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KNOWN FACTORS ASSOCIATED WITH THE ETIOLOGY
OF MALIGNANT NEOPLASMS

BY

LEONARD B. MOYER

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NEOPLASMS

Introduction

This paper is intended as a review of the cancer literature in so far as it concerns the etiology of this disease. Perhaps no subject receives more attention at the present time, than does this one, but much of the literature refers to similar investigations carried out by different workers, and hence the work is often an unnecessary repetition or imitation of that of some well known investigator. It is my purpose here to sift the golden kernels from the chaff, to consider only logical points, and to concentrate without using barren material, the known information concerning the etiology of malignancy. I have mentioned in the following pages, a few of the best supported theories, merely for the purpose of clarifying the wherefor of certain research. Supposed etiological factors which have not been subjected to experimental investigation of adequate kind and degree are given little consideration here, even tho they be widely mentioned in the current literature. A bonifide etiological agent should be constant enough to serve as the most logical explanation after the most rigid statistical and experimental scrutiny. The cause of malignancy of course is not known, that is the fundamental factor that actually causes normal cells to become malignant; however several secondary or inciting causes are well known. To find more of these and to apply known facts is well worth while. If I may quote (1) " The intelligent cancer worker does not expect to miraculously find a sudden cure, or to suddenly discover the cause, but by careful and logical application of what is learned gradually by thousands of investigators, he knows that the cause of the change from normal to malignancy

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must be obscure indeed if it is to evade him for all time."

Nature of the Malignant Cell

All Malignant neoplasms have a cell as their unit. The cells of the various kinds of new growths differ considerably from each other, however points of similarity of appearance may be observed in all highly malignant growths, this is likewise true of tumours of low malignancy. It is quite well established that if marked disproportions exist between nucleus, nucleolus, and cell body, the growth is highly malignant. The nearer to normal the cells appear the lower is the degree of malignancy. The cancer cell is not malignant from the beginning (11). It was a normal or at least a harmless body cell originally, to which something has happened, either thru some peculiar kink in its development or because of some shock it received it has divorced itself from the natural growth control of the body. Other cells develop from it, and the wild growth continues at the expense of the normal cells of the body.

In a general way the malignant cell is similar to a normal cell but it possesses different physiological powers and life (2). It invades and destroys surrounding tissue cells without order or control, while a normal cell will not function at all unless to serve the good of the whole community of cells which makes up the body. The invasive and infiltrative nature of malignant cells are the chief distinguishing points that the pathologist relies on in microscopic diagnosis of malignancy. Then too the wild disorder of the cells and often the numerous mitotic figures serve to clinch the view. The malignant tumour as a whole usually shows a lack of the normal architecture which is characteristic of the organ from which the growth arose. Even in vitro, as in the body, malignant cells have been shown to display destructive infiltration (12). Toxins or ferments must be elaborated by the growth which damage the normal cells, or the latter

may be deprived of some substances necessary for their continued existence.

Boveri's (13) theory of a change in the chromosome constitution of the normal cell, as the cause of malignancy has been tested experimentally. Ehrlich's strain of mouse carcinoma and spontaneous mammary tumours were cultured in vitro. The figure 40 is given by recent writers as the normal number of chromosomes (13). In the majority of malignant cells the number of chromosomes was considerably less than this, usually 32 and 36, in some but 24. In some of the preparations very large cells were found which contained abnormally high numbers of chromosomes, as many as 80. Most of the mitoses were normal, so the abnormal numbers given were probably not due to abnormal mitoses. These findings either support Boveri's theory or point to extreme abnormality of metabolism in the malignant cell (13).

It is fairly well established that overgrowths of tissue such as that produced by inflammatory reaction, irritants, etc., frequently become malignant. These precancerous lesions must therefore contain precancerous cells, cells which are neither normal nor malignant. Microscopical examination usually cannot be relied upon to determine which type of lesion is most apt to become malignant, because true malignant cells are characterized by infiltrative growth, and in most precancerous growths the cells are not perceptibly different from normal. Cancer never develops in sound tissue (14), but it is believed that metastatic growths will thrive in healthy tissue. The fact is established that malignant cells extend both by direct extension and by being carried in the blood and lymph. This represents a further departure from normal. Normal body cells do not break loose from the region in which they arise, with the exception of the cells of the circulating fluids, without having died previously, or without being destroyed soon after so doing, at any rate they never attempt to reconstruct the or-

gan from which they arose. Metastatic tumour cells do produce an imperfect histopathological picture of their organ of origin.

