondents are satisfied with the price of the products.
- 80% of respondents are satisfied with the location of the store.
- 50% of respondents are satisfied with the staff's attitude.
- 40% of respondents are satisfied with the variety of products.

Based on these findings, it is recommended that the company should focus on improving the price of the products and the variety of products. Additionally, the company should continue to maintain the high quality of service and the positive attitude of the staff.

Nutrition may be considered as environmental and is an effective agent in carcinogenesis, in addition to other environmental and genetic factors.

IS CANCER INHERITED?

Cancer is a character, and strictly speaking, characters are not inherited. However, the genes in the chromosomes, the other nuclear as well as the cytoplasmic inclusions that go to make up the fertilized egg, are inherited. Cancer as a character is affected by the genetic constitution or genes.

The problem is not so much whether cancer is inherited, but rather how cancer might be inherited. The average student of cancer considers a genic character to mean a genic character difference. In other words, not why does John have cancer, but how did it happen that John has cancer and Mary does not. The answer is that the difference may be due to genetic or environmental or hormonal factor differences.

However, through experimentation with known homozygous strains of mice, it is often possible to determine which of the genetic, environmental or hormonal factors are causative agents in producing mammary tumors. Little (1944) has presented the reasons for the importance of using "pure" strains, as follows:

"The search for factors which influence incidence of cancer depends first on the isolation and maintenance of strains homogeneous within reach as regards chromosomal genetics and differing from one another in the same respect. By using various types of crosses and thus being able to contrast genetic variation with variation in both internal and external environment acting on uniform genetic material, one can begin to get a picture of what some of the strain differences mean in a biologic or even in a chemical way."

Bittner (1937) performed a series of experiments illustrating the experimental method, in which he bred known strains of mice and noted the tumor incidence in their litters. The difference between the high tumor incidence of strain "A" breeding females that had been nursed by their own mothers and the low tumor incidence of strain "A" breeding females that had been foster nursed by strain C 57 black mothers was clearly attributed to a difference in the milk factor. It could not be a genetic difference because both groups had the same genetic constitution. The low tumor incidence of C 57 black females nursed by their own mothers and the relatively high tumor incidence of C 57 black females foster nursed by strain "A" breeding females was clearly a difference of milk factor.

The difference between the high tumor incidence of strain "A" breeding females nursed by their own mothers and the lower tumor incidence of strain C 57 black breeding females foster nursed by strain "A" females was a genetic factor. It could not have been a milk factor, since both groups received the same milk. The difference between the high tumor incidence of strain "A" breeding females and the low tumor incidence of virgin females of the same strain could not have been a milk or a genetic factor difference, but it was clearly a hormonal difference, since they received the same milk, were genetically similar, and only the hormonal factor varied due to breeding (pregnancy, parturition, lactation).

Furthermore, the difference between the high tumor incidence of breeding strain "A" females nursed by their own mothers and the low tumor incidence of C 57 black females nursed by their own mothers was both a milk factor and a genetic factor difference.

The internal environments of even relatively homogeneous inbred animals living under controlled laboratory conditions are very complicated. It is extremely difficult to evaluate the part played by genes, hormones, diet and other factors in the production of cancer cells. For example, Dunning and Curtis (1946) have shown that although a strain of rats was developed that had a low incidence of lymphosarcoma, this tendency was inextricably tied up with the genes affecting longevity. It was found that when the strain was bred for longevity, the incidence of lymphosarcoma increased. Yet according to the methods used in determining the genetic environment, the genes for lymphosarcoma were uniform in both strain (long-lived and normal-lived).

Using the technique described by Little (1943) Wooley, Fekete and Little were able to observe differences in hormonal balances. By doing early gonadectomies on mice of three different strains, the investigators found three distinct and characteristic adrenal gland responses. Strain C 57 black mice adrenal glands showed no particular change. In strain dba mice the adrenal glands hypertrophied. Finally in strain CE mice hyperplasia of the adrenal glands continued until cortical carcinomas of that gland developed in 95 per cent of the treated (gonadectomized) mice. In these cases the development of cancer depended largely upon hormonal balances which varied with the species.

Certain investigators such as Blank (1944) prefer to speak of the susceptibility to cancer development as the inherited character. However, considering this to be the case, this is in reality merely a consideration of the chain of events leading to the actual cancer and a recognition of the preceding link instead of the end link, cancer itself.

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THEORIES BASED ON SOMATIC MUTATION

Before proceeding with a study of the methods of transmission of cancer through germinal genes, a theory first formulated by Boveri (1929) and more recently adopted by others, should be considered. This theory, in brief, states that a cancer results from a change in the chromosomes of the somatic cells, i.e. somatic mutation. A mutation is a change in a gene, potentially capable of being transmitted. It may take place in either germinal or somatic tissue. If it takes place in somatic tissue, it cannot be sexually transmitted, but it may be asexually propagated, particularly in plants. This has been established by experiments done by Demerec (1931) in his work with delphiniums. In an attempt to learn the modes of transmission of mutants that appeared intermittently in cultivated delphiniums, he noted that the purple mutant which showed up in cultivated pink flowers consisted of a change that occurred in a single cell of the petal. If the numbers were small, a mottled appearance ensued. If the change occurred early in the embryology of the flower, large spots appeared; if the change appeared when the flower was mature, small spots resulted. Particularly important was his observation that the incidence of the numbers of purple cells remained high in flowers that were asexually propagated (cuttings); the incidence was low again in the next generation when the purple flowers were allowed to go to seed and then planted and grown. The incidence of purple cells in the mutant purple flower was as high as one in nine, yet this dropped consistently to one in eight hundred fifty when sexual propagation of the mutant was allowed to take place. Thus he noted that asexual propagation of the mutant retained the qualities that permitted the

mutant to perpetuate itself, while sexual propagation dilutes it.

Furth (1944) found that similar conclusions may be reached with animals, i.e. transplantation of mouse tumor. According to him and his associates, the ability of the transplanted neoplasm to "take" in the host is measured by the genetic make-up of the host and the neoplasm; there must be some relationship between the two. They determined that this relationship is not consistent, since there are genic differences among tumors which are the result of somatic mutations. Therefore, there will be differences in the "take" frequencies among the hybrids.