Malignant cells contain more salts than do normal cells of the same regions (15). In the rat liver spontaneous tumours were found to have eleven percent more salts than did normal rat liver, while that portion of the liver not involved in the tumour had a thirteen percent higher salt content than did normal liver. In this connection Rohdanburg (16) believes that the killing of cells by a chronic irritant, their becoming acid, undergoing autolysis, breaking up of their protein combinations, and their liberation of salts, all of which is repeated again and again, produces a hypertonic condition of the tissues locally, until a cell group arises that has an excess of mineral constituents. Then in order to dilute these cells the body fluids rich in nourishment flow in and the cells are overfed and become overactive.

Volumes could be written on the behaviour and peculiarities of malignant cells, if all the experimental and theoretical literature were to be considered, however perhaps one of the most comprehensive reviews of the cytology of cancer was printed by J.R. Ludford in 1925 (17). His conclusion was "there exists for the malignant cell no precise morphological diagnostic character of any kind."

Survey of Outstanding Experimental Carcinogenesis

The experimental production of cancer was first accomplished by Johannes Fibiger^{in 1919} by feeding rats with the cockroach *Periplaneta Americana* (20). Previous to this a few workers had successfully transferred malignant growths from one animal to another (45). Jensen observed that the small piece of transplanted cancer tissue grew exactly as transplanted and did not infect the host in the manner that tissue from infected wounds did when transferred to other animals. He recognized an essential difference which many observers consider as evidence against the infective theory of malignancy.

Russel, Hoagland, Ehrlich, Apolant, Schone, Murphy, Gaylord, Clowes, Rohdenburg, and Ewing, (41) investigated the so called immunity which appears occasionally in tumour bearing animals, and all of them came to the conclusion that it differs markedly from the immunity following infectious diseases. This immunity does not prevent the development of a spontaneous new growth (72), and is brought about in an animal by the absorption of cells from another of the same species. Two or three months is about the limit of the duration of the acquired form of immunity. Some animals apparently have a natural immunity which will be discussed at length elsewhere in this paper. It is impossible to produce an immunity against many highly malignant tumours (73).

Tumours of the mouse and rat have been been transplanted by numerous workers. In 1911 Paton Rous (42) published an account of a fowl sarcoma, which he was able to transfer thru a series of chickens by inoculating dead cells, or by means of a cell free Berkefeldt filtrate. All mammalian tumours however with the possible exception of a lymphosarcoma of dogs (4) have only been transferred by the inoculation of living cells. At first the specificity of the Rous sarcoma was very strict, since the growth could only be transferred

between fowls related by blood. It was a freely metastasizing, spindle celled, osteo-sarcoma which killed the host within 28 days, and whose malignancy was enhanced by passage. Now, however the tumour grows readily in fowls other than those related to the original fowl in which it appeared which was a Plymouth Rock. The Plymouth Rock breed is still by far the most susceptible to the tumour.

Rous described another filterable tumour in 1912 (4), an osteochondrosarcoma which was benign at first but became malignant after a few transplants. Like his first tumour it can be transferred by the inoculation of dead cells or cell free filtrates.

Again in 1914 Rous reported a third filterable tumour, a spindle celled sarcoma with blood sinuses, which he was able to transfer by means of living cells and cell free filtrates but not with pieces of the dried tumour (4). Rous realized that the causative agent was a filter passer, but because of the fact that he could not cultivate it outside of the body he hesitated to call it a virus. Many investigators regard the Rous group of tumours as either entirely exceptional or as not being true new growths. However it is the general consensus of opinion that they do answer every test that may be put forward as a criterion of malignant new growths.

Gye (43) believes that the Rous agent is a virus, and gives as evidence the fact that acriflavine destroys its infectivity in the presence of fresh horse serum, and that the diminishing of its virility is governed by the viricidal activity of the horse serum. This, he contends is very similar to the action of the same substance on the virus of bovine pleuropneumonia.

R. Erdmann (44) has successfully transmitted the Flexner-Jobling rat carcinoma by what he regards as cell free filtrates, altho this is not generally accepted as true. Of 30 rats inoculated 12 contracted the carcinoma.

Yamigiwa and Itchikawa (46) successfully produced malignant growths by applying tar to the skin of experimental animals. Attempts had long been made by European workers to accomplish this, but without success. Pathologists had realized for a considerable time that transplanted tumours had numerous drawbacks to the successful study of tumour etiology, since they grew in the new host exactly as grafted twigs grow and did not infect the host. For this reason the two Japanese workers really contributed a great deal to the sum total of experimental carcinogenesis.

Bullock and Curtis (47) in 1920 produced a sarcoma by infesting rats with the immature stage of a tapeworm that passes its' adult life in the cat. This growth affects the framework of the liver but does not injure the working cells except by pressure, etc.

Recently Murphy (61) claims to have produced a Rous sarcoma in Fowls by injecting a normal testicle extract.

Luther Heidenhain (21) states that he has produced carcinoma in rats by injecting material from a human chondrosarcoma. Kutchevski and Ssinelnikoff (62) claim that they successfully inoculated rats with a human melanosarcoma in 1925.

Warburg (63)(64) has published the results of his observations in regards to the great amount of glycolysis in malignant tissue. This has brot forth another element in the study of etiology of malignancy. He found large amounts of lactic acid in cancer tissue. He thinks that malignant growths have an abnormal ability to split sugar to lactic acid both in aerobic and anaerobic media.

Brüda (65)(66) has attempted to throw out the function of the reticulo-endothelial system by injecting india ink to saturate the cells of the system, and also by removal of the spleen of mice. He concludes that animals treated in this manner are more susceptible to tumour growth and considers resistance to cancer to be based on the

condition of the reticulo-endothelial system.

It is entirely reasonable to believe that all of these workers have contributed considerable to the ultimate solution of the cancer problem, but it is certain that animal research alone cannot accomplish the entire aim since laboratory conditions and the experimental animals do not approach natural life conditions of human beings. In general we may say that the experimental investigation of cancer follows two chief lines (1. The use of chemical irritants. In this connection Berenblum (66) developed an interesting point. He found that the carcinogenic powers of either tar or carbon dioxide snow were not enhanced by applying the two together. He concluded that tumours will not develop if the intensity of irritation is too great. 2. Tumour filtrates are rapidly assuming a leading role in the study referred to. The great gaps in our knowledge must surely be gradually bridged by the great amount of experimental work that is being done, but at present there appears to be no immediate prospect of solution.

Brief Resume of Theories of Cause of Malignancy

Numerous theories have been advanced to explain why malignancy occurs. While many of the secondary causes are known the fundamental cause or causes as yet can only be surmised. This does not mean that we cannot definitely exclude many of the theories that have no reasonable scientific basis. Sufficient research and careful investigation has been completed to enable us to consider the problem logically. I do not wish to theorize here, but merely desire to mention the most logical theories of etiology with the opinions and evidence advanced in their support.

Malignancy of all types is generally considered under the general term, cancer. We may say that a carcinoma is of epithelial or glandular origin, while a sarcoma is of connective tissue origin yet they may be and probably are caused by the same external agent (2). The cells of a few carcinomata have the power of transforming the connective

tissue stroma to a sarcoma, which may even overgrow the former (71). A case is on record (2) in which a woman was operated for advanced carcinoma of the breast, ~~after~~ two weeks a medical student aged 21 removed some fluid which had collected under the scar, and while so doing accidentally plunged the needle of the syringe which he was using, deep into his own palm. A small amount of the fluid from the woman's wound entered his tissues. After two years a painful hard swelling appeared at the site of puncture, and his axillary glands enlarged on that side. Shortly thereafter several small tumours appeared in his forearm and arm, and his arm was amputated. The original mammary tumour was a spheroidal celled carcinoma, while the tumours which appeared in the student's arm were spindle celled sarcomata. In this case of course there is no way to prove that the injury rather than some substance in the carcinomatous fluid caused the neoplasms in the student's arm, but it seems rather more likely that the latter was true. This agent may have been a malignant cell and a simple transplant, but whatever the mechanism it favors the belief that the etiology of sarcoma is the same as that of carcinoma.

The theory of a specific parasitic agent has some supporters (3) (75)(76), however the only experimental evidence in its favor which may be taken without reservations is that furnished by the Rous Sarcomas (4)(5). These sarcomas are propagated in chickens by means of cell free filtrates, or by living cells, and no one disputes the fact that a filter passer causes the growths, however it may be of the nature of an enzyme rather than a virus (2). Such well known investigators as Murphy and Leich (77) maintain that the agent is ^{not} a virus, but an enzyme, and base their conclusions on the fact that typical Rous sarcomata may be produced by the injection of normal testicular or pancreatic (fowl) extract into fowls. Gye (2) maintains that it is a virus. Rous (4) does not commit himself, and calls it merely a filterable