Tyzzar (1916) noted previously these variations in neoplastic transplant "takes", but he formulated his own theory regarding the reasons for such behavior. According to Tyzzar, immunity to transplanted tumor is based on "foreignness" or incompatibility of tumor and host. The degree of foreignness is not sufficient for the production of "markedly cytotoxic or cytolytic sera", as when different species are employed. However, it seemed to him probable that an "immune body" formed which, in the presence of the living tumor which acts as an antigen, causes a reaction in the tissue around the tumor so that the tumor becomes isolated and is ultimately destroyed. Through experiments in breeding a highly susceptible strain to an almost non-susceptible strain (to transplants) he observed that the "take" frequencies of neoplastic transplants varied

as might be expected in those cases where the mode of transmission is one of multiple factors. He concluded that both susceptibility and non-susceptibility were inherited, not as a single unit factor, but apparently as a complex of genetic factors. He further stated that it was a factor difference that determined the amount of "likeness" or "foreignness" between host and transplant.

Nevertheless, he was cognizant of the fact that even tumors from homogeneous mice show transplantation differences. This he attributed to the "acquisition of new characteristics by the soma", in other words, somatic mutation.

In contrast to the above theories, Riley (1940) determined that a single subcutaneous injection of heparin into mice at the expected time of the manifestation of dibenzanthracene induced sarcomas often led either to a localization of the tumor or to a complete inhibition of it. Exactly how this occurs is not known, but Fisher (1947) suggested that heparin or other similar colloids caused a strong negative charge which may be bound to the basic groups that arise at cell surfaces as a result of injury. Therefore, according to Riley (1948) if an area of transplantation is extensive enough to cause the mast cells which line the capillaries of the loose connective tissue to discharge heparin from their granules, an inhibitory effect upon the tumor growth may be encountered, irrespective of the genic background of the recipient.

Chromosomal aberrations have been shown to exist in the neoplastic tissue; yet these changes which seem to uphold the somatic mutation theory are not necessarily the cause of the tumor, but may be the result of the rapid cellular proliferation. Neither does it seem necessary to assume that chromosomal change occurs immediately preceding cancerous growth, since it can be observed that changes or differentiation occur when the cell changes with no chromosomal abnormalities from one type to another, e.g. from epithelial cells to epidermal glandular forms.

A further refinement of this hypothesis might be that certain genes are definitely known to influence mutation rate and are called rate genes. If the above hypothesis is correct, certain genes could conceivably influence the somatic mutation rate. However, this idea has also to be satisfactorily proved.

Murphy (1935) asserted that viruses act upon the chromatin causing a mutation, and this leads to proliferation and to cancer itself. Although other theories have been formulated, adequate evidence for this interpretation appears to be lacking. For example, Needham's Theory (1942) concerns carcinogenesis caused by virus with neural plate induction. In other words, extracts of the virus, or virus products, act as evocators and cause the tissue to be freed of the limiting action of its field. The result is the rapid and uncontrolled proliferation of the cells. That an uncontrolled proliferation of cells ex-

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ists is the only observation upon which most oncologists agree as an explanation of the manifestation of cancer.

THE UNIVERSITY OF CHICAGO
DEPARTMENT OF CHEMISTRY

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METHODS FOR OBTAINING ACCURATE INFORMATION OF CANCER INHERITANCE

Almost all accurate information pertaining to the inheritance of cancer has been obtained through breeding studies. As was previously stated, some of the early work was characterized by false information and wrong impressions derived from using impure or heterozygous stock, and the final results were often obscured by such use, for heterozygous stock is considered unsuitable for the analysis of non-genetic factors. Realization of the inadequacy in these impure stocks led to the development of a large number of highly inbred strains of mice in which cancer can be observed to be in a fixed relation to the genotype.

Inbreeding is a genetic process, whereby a certain characteristic for a specific strain is positively developed. As a result, homozygosity is established. Since, in determining these characteristic genotypes for each strain, characteristic tumor incidences were also established, it follows logically that the tumor incidences were governed by the genotypes. Probably the greatest source of information on tumor inheritance is drawn from the tumor incidence data compiled by Dr. Little. A complete list of inbred mouse strains has been published by Snell in 1941.

To illustrate the importance of the careful use of selected breeding stock, the experiment by Andrevont (1943) wherein he demonstrates the necessity of using highly inbred strains, is cited. He mated strain C 57 (black resistant) and strain I

(resistant) mice and found that the degrees of resistance in their offspring varied from equal to parents to slightly less than the total resistance of both parents. Thus he concluded that in species which do not approach genetic uniformity, it is difficult or impossible to predict the occurrence of tumors on the basis of tumorous or non-tumorous ancestry. Even though he was working with known strains he found that variations developed. The determination of the genotype as well as the phenotype was thus revealed as an important consideration in selected breeding.

The first part of the document discusses the importance of maintaining accurate records of all transactions. It emphasizes that proper record-keeping is essential for the success of any business and for the protection of the interests of all parties involved. The document then goes on to describe the various methods and procedures that should be used to ensure the accuracy and reliability of the records. It also discusses the importance of regular audits and the role of the auditor in verifying the accuracy of the records. The document concludes by stating that the proper maintenance of records is a fundamental responsibility of every business owner and manager.

MULTIPLE FACTORS AS A MODE OF INHERITANCE

According to the data compiled by Little (1943) it may be deduced that all tumors cannot be grouped as a single character controlled by the same gene or gene complex. If such were the case, a highly inbred strain might be expected either to develop all types of tumors, or to be resistant to all types of tumors. However, this does not occur. No strain of mice is known that develops all types of tumors consistently. On the other hand, no strain of mice is completely resistant to all types of tumors. The results of his studies show that one strain may be highly susceptible to one type of tumor and resistant to another type; another strain may be highly susceptible to the second type and resistant to the first; a third strain may be susceptible to only one of three or four types and resistant to the rest. The type of tumor that develops in the animal is dependent largely upon the animal's susceptibility to that particular tumor, rather than to tumors in general.

All these facts may be condensed into a statement that is agreed upon by most oncologists, namely, that the different types of cancer may be considered as different manifestations of different diseases, the inheritance of which probably involves different gene complexes. Unless the environmental variations are the cause of these different tumors, which seems most unlikely, it should be assumed that it is not in-

herited as a single trait, i.e. a unit character. This is in accord with the generally held concept of cancer, namely that it is not a single disease but a group of diseases.

To support the concept of multiple factors, the experiments of Bittner (1941) may be used. He reported a cross between one strain of mice which produced, in virgin females, no carcinoma, and another strain which normally produced ninety per cent carcinoma. The F_1 hybrids produced 87.5 per cent and the F_2 hybrids produced 67.3 per cent. He pointed out that this result coincided rather closely with the prediction based on the action of a single dominant gene. However, this may also be an example of multiple factors since a further segregation of the genes had occurred from the F_1 to the F_2 generation.