agent. It is difficult to state positively whether or nor the Rous group of sarcomata can be considered as significant in so far as the etiology of mammalian tumours is concerned for definite proof of inoculating mammalian new growths of any kind by means of cell free filtrates is lacking, and this is not because only a few attempts have been made. A sufficient amount of work has been done on this phase of the problem, that we can definitely state that if there are any tumours in mammals which can be propagated in this manner they are exceptions to the rule. Malignancy does not behave as an infectious disease. There is no evidence of nurses or physicians contracting the disease from a patient. It is barely possible that the attempts which have been made to transmit mammalian tumours by other than direct transplantation of the malignant cells were not correctly done. Any reported cases of transmission of tumours by subcutaneous or intraperitoneal injection of blood from animals with malignant disease are probably to be explained by saying that tumour cells were carried in the blood. W. Nakona (6) was able to transplant a rabbit sarcoma by means of blood transfusion. He actually found sarcoma cells in the blood used for the transfusion. In one of his cases the transfused rabbits developed sarcomata in practically every organ of the body. No doubt then the supposed indications of the infectiousness of malignancy are due to the fact that the malignant cell will set up metastatic growths in the bodies of animals other than that in which it originated.

Direct inoculations of cancerous material into man in purposive experimentation have failed to produce malignant new growths(7). In 1908 material from mammary cancers were injected into several patients at the Hospital St. Jones. The only result was inflammatory reactions at the sites of inoculation(8). Senn(64) inoculated himself with a carcinomatous lymphatic gland. A pea sized nodule appeared at the point of inoculation, but vanished leaving no trace after two weeks.

In the older literature numerous references are made to cases of supposed direct transferrance of malignancy from wife to husband or vice versa. However since most of these cases are supposed to have occurred before the microbe was known to medicine they probably were mostly cases of infectious granulomata. Numerous and painstaking scientific attempts have been made to isolate a parasite in cases of cancer, but no absolute reliable success has attended any of these ventures. In view of the fact that no positive evidence of infectivity has been uncovered that cannot be explained by transfer of the malignant cell, most of the better known workers in this field have abandoned the parasitic theory.

Tiersch (9) believed that malignancy was due to a disturbance of the equilibrium between epithelial and connective tissue, caused by senile atrophy of the latter, without atrophy of the former. The defense mechanism of the connective tissue being lowered, the more vigorous epithelial tissue could easily infiltrate and replace it. This theory of course has many points of weakness in view of our present knowledge of the disease.

Various modifications of the embryonal rest theory have attracted numerous supporters. Conheim (10) originated the theory, which assumes that an excess of cells are produced in early embryonal life. These excess cells are supposed to possess the inherent power of proliferation and are segregated early, probably in the interval between differentiation of the germ layers and completion of the foundations for the various organs. He pointed out the embryonal appearance of tumour cells and also the fact that congenital and early post natal tumours are not uncommon. His contention was that the tumour need not be congenital in origin, but that its foundation is. He did not mention the conditions necessary for initiation of malignant growth in the embryonal rests, altho he suggested that repeated arterial congestion or inflammatory

hyperemia are very apt to play important parts. He also thought that normal tissues are able to hold the rests in check, but that trauma, chronic irritation etc., weakens this restraint and permits proliferation of the cells. There is considerable evidence to support at least a part of his theory, for example; pigmented naevae are known to consist of cells which closely resemble embryonal tissue, and too, they are relatively common seats of malignant disease. It is not easy to conceive of groups of embryonal cells remaining stationary until old age in the majority of cases, or of a widespread distribution of these rests which would be necessary to explain the experimental cancers caused by tar, and other forms of chronic irritation.

Virchow (10) is responsible for the irritation theory and much of his original hypothesis has withstood the test of experimental study. It is interesting to consider the fact that there was no experimental evidence of the role of chronic irritation in carcinogenesis at the time he propounded the theory.

Authentic Causes of Malignancy

Putting aside all theoretical considerations, we know that I. Chronic Irritation; II. Age and III. Susceptibility a. inherited b. acquired, are authentic causes of cancer.

Perhaps age itself is not as important in the development of malignancy as is commonly thought. However cancer is rare the first thirty years of life, but beyond the age of 70 there is not the further rise in incidence that is to be expected if we believe that the majority do not reach the cancer age (17). In a recent analysis of 3,500 autopsy reports in Germany, covering a period of four years, there were 13.8 percent of carcinomas, after excluding subjects under thirty years the percentage became 17.3%. Among those aged 61 to 70 there were 20.46% of cancer deaths, and from 71 to 80 the percentage rise was very insignificant, being 20.9%. Over the age of 80 there was no

further increase in incidence. Even the malignancy is ten times as frequent at 80 as it is at 30 (18), it is important to bear in mind that cancer does occur in young people, and much oftener than is commonly believed (74)(78). When young people are affected the growth is very much more malignant than when older people are concerned (79). Dr. Quigley of Omaha, ascribes this fact to the better condition of the lymphatics in young people, insuring free metastasas. When the age incidence of carcinoma is compared with that for sarcoma (18), we find that both become more frequent as age increases, up to a certain point, and then the incidence falls in both cases. The decline in the case of sarcomata sets in at about age 50, while that for carcinomata occurs ten to fifteen years later. We now know definitely that sarcoma occurs most commonly in people over thirty-five (19), altho a few years ago it was a common thot that this was a disease of young people primarily just as carcinoma was a disease of older people. It may not be irrelevant to state that sarcoma is very rare in extremely old individuals.