As yet, none of the mouse tumors has shown clear cut single character inheritance. If a certain type of tumor were inherited as a unit character, that is, if T stands for a tumor gene, presumably dominant, and t, its recessive allele, then after selective inbreeding strains TT and tt should evolve in which the former should have a high cancer rate and the latter a low one. This does not occur in actual practice. There is a distinct gradation in the incidence ranging from one to ninety per cent. Aside from ruling out unit-character inheritance, this gradation indicates another possibility, the multiple factor aspect of inheritance. This method of transmission has been investigated thoroughly, particularly among plants, but

until recently it has not been stressed in cancer.

Andrevont (1939) was one of the first to recognize that this method of inheritance could be a possible answer to the question as to how certain types of tumor could be inherited. He began to note that in pulmonary cancer there seemed to be no definite incidence rate, but that all were susceptible to a more or less degree. Then, after much experimentation, he developed two methods of determining the approximate degree of susceptibility to lung tumor.

The first was to measure the latent period, namely the time that it took for the cancer to manifest itself in the lifetime of the mouse. He noted that in highly resistant strains, the latent period was longer. In the highly susceptible strains he found that this period was comparatively short, varying in length, determined by the degree of susceptibility.

It was also discovered by him that the number of nodules in the lungs closely correlated with the latent period, that is at a given age, a more highly resistant strain had fewer nodules than a strain of high susceptibility at the same age. Thus he was provided with a quantitative method for determining the cancer incidence.

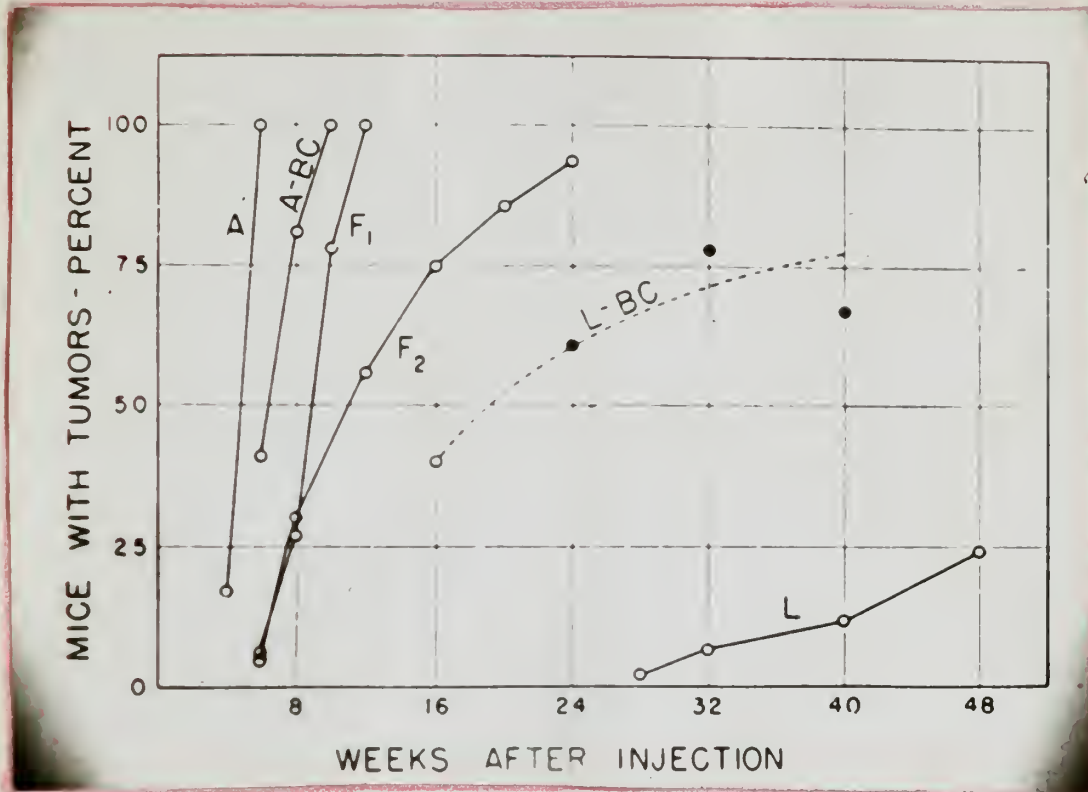
The multiple-factor mode of inheritance has been postulated as early as 1908, when East and Nilsson Ehle, working independently, first formulated this concept. East's work was with corn, and by using his own figures, multiple factor inheritance

can be illustrated. He used two strains of corn; one with the length of ear ranging from 5 to 8 cm. and the other, from 13 to 21 cm. The F_1 hybrids were intermediate, ranging from 9 to 15 cm., the F_2 hybrids were also intermediate, with a range from 7 to 21 cm., displaying a greater range than the F_1 . The fact that the F_1 was intermediate could possibly be attributed to environmental differences, but when the F_2 showed such a definite increase, the most plausible explanation is the further recombination of factors for length of ear. It could not be a single factor inheritance for although the F_1 might possibly be similar due to incomplete dominance, the F_2 would segregate into but 3 groups, e.g. (1)TT (2)Tt (1)tt. If the number of factors is increased to 2, T and A, including their respective alleles, the number of groups in the F_2 is increased to 9, e.g. (1) TTAA (2) AATt (2) AAtt (4) AaTt (1) aaTT (2) Aatt (2) aaTt (1) aatt and (2) TTAa. A lapping over so as to form a continuous smooth curve will result if further factors are added.

The results of Heston's work (1942) on pulmonary tumors indicate that this method of inheritance is one way in which one type of cancer is inherited. His method was one of breeding and was quite similar to Andrevont's. Heston, by two series of experiments, was able to determine satisfactorily the multiple factor inheritance of pulmonary tumors. The first test confirmed the susceptibility to spontaneous tumors, while the second confirmed the susceptibility to induced pulmonary

tumors. The purpose of the latter test was to measure the time that elapsed between an injection of dibenzanthracene, which is a carcinogen, or a cancer-inducing agent, and the first appearance of cancer nodules. He used two strains of mice: strain A which was highly susceptible, and strain L which was highly resistant to cancer. Strain A mice were mated to strain L to produce the F_1 hybrid. The F_1 hybrids were inbred to produce the F_2 hybrid, and the F_1 hybrids were backcrossed to each parent strain to produce both types of backcrossed generations (A - BC) and (L - BC). Sample groups were sacrificed at regular intervals and the animals with tumors were noted and also the number of nodules was recorded. The following chart (page 30) indicates that a genetic factor was involved and the most striking evidence of this is the increase in the variability of cancer susceptibility of the F_2 generation.