Johannes Fibiger (20) found that age itself was not a factor of importance in the development of carcinoma in the rats fed with the cockroach previously mentioned. Young rats appeared to develop the disease quite as readily as did older ones, however he points out that in the natural state an old rat is more likely to develop carcinoma, simply because he is exposed oftener as a rule, to the responsible chronic irritant. The length of time that the gastric mucosa was exposed to the irritant apparently was more important than the age of the rat. We know that this evidence does not void the fact that most human malignant disease occurs after the age of thirtyfive. The age of the tissue in which the neoplasm starts is probably more important than the age of the patient (80), which may account for the fact that uterine and gastrointestinal malignancy occurs most commonly in middle age, while that of the skin is more common in aged persons. Whatever the

mechanism age is definitely a factor of importance in human malignancy. Since this may occur in any type of pathological tissue it is reasonable to believe that age lowers the resistance of tissue cells and permits the initiation of neoplasms that would not be possible if the wearing out process had not been involved. On this premise the malignancies of the young could occur because of improper development or premature senescence plus the necessary direct inciting factors.

Chronic irritation has been proven as one of the causes of malignancy(21). Projecting teeth, tobacco, mechanical irritation from pipes, improperly fitting dentures, etc., are frequently shown to be inciting causes of oral cancer (22). Eating of hot rice, chronic ulcers of the pylorus, leucoplakia of the vulva, childbirth tears of the cervix, chronic mastitis, chronic ulcers of the skin, use of the kangri in Kashmir, pressure of the dhobi string in Indian washerwomen, the betel nut, bilharziosis (bladder, rectum), aniline (bladder), soot (scrotum of chimney sweeps), tar (hands and arms), paraffin (hands, arms, and scrotum), X-rays and radium (hands particularly); are only a few of the many sources of chronic irritation that the human race is subjected to in industry, and the other conditions of natural life. These factors are definitely concerned in the etiology of malignant new growths. In many cases these irritants have ceased to act several years before the neoplasm appears, or it may appear while the irritant is acting (5). It is therefore quite plain that many cancers would not have developed if the patient had been protected against the irritant responsible in each case. We do not yet know exactly how the irritants act, but we do know that chronic ulcers, scorching hot foods, and beverages, etc., are tolerated with a high degree of danger (11).

The local response of tissue according to experimental evidence (14) depends upon general systemic factors which may either delay or

hasten the onset of malignancy. Murray (23) found in a large number of mice subjected to tar painting, that carcinoma developed in a few after four months of painting, in a larger number after six months, and in others not until after eight, ten, or twelve weeks. Some of the mice were so resistant that neoplasms would not develop even after years of continuous tar painting.

Certain irritants such as tar have been known to be associated with the appearance of carcinoma in human beings, for many years. This fact stimulated the early workers to attempts at artificial production of new growths in animals by the application of various irritants(20). As previously mentioned none of these attempts were successful until Fibiger observed the effects of feeding rats with cockroaches of a certain kind. Actual production of external cancers was first accomplished by Yamigiwa and Itchikawa by applying tar to the ears of rabbits. Their success confirmed the belief that tar workers developed cancer because of the irritation of the tar. Previous attempts had failed because insusceptible animals had been used or because the irritation had not been continued for sufficiently long periods of time. The two Japanese workers later found that white mice were even more susceptible to tar carcinogenesis than rabbits, while fowls, rats, and Guinea pigs were very resistant.

While the skins of fowls and rats are highly resistant to the action of tar, their connective tissues are not, and the reverse is true of mice and rabbits.

Another form of chronic irritation which has served to produce experimental cancer is that produced by the tape worm of rats, which originates in the connective tissue framework of the liver, and will uniformly produce cancer in the liver of susceptible rats. The same tapeworm has been found quite frequently in the liver of mice but never produces a neoplasm in this animal.

One of the most frequent sites of cancer of the female is the cervix. Here we know that cervical erosions play a definite role (24). Old cervical lacerations are followed by an inflammatory exudate which flows over the epithelium of the cervix keeping it constantly irritated. While there is no one cause of cervical cancer this exudate insures both a bacterial and a chemical irritation of the area. Carcinoma of the cervix is ten times more common in women who have borne children, and who have not had their cervical lacerations repaired properly (5). In women who have borne children, but whose lacerations have been properly cared for the incidence of cancer is but slightly higher than that for nulliparous women. This then should serve as further proof, if such is needed, of the great importance that chronic irritation plays in the causation of malignancy.

Recently investigators have learned that many carcinogenic substances have a similar blue-violet fluorescent spectrum, which becomes intense in a beam of ultraviolet light (25). It is possible that this knowledge may be helpful in determining which lubricating oils, etc., are dangerous to use.

Numerous types of tumours may follow the application of various irritants to the skin of animals (26). In a recent classification of 4000 such tumours the authors group them into: **MALIGNANT**

I. Spino-cellular with a. cystic, b. scirrous, c. hyaline, d. basal celled, e. medullary celled characteristics.

and II. Normal Spino-cellular types

BENIGN

I. Tiny thickened areas of epithelium which produce a small mound just visible to the naked eye. II. Flat warts. III. Papillomata. 29,100 experimental animals were utilized and the effects of various carcinogenic substances may be seen by referring to the following chart :

	Animals Used	Benign	Malignant
Coal gas tars -	800	93	106
Synthetic tars -	8,800	1,086	1,281
Shale oils -	10,000	977	307
Petrol oils -	6,100	183	43
Other oils, etc. -	500	0	0
Pure compounds -	2,900	15	6
Totals -	29,100	2,354	1,743

After careful consideration of the experimental and statistical evidence, we may repeat that chronic irritation is a cause of malignant neoplasms. Many of the sometimes suspected factors, such as diet, soil, and climate may be ruled out by consideration of the fact that malignancy affects all forms of life down to the reptiles. Therefore habits and customs which are peculiar to man, except in so far as they concern chronic irritation must have little to do with the etiology of this disease (19).

Susceptibility and Heredity

Undoubtedly a predisposition to the development of malignancy exists in certain individuals, which I believe may either be hereditary or acquired. Experimental evidence points to the fact that the site must be prepared or predisposed before malignancy may develop (21). Laville (22) refers to this as the 'terrain pré-cancéreux'. Hereditary influence upon tumour incidence has been proved by animal experimentation (26). Maude Sly (2) has carried out numerous experiments on the influence of heredity in the development of mouse tumours. Inbreeding of tumour bearing animals greatly increased the incidence in succeeding generations. She utilized a pedigreed strain of mice which had been under her observation for fifteen years. All of the tumours studied were spontaneous. She performed over 30,000 autopsies and observed over 4,000 such spontaneous tumours. She concluded that:

- I. Neoplasm hereditary factors behave as Mendelian recessives
- II. Double cancerous parentage produce 100% tumour strains, excepting some individuals who die before the cancer age of infections.

III. Single cancerous parentage yields heterozygotes (transmitting but not themselves cancerous) in the first hybrid generation. These whether inbred or hybridized with other heterozygotes yield in the next hybrid generation non-cancerous, heterozygotes, and cancerous progeny in the proportion of 1:2:1.

IV. The mating of a carcinomatous with heterozygotes individual yields approximately 50% cancerous and 50 % heterozygous offspring.

V Double non-cancerous parentage yields 100% non-cancerous .

VI. The tendency to tumours of specific organs and of specific types is also inherited. For example her stock yielded strains of 100% alveolar carcinoma of the mammary glands, or 50 % liver adenoma, or 37 % kidney tumour.

All of these animal experiments are, of course, primarily carried out to learn more about human malignancy. The last conclusion above seems to be borne out in many human families. Sibley observed cancer of the left breast in a mother and her five daughters; Kirtway saw cancer of the breast; and Paget Cancer of the uterus in mother, daughter and granddaughter. Newton reported retinal gliomata in 10 of 16 children in one family with healthy parentage (27).

Bashford and Murray (28) were able to increase the incidence of mammary carcinoma in 340 mice of recent cancerous ancestry to 18.2 % as compared with 8.6 % in 223 mice with remote cancerous ancestry.