The first part of the document discusses the importance of maintaining accurate records of all transactions. It emphasizes that every entry should be supported by a valid receipt or invoice. This ensures transparency and allows for easy verification of the data. The second part of the document provides a detailed breakdown of the financial data, including a list of all accounts and their respective balances. It also includes a summary of the total income and expenses for the period. The final part of the document concludes with a statement of the net result and a recommendation for future actions. The document is signed and dated at the bottom.



*The RESULTS OF A CROSS BETWEEN A HIGH CANCER INCIDENCE STRAIN AND A LOW CANCER INCIDENCE STRAIN OF MICE.

The F₂ shows a greater increase in the variability of cancer susceptibility than the F₁ generation. See page 29.

*From Heston, W. E. 1942
Genetic analysis of
susceptibility to induced
pulmonary tumor in mice.
J. Nat. Cancer Inst. 3:72

Thus, when the susceptibility is measured by the latent period, it is safe to assume that at least some part of this increased variability of the F_2 generation was caused by the segregation of genetic factors. The F_2 generation shows all gradations in degree of susceptibility between the two parent strains. The interpretation of such results can only be that the character is inherited on a multiple factor basis. Almost identical results were noted upon an analysis of the number of nodules occurring at specified periods in these same animals. Similar results were noted with the experiment concerning the susceptibility to spontaneous pulmonary tumors in mice.

Heston (1941) was able to lend further evidence for the multiple factor theory by demonstrating that the susceptibility to induced pulmonary tumors is associated with more than one chromosome in the mouse. It offers further proof that multiple genes are at work in controlling the degree of susceptibility of mice to this type of cancer.

He mated strain A normal mice to strain W homozygous for three recessive genes (shaker, waved coat and flex tail). It had been determined previously that linkage occurred between these characteristics and cancer susceptibility, so that the genes for cancer could be traced by these characteristics through generations. By the following method he was able to determine which mouse had more genes for cancer susceptibility. If the multiple factors had been the mode of transmission,

then the strain showing all three tracer characteristics (wave, shake, flex) should have been the most susceptible. Although enough mice for positive proof could not be obtained in the litters, the results are significant for they proved to be almost as accurate as the ideal case might be. For example, assuming the normal genotype to be AAEECC and the strain W aabbcc, the F_1 would yield AaBbCc. A backcross to strain W would yield the following: AaBbCc; AaBbcc; AabbCc; Aabbcc; aaBbCc; aaBbcc; aabbcc; aabbcc. According to expected results, the normal mice, since they had fewer genes for susceptibility, should be the least susceptible, while the mice homozygous for all three recessive genes should be most susceptible since they would have more genes for susceptibility. These offspring would have from three to six cancer-linked genes, since only three factors are involved.

In the experiment, the results tallied closely enough to their hypothetical case to allow the author to observe that multiple or cumulative factors were involved in the transmission of this type of induced sarcoma. Any deviation from the anticipated tumor incidences might be ascribed to a variance in the potency of the susceptibility factors which are linked to different genes. This possibility is to be the subject of future experiments by Heston.

Burdette (1948) has added further proof to the theory of multiple factors as applied to the inheritance of cancer. His

methods were also those of breeding. He mated strain C₃H mice which are more susceptible to induced sarcomas, to strain JK mice which were less susceptible. The F₁ generation showed intermediate susceptibility when compared to their parents. This in itself is partial but not definite proof of the presence of multiple factors. Therefore he made reciprocal backcrosses of the F₁ and showed that a great difference occurred in susceptibility (as measured by induction times) in the crosses. When the F₁ were mated to the JK parent the induction time was decreased and vice-versa with the alternate backcross. According to the author, this is usually interpreted as excellent evidence of multiple genetic factors.

The carcinogen used was again methylchloranthrene. Induction time was the time from the injection of the carcinogen to the first observable sarcoma.

APPLICATIONS TO HUMAN CARCINOMA

Heredity studies of cancer in man are difficult because of the long period between generations, the small families, lack of family history data, uncertainty of diagnosis and the unfeasibility of test matings. Therefore, to obtain material subject to adequately controlled conditions so that repeated observations can be verified, it has been necessary to study the disease in animals.

According to Wells (1930) certain facts must be established

"That cancer in animals is the same disease that it is in man; and that the rules of heredity are the same in animals as in men."

That human carcinoma is an inherited condition was proved beyond doubt in a report given by Macklin (1940). Her report was based on an analysis of tumors in monozygous and dizygous twins. There are two types of twins: those from a single fertilized zygote, with identical heredity possibilities, and those from two fertilized zygotes whose genetic make-up may be as different as those between any other offspring of the same parents. According to Macklin, a comparison of similarities in identical twins with similarities in fraternal or dizygous twins gives a clue to the role played by heredity in producing certain traits and characters. For example, if the blood types of identical

twins were alike in more cases than the blood types in dizygous twins, it would be assumed that heredity was a potent factor in blood type determination. If there were no differences observed, then such a statement could not be made. Thus, if tumors were dependent wholly or in a large part upon genetic factors, then identical twins should resemble each other with the respect to the presence or absence of tumor, more often than fraternal twins. However, there is an objection to this type of generalization.

It has been stated that studies of pathological conditions in twins are more liable to be recorded if both twins show the condition than if only one twin is affected. Macklin, however observed that the same amount of selection would occur in reporting dizygous twin pairs in which both are affected. She published fifteen cases of monozygous twins in whom tumor incidence and manifestation based on age at which the tumor occurred, the type of tumor and the site of the tumor, all agreed closely in both individuals of the set.

In eight cases where such agreement could not be noted, it was explained that several other factors might have been involved:

- a. environmental factors may have played an important role.
- b. the twins might not have been truly monozygous, as it is only with the greatest diffi-

culty that physicians have been able to determine this point.

c. the time for the appearance of the tumor in the second twin may have been longer than in the first.

d. a third type of twin is postulated where the egg, upon fertilization, throws off a sufficiently large amount of cytoplasm with the first polar body as to make a second mature oocyte.