It is apparent from the results obtained in tar painting and other experimental work that some mice as well as other animals, will not develop carcinoma no matter what irritant is applied to them. The susceptible animals will not develop further tumours from artificial irritation after having one removed surgically (29). Mice with spontaneous mammary tumours likewise have failed to develop tar cancers after successful surgical removal of the former (14). The conclusion may be drawn from this that a form of immunity has

been developed by the tumour bearing animal, so that it is at least more difficult, if at all possible, to induce further malignant growths. On the other hand by selective breeding of mice, some investigators (14) have been able to so increase the susceptibility of certain strains that some of the young were born with the disease.

Predisposition as an important factor in the development of malignancy is quite definitely proven by the experiments of such men as Choldin (67), who was able to markedly increase the rapidity of development of cancer in mice by injecting small amounts of indol and arsenic before painting with tar.

Fränkel (69) found that hens were four times as susceptible to inoculation of the Rous sarcoma filtrates during the laying period as they were during the fall and winter months.

Flaszen and Wachtel (70) claim to have successfully inoculated a mouse with human carcinoma of the cervix after carefully preparing the mouse by alkalization. They assert that human cancer will grow readily in lower animals if the latter are properly prepared for its inception.

Heredity is believed to play an important part in human malignancy as well as in that of the lower animals, for it is difficult to explain on other grounds how some families could have so many members suffering from the disease. Perhaps as M. and P. Guerin (30) supposes, cancer is never directly inherited, but plays an important indirect part by setting up a predisposition to malignant disease. The fact that it is practically impossible to learn whether or not the forebears of a patient had cancer for more than a generation or two back, renders accurate study of the effect of heredity in human cancer, practically void. Human matings are made at random which probably keeps inherited tendencies at a low level (20). The rare instances of so called cancer families reported in the literature cannot be ever looked because the history is so striking in many cases that it must be more than mere coincidence, for example cancers of the same organ occasionally occur in a large percentage

of the same family in the same generation. One notable example is the Bonaparte family, Napoleon I, his father, brother, and two sisters are all said to have died of carcinoma of the stomach. Numerous other similar cases are of record, but it is scarcely necessary to cite them. These facts suggest Maude Sly's findings, previously referred to in this paper, in which she was able to develop strains of mice with special organ susceptibility to malignancy. It is true that the cancer families are comparatively rare and may be considered as extreme examples. Extensive studies of heredity statistics have yielded very confusing results. Sly's conclusions cannot be ignored in so far as selected strains of mice and selective breeding are concerned, but her methods cannot well be applied to human beings, and therefore I believe that heredity plays a minor part in human malignancy, for the reason that tendencies towards resistance or susceptibility must be so juggled by the chance matings that the hereditary factors only rarely markedly increase the incidence of malignancy in any one family. The life insurance companies have carried out exhaustive research on this subject, and all of them agree that history of cancer in a prospective client's family does not materially increase his chances of dying of the disease.

Beyond stating that marked individual susceptibility to cancer does exist, we cannot go with certainty. Since congenital anomalies are frequently hereditary, and also are frequently the sites of cancer, it is not unreasonable to believe that many of the malignant growths which occur in the same organ of several members of a family are primarily due to such developmental defects.

Some races of people appear to be highly resistant to malignancy. Carcinoma is said to be very rare among full blooded American Indians (31). So rare in fact that many cancer workers claim that it occurs only among Indians with mixed blood. However Hoffman (32) in 1928 concluded that full blooded Indians do have cancer, but that its incidence is very low among these people. Records at reservations are usually

lacking and the Indian is very reticent. The number of Indians dying of unknown causes was 18 percent in the Indian registration district in 1925, but in spite of this it is difficult to explain why so few cancer deaths are recorded among full blooded Indians. True the average age of the Indian is less than that of the white man, for their infant mortality is terrific, and Tuberculosis accounts for about 22 o/o of their deaths, but they must possess a natural resistance to malignancy.

Cancer is supposed to be rare among most primitive people, but if the shorter average life, and the lack of records, autopsies, etc., are considered there will probably be little difference in incidence. In the hospitals of China where autopsies are performed regularly, very little difference in incidence is found there as compared with European hospital records (33). Cancer of the penis is said to be unduly high in China (34). One author (34) ascribes this fact to the treatment of venereal diseases by external application of strong irritants such as cantharides, ginger, etc., by the Chinese physicians.

Regional and National Incidence

Cancer belts are quite frequently mentioned in current literature. These (20) are probably best explained by a preponderance of people in the cancer age in most of these places. For example a certain section of a city may be almost entirely inhabited by retired farmers, or retired business people well up above forty years of age.

In the United States morbidity rates for diseases of advanced life are always higher among the foreign born (35). These are particularly high among the Irish and German foreign born, while those from Italy, Poland and the states which formerly made up the Austro-Hungarian Empire have a much lower rate of morbidity. However foreign born people on the average are older than the native born. The crude death rates in the U.S. by nativity for cancer in 1927 were: native born - 81.2 ; foreign born - 180.2. These ranged from 105 for Italians to 428 and 480 for

Irish and Germans respectively. The conclusion is drawn (20) that this difference is to be accounted for by the age composition of the national groups. It is this fact particularly that prompts me to mention these statistics. So many conclusions are drawn without consideration of such truths as, that the German and Irish immigration was at its peak long enough before that from Italy, Poland, Austro-Hungary, and others, that a much larger percentage of the German and Irish foreign born are in the cancer age than are those from the other countries mentioned.

Studies of vital statistics of New York state (36) reveal very little difference in rate of cancer deaths between urban and rural districts, altho the urban rate was slightly higher. Some authorities consider this due to more exposure to carcinogenic substances in the various urban industries. Statistics from one state alone are not all conclusive and perhaps not enough attention has been paid to this truth.

One point stands out in the literature above all others in regards to national incidence of cancer, and that is that the highest cancer death rates are reported from countries which are the most progressive and keep the best records. The skill of the physicians in diagnosis is also apt to be far superior in these countries. In this connection Wells (20) states that an error of at least thirty percent in the matter of properly stating cause of death, exists even in the most modern hospitals. This is partially due to the difficulty encountered in obtaining autopsies, and the natural reluctance of many families to have cancer and other vile diseases appear on the death certificate, because of the fancied stigma attached thereto. Frankly then, little evidence of a positive nature is to be found in the literature of any marked difference in the incidence of malignancy among the civilized peoples of the world. Of course we cannot overlook the increased frequency of cancer of certain sites exposed to special forms of chronic irritation peculiar to practically all of the people of a region or country, such as have been mentioned previously in this paper in connection with the betel nut chewers

of India (oral Carcinoma); the eating of hot rice by the Japanese (ca. of the oesophagus); etc. Recently, widely recognized workers representing practically all the races of the world have submitted statistics which show that carcinoma and sarcoma occur very frequently among uncivilized peoples (48)(49)(50)(51)(52)(53)(54)(55)(56)(57)(58)(59)(60). However it appears that the proportional frequencies are different.

Increase of Cancer

In consideration of this subject practically as much evidence is to be found for as against it. However in the Fourth Preliminary Report of the San Francisco Cancer Survey (38), the conclusion is reached that cancer is unquestionably on the increase in proportion to the population, but that wide variations exist in its' local incidence according to the parts affected. 35,000 death certificates from several states are considered, and since the insurance company that initiated the report were interested primarily in the actual status of cancer in this country, it is quite certain that their conclusions are valuable.

A few statistics taken from the U.S. Vital Statistics follow, which also show that there is a very great and consistent increase in the rate of cancer deaths thru the past three decades:

Year	Rate	Year	Rate
1900	63.0	1913	79.0
1901	64.3	1914	79.6
1902	65.1	1915	81.4
1903	68.3	1916	82.2
1904	70.2	1917	82.0
1905	71.4	1918	80.3
1906	69.1	1919	80.5
1907	70.9	1920	83.4
1908	71.5	1921	86.0
1909	73.8	1922	86.8
1910	76.2	1923	89.4
1911	74.4	1924	91.9
1912	77.1		

An adjusted cancer death rate for the United States registration area shows an increase in the death rate from 87.8 per 100,000 population in 1920 to 102.2 in 1927. During these years the rate for each

sex below the age of 45 showed little change, but for older ages there was a continuous increase.

Dr. Stevenson(49) believes that he has evidence of an actual increase in the incidence of malignancy, in that the statistics show a great increase even in organs and parts where the diagnosis has always been easy, such as the skin, buccal cavity, etc.

Of the total cancer deaths reported in this country in 1927, 56.1 percent were females, and 43.9 percent were males. The male population in the registration area is greater than the female, so apparently the incidence is greater among the females in this country.

The bare facts as presented by cancer statistics point to an increase in all countries of the world where accurate records are kept. However with the advance of scientific medicine the average age of man has practically doubled in the past two hundred years'. This means that more and more people in proportion are living to reach the cancer age. Even so the rapid year by year ^{INCREASE} has far outpaced the percentage increase in length of life. The large cities of the world show the greatest increase (40). Cancer of the stomach kills the most victims, and cancer of the uterus holds second place, these two sites have led as long as records have been kept. Cancer now holds fourth place (38) among the leading causes of death in the United States, being surpassed only by 1. Heart disease; 2. Pneumonia; 3. Cerebral apoplexy.

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