Thus, if this second egg were fertilized by a different sperm, the resulting offspring might be different with regard to tumor inheritance, particularly if this characteristic is male-sex-linked.

In dealing with the fact that cancer is the same disease in animals as in man, the case of mammary gland cancer of mice and the mammary gland cancer of man may be cited. If the normal mouse lactating mammary gland tissue is compared with the tissue exhibiting carcinoma, the same sort of difference as in human mammary gland cancer can be observed. They behave the same in most respects. Another example might be that of a mouse which was examined by Wells (1930) which he described as having had a broken tooth which irritated the mucus membrane of the mouth, and resulted in the development of squamous cell carcinoma of the mouth. In this case the cancer invaded the base of the skull and pro-

duced pressure on the central nervous system, as such a carcinoma might have done in man.

The following experiments, performed by Seed (1940) and his associates upon human subjects, when compared with similar experiments on laboratory animals, appear to offer further proof that cancer in animals and humans is indeed similar.

Colchicine, the alkaloid derived from the autumn crocus, is the most potent of the mitotic poisons known. It has been used in experimental genetics to produce chromosomal aberrations in one form or another, but not until lately has it been used in the treatment of cancer. According to Amorosa (1935) it had been noticed that a minimal injection of colchicine into an animal caused first a stimulation of activity and later an arrestation of mitotic activity in the metaphase. It was believed by Seed (1940) that such results might be aids in cancer therapy. Four patients with cancer in advanced stages were treated by him and his associates. The first two succumbed to colchicine poisoning in twelve days. However, the other two showed rapid and continued regression of the cancer growth. Nevertheless, after eighty days, the tumors began to proliferate greatly and the patients died. The colchicine had affected the new squamous cells of the newly developing vascular system of the tumor and ultimate necrosis took place. Doses large enough to affect all of the cancerous cells could not be given due to

the deleterious effects on the normal cells of the patient. The conclusions drawn were that although the colchicine was effective, the general toxic effect was too great to produce any curative results.

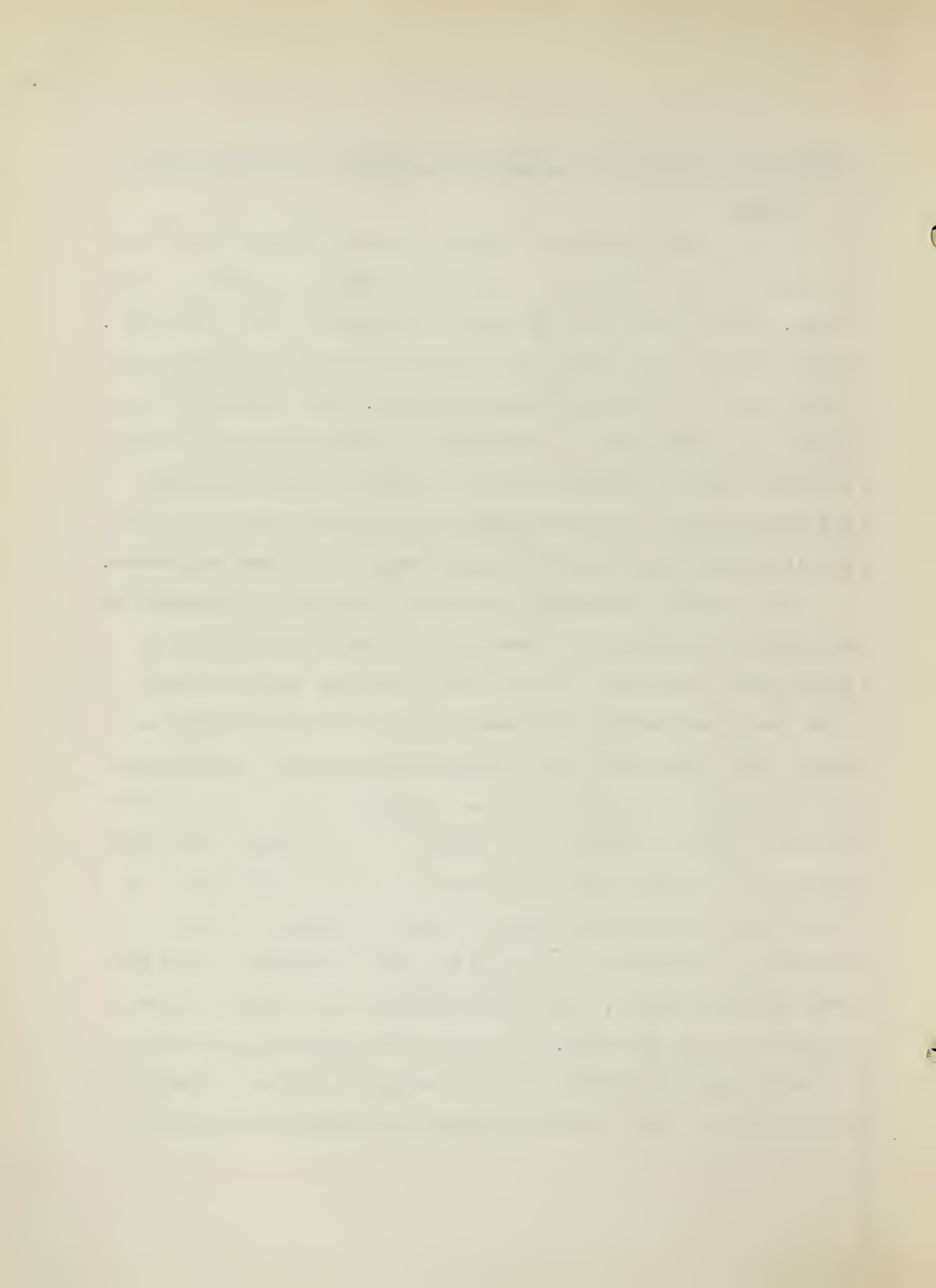
Previous to this work, Lits, Kirschbaum and Strong (1938) working with horses and mice, demonstrated that although regression of lymphoid neoplasms occurred with treatments of colchicine, recurrent neoplasms occurred in every case, and death always ensued. Similarities in the effects of the colchicine upon mitosis in both the aforementioned experiments are striking. In both animals and man, the effect was upon the mitotic spindle which degenerated, thus effectively halting mitosis, and was finally shown by the fact that the chromosomes actually came closer together and became quite granular.

To identify the laws of heredity in man and animals as being similar, it is only necessary to recall the fact that the principles of genetic transmission of genes were discovered by Mendel working with plants, garden peas, and that zoologists found that these principles applied to all species of animals with which they performed breeding experiments. There is little reason to suppose, therefore, that what holds true for all other multi-cellular living forms will not hold for man. It is only necessary to review the case of color-blindness in man to find a classical example of a case which is definitely subject to the Mendelian principles of inheritance.

DIFFICULTIES INVOLVED IN OBTAINING ACCURATE CANCER INCIDENCEDATA:

It has been extremely difficult for the average physician to obtain a true picture of hereditary lines of cancer in families. There seem to be two basic reasons for this difficulty. Family histories are often very obscure, since the diagnosis of cancer has only recently become specific. When familial background involves cancer, the patient is often reluctant to tell of such a history because of social shame or fear of stigma. The inaccuracies of cancer diagnosis of several years ago make for inadequacies and unreliable statistics on cancer incidence.

As a result of studying many case histories and drawing up as many different charts describing the modes and methods of inheritance, very few investigators have been able to agree upon the actual method of transmission of cancer in human beings. The reasons for this disagreement are easily understood, for cancer may be shown to act as a dominant characteristic in one case and as a recessive in another. It may skip one generation or it may skip three generations. These differences of opinion as to the mode of transmission of cancer in human beings might also lend emphasis to the first statement which was made by Wells (1930), namely that heredity in animals and man operates in the same way. Just as investigators in the field of human genetics differ as to the method of cancer transmission so do workers in the field of animal experimentation differ in



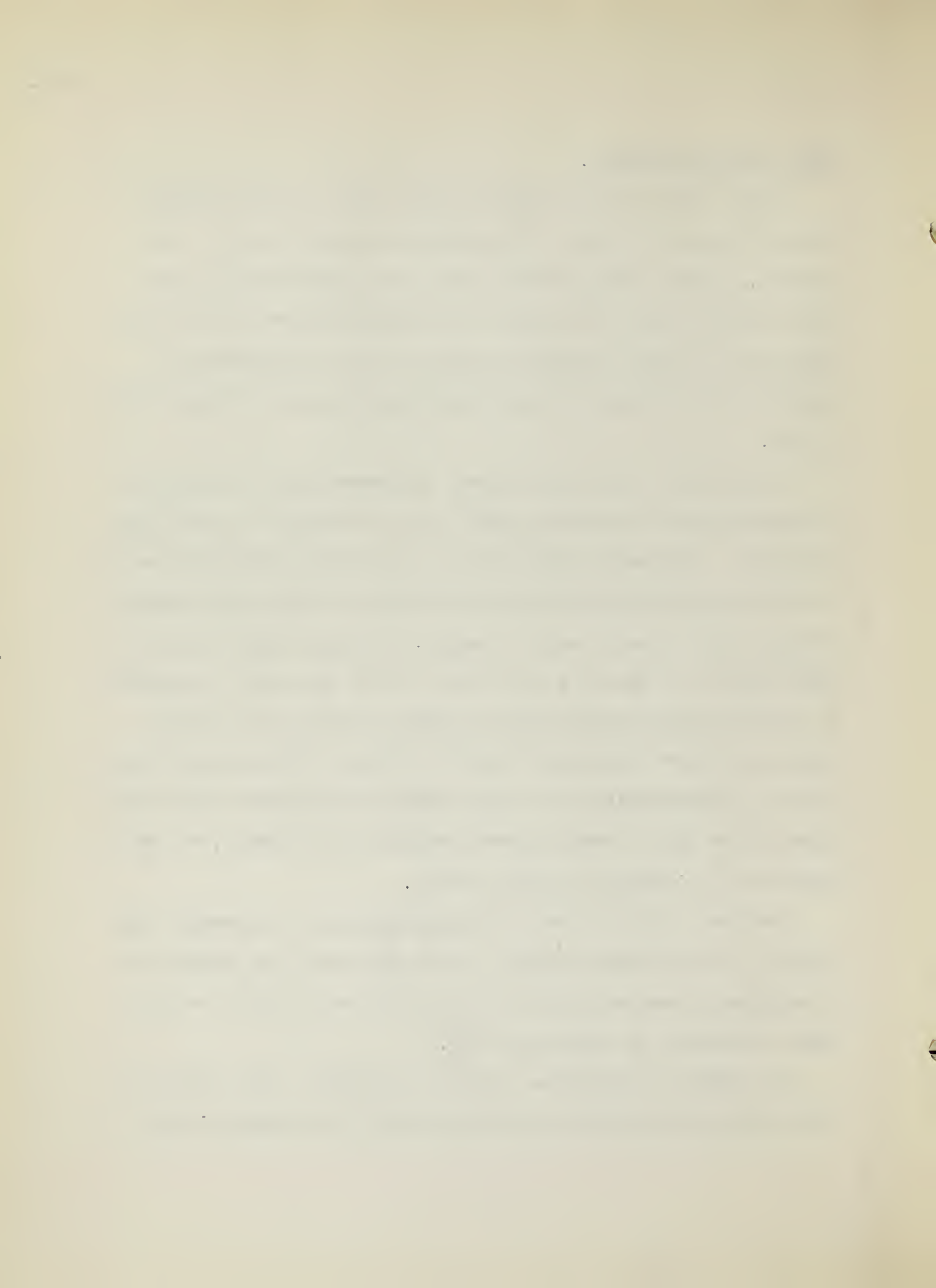
their interpretations.

Slye (1928) in her report stated that in five thousand cases of cancer in mice, five thousand cases acted as a recessive. Then, Little (1928) using the same material upon which Slye's report was based, found that cancer did not act merely as a simple Mendelian recessive, but sometimes as a dominant and frequently showed no specific mode of inheritance at all.

That this variation in modes of inheritance is operative is demonstrated by Macklin (1939) in an analysis of two types of tumors. Xeroderma pigmentosum, a cancerous degeneration of the skin accompanied by hypersensitivity to light was traced through three generations of humans. Macklin stated that this inheritance was due to a recessive factor, because it appeared in children whose parents were normal and who were related closely by first and second cousin matings, and because it appeared in approximately the same number of children which were expected in such a cross (three dominants, or normal, to one recessive or cancerous in this case).

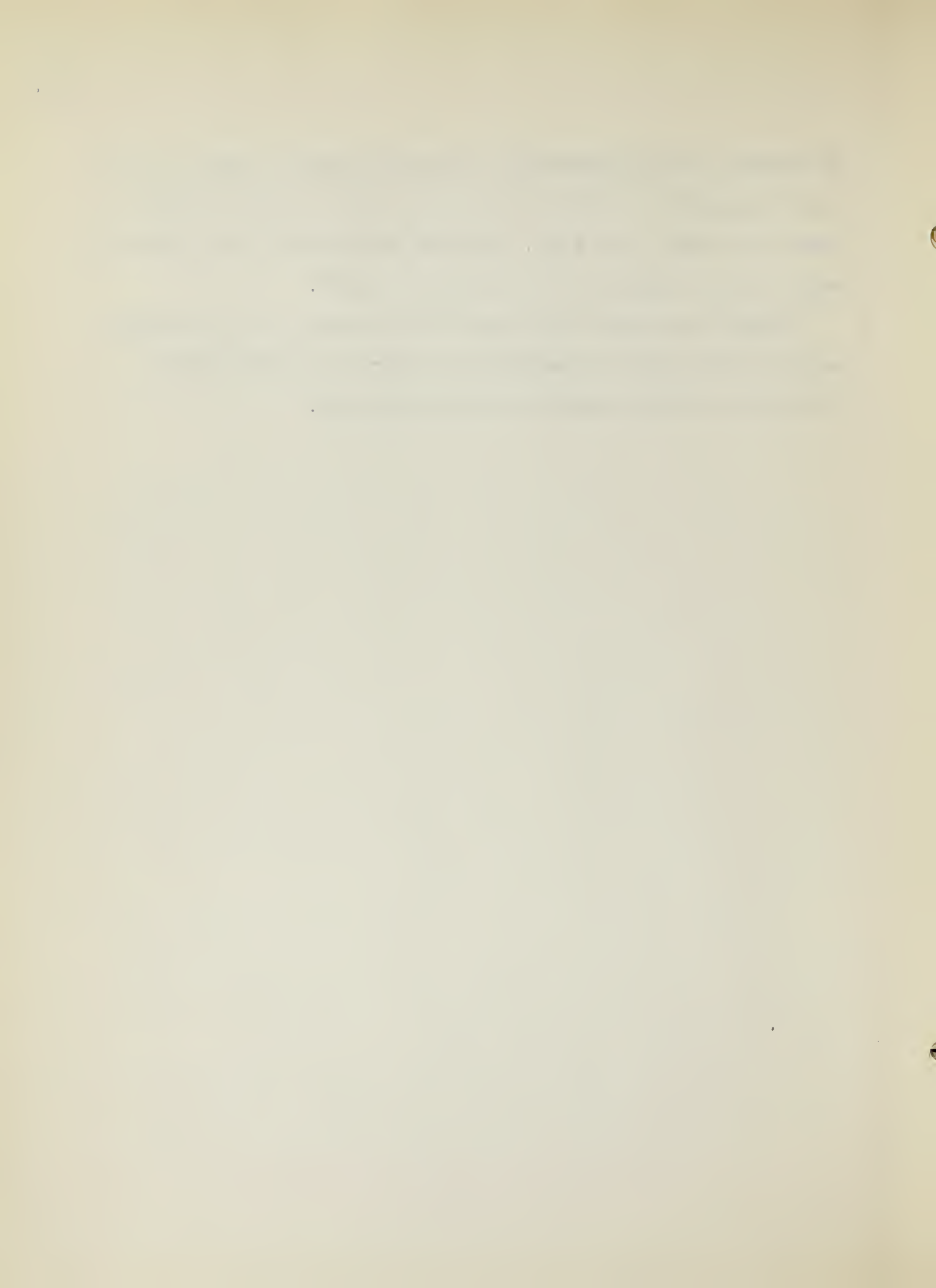
However, in the case of retinoblastoma, a cancerous condition of the retina, Macklin stated "(It) does not behave as if dependent upon recessive factors, but as if due to a dominant mutation, for the most part."

In order to eliminate, as far as possible, the loss of potential tumor patients by death before the tumor had time



to develop and the opportunity for environmental agents to act upon the growth of cancer, two tumors, both of which appear in early childhood, were used. Macklin observed that an identical basis for all tumors will probably be futile.

"There is as much likelihood of all tumors being dependent upon the same genetic foundation as there is of all defects, for example, being inherited in the same way."



POSSIBLE METHODS OF CANCER PREVENTION IN MAN

If a long history of cancer is known to be a part of a man's pedigree, a practical application of the knowledge gained in our present day studies of cancer is possible, since it is reasonable to assume that hereditary differences are concerned with the incidence of tumors in the human populations.

The situation among human populations is highly complex, involving the inter-action of many genetic and environmental factors. An individual who has a single case or two of cancer appearing in his family tree has no great cause for worry. But the individual who has a family history of recurrent cancer should take certain precautions. Dunlap and Warren (1941) noted the carcinogenic powers of coal tar products, which would indicate that an individual with cancer background should avoid chronic irritation of any form, should not smoke, should not engage in an industry involving contact with mineral oil, tar, paraffin or other irritating products which might lead to the production of cancer. A man who has a history of multiple incidence of carcinoma in his family should not marry a woman who has the same type of family history.

Cancer as a disease of mankind probably will never be conquered until preventive measures are considered. These preventive measures consist primarily of periodic physical examinations. Finally, eugenic control of high cancer ratio

families through the intelligent cooperation of all men must be practised.

CONCLUSIONS

A study of current and pertinent literature on cancer and its genesis was made. The modes of transmission of inherited carcinoma in animals was reviewed. Based upon the research of workers in this field reported in this paper, the following conclusions are drawn.

(1) It has been found that cancer can be produced at will in experimental animals, by the application of pure chemicals, and spontaneous cancer can be obtained in experimental animals under controlled conditions, by the application of genetic principles. Research workers (Dunlap and Warren, (1941) have been able to isolate the carcinogenic agents in coal tar and it is to these agents that ^{the term} "pure chemicals" is referred.

(2) It has also been established that the body manufactures substances which are carcinogenic agents. One of these substances is the female sex hormone. The injection of this hormone has brought forth the appearance of at least one type of tumor, carcinoma of the mammary gland (Bonser, 1937).

(3) It has been further established that cancer of the mammary gland, and perhaps other types of tumor as well, can be induced only in conjunction with the proper susceptible genetic constitution. For example, various responses are brought about in different purebred strains of mice by

identical hormones (Bittner and Huseby, 1946). A mouse belonging to a susceptible strain will give rise to a tumor by the influence of adrenalin. Another strain of cancer-resistant mice died under the same influence, without showing any trace of cancer. Thus the production of cancer by the pure chemical is not due to pure chance. It is greatly determined by inherent factors. As an end result, cancer is the resultant of many forces which have exerted their force on the animal for varying periods. Thus it is probable that in order to determine the mode of the inheritance of cancer, each type of tumor will have to be analyzed as a separate entity and the relative effects of extrinsic and intrinsic factors estimated.

(4) It has been postulated that certain viruses, or other causative agents (Needham, 1942) have induced chromosomal aberrations which in turn causes a somatic mutation which results in the rapid and uncontrolled proliferation of cells. In other words, cancer manifests itself.

(5) Transplantation studies have further supplied proof of the genetic importance with regard to cancer manifestation. It has been established by Furth (1944) that the cancer cell is controlled by an intrinsic or genetic constitution and that this genetic constitution is variable and its deviation from the original genetic constitution of the normal cells of the organism is presumably due to somatic

[The text on this page is extremely faint and illegible. It appears to be a multi-paragraph document, possibly a letter or a report, with several lines of text visible but not readable.]

mutation.

(6) The modes of transmission of the genes influencing cancer susceptibility vary. Yet in many of the cases enumerated in the body of the text (pages 20, 26-32) evidence seems to point to multiple or cumulative factors as a solution to the problem of inheritance of many types of tumors previously regarded as having no specific type of inheritance at all.

(7) The progress that has been made in heredity studies has been most successful when lower mammals have been used. Man is an unsatisfactory subject for such studies because of:

- a. Small families.
- b. The lack of accurate family histories.
- c. The unfeasibility of test matings.

(8) It has been further concluded that just as in the lower animals, cancer in man is under genetic influence. The work of Macklin (1940) has been used to substantiate these conclusions. Furthermore, Wells (1930) described a mouse with a squamous cell carcinoma that developed just as it would have done in man.

(9) Since it had been established that coal tar products contain carcinogenetic agents, it seems logical that a person with a family history of cancer would do well to avoid contacts with these agents; and finally, eugenic control of

high cancer incidence families seems to be a prerequisite to cancer prevention and cure.

ABSTRACT

Evidence is presented to show that carcinogenesis is affected by heredity. However, of equal importance are internal factors such as hormonal, environmental and virus influences. The works of Strong (1935), Russell and Green (1943) and Andrevont (1948), among others, are used to show the inter-relationship of these factors.

The entire theory was set down in formula form by Loeb in 1916; $HS=C$, where H stands for the heritable gene, S for the external environment, and C the resultant cancer.

There are various theories as to how cancer occurs. Many of the statements can be reduced to the theory of somatic mutation, which causes the rapid and uncontrolled proliferation of the cells. However, the means whereby the cells become mutants has been attributed to various methods. Bittner's virus factor, Murphy's virus acting upon the chromatin and Needham's theory of the evocator action of the virus extract compared with the neural plate induction in embryology are all briefly discussed.

The methods for obtaining accurate information on cancer inheritance are discussed at some length.

The importance of inbreeding and of using the resultant pure bred strains is stressed by citing the classical argument between Slye and Little (1928), whose work on the same animals gave diametrically opposite results. In ordinary cases of in-

breeding, it is usually possible to develop an animal strain that is either pure recessive or pure dominant. However, by using data compiled by Dr. Little and his associates (1943), it has been demonstrated that by examining highly inbred cancerous mice of known parentage, no pure dominants or recessives are found. To the contrary, none of the strains develops a one hundred per cent susceptibility to all types of tumors, nor are any one hundred per cent resistant. All the intermediate percentages are found. This seems to indicate that the method of transmission is one of multiple factors. Added proof of this method of transmission is suggested by the works of Andrevont and Heston whose work on the pulmonary tumors of mice seems to corroborate the multiple factor method.

The difficulty involved in studying the heredity of cancer in human beings is explained by the small families involved, the reluctance of families to offer accurate information, the long period between generations and uncertainty of diagnoses. Man and the experimental animals used are both multicellular organisms. They probably both obey the Mendelian laws of inheritance. Therefore, the data obtained from animal experimentation can be reasonably applied to human beings. Wells (1930) described a mouse with a broken tooth which irritated the mucous membrane of the mouth. The resultant cancer spread to surrounding areas and caused ultimate pressure on the brain. Identical symptoms of cancer have been noted in

human patients.

Although it is likely that human beings obey Mendelian inheritance laws, no definite evidence has been presented that human carcinoma obeys these laws. This is not to suggest that the law has been broken, but merely to show that the mode of transmission is probably one of multiple factors complicated by external factors such as the aforementioned hormonal and environmental influences. The relation of Mendelian laws of heredity to the incidence of cancer may be produced by a somatic mutation. The rate of occurrence of this mutation is in turn influenced by genetic factors.

Certain measures have been recommended for the future control of this disease which strikes one person in eight in the United States. Persons whose family tree shows a large percentage of cancer should avoid chronic irritations of any form. They should refrain from working in industry where they may be exposed to any of the carcinogens such as mineral oil, tar or coal tar products, paraffin or the other carcinogenic agents.

Finally, as a general preventive measure, a person who has a family history of multiple carcinoma should not marry a person who has a similar history. Eugenic control of high cancer ratio families is in the long run a possible way of eradicating this disease.

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The first part of the document discusses the importance of maintaining accurate records of all transactions. It is essential to ensure that every entry is properly documented and verified. This process helps in identifying any discrepancies or errors early on, preventing them from escalating into larger issues.

Furthermore, the document emphasizes the need for transparency and accountability. All stakeholders should have access to the relevant information, and any changes or updates should be communicated promptly. This ensures that everyone is on the same page and can make informed decisions.

In addition, the document outlines the various roles and responsibilities involved in the process. Each team member should understand their specific duties and how they contribute to the overall goal. Regular communication and collaboration are key to successful outcomes.

The document also addresses the challenges that may arise during the implementation phase. It provides strategies to overcome these challenges, such as seeking advice from experts or conducting pilot tests. Flexibility and adaptability are crucial when facing unexpected situations.

Finally, the document concludes by highlighting the long-term benefits of a well-implemented system. It can lead to increased efficiency, reduced costs, and improved customer satisfaction. By following the guidelines provided, organizations can achieve their desired objectives and maintain a competitive edge in the market.

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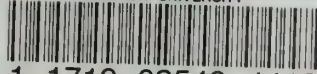
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