THE NATURE AND ETIOLOGY OF CANCER

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I

EVIDENCE FROM COMPARATIVE PATHOLOGY AND EXPERIMENTAL CANCER RESEARCH

Most of the major problems of medicine that can be solved by the study of human material alone have been settled as far as available methods and materials permit. Most of our remaining problems apparently will have to be settled by work with animals, which furnish the essential possibility of control of observations and results, a feature difficult, often impossible, when human material must be used for our investigation. This is particularly true of cancer, whether we are seeking light on the cause or the treatment. Cancer is a disease of such protracted development and course, so variable in its manifestations and duration, often so difficult of diagnosis and differentiation, that satisfactory study of many fundamental problems on the basis of clinical observation is almost or quite impossible.

A new impetus to cancer research was received when, through the study of cancer in animals, the investigative work was put upon an experimental basis. Cancer research had come almost to a point of complete despair at the end of the 19th century. Pathologic anatomy had established the relation of cancer tissue to

1 Three lectures delivered under the Colver Lectureship at the College of Medical Evangelists, Los Angeles, Cal., Feb. 17, 18, and 19, 1931.
normal tissue and had provided a basis for descriptive classification which permits of indefinite division into groups and subgroups—an entertaining process that is still going on, whether profitable or not. Bacteriology had exhausted its first enthusiastic expectation of settling the nature and cause of cancer, as it had triumphantly done with so many other diseases, and was beginning to think that after all there might perhaps be something in what the pathologists said about cancer probably not being a specific infectious disease. Protozoologists had become a little weary of working out the life cycles of the protozoa that caused cancer, after disillusionments that shattered pride and dispelled vanity. Chemistry had found its feeble attempts to determine something chemically characteristic of cancer to be futile, and virtually abandoned the subject. There seemed to be no particular way for advance in the study of one of the most important of human diseases. What was being done on cancer research in the gay nineties was mostly in the nature of grasping at straws.

The renaissance of cancer research came when it was found that laboratory animals could be made to have cancer, more or less at man's will. This made it possible to put cancer research on the basis of an experimental science, with planned investigations in which the vitally important matter of adequate control could be provided for.

Three major steps have marked the early stages of the study of cancer by experimental methods. The first of these, and the one which put a fresh breath of life into despondent cancer research, was the demonstration, at the beginning of this century, by Jensen in Copenhagen and Leo Loeb in Chicago, that carcinoma and sarcoma could be transplanted and retransplanted in mice and rats for an apparently unlimited time. In fact, Jensen's mouse carcinoma is still being transplanted, over thirty years after its original removal from the mouse in which it started. The cells of this cancer now growing in laboratory mice are direct descendents of the cells of the original Jensen cancer mouse. As the maximum age reached by mice is about three years, this fact suggests that cancer cells are immortal, as apparently all cells are if they can be freed from the limitations of life of the organism as a whole. Carrel has carried connective-tissue cells eighteen years in tissue cultures in his laboratory.

Earlier experimenters had transplanted tumors into animals, but the significance of their limited observations was not recognized and the work was not followed up.
Although we now realize that the amount we can expect to learn about cancer from transplanted tumors is quite limited, because of fundamental differences in transplanted and spontaneous tumors, nevertheless this discovery was of tremendous importance because it stimulated interest in experimental cancer research and yielded not a little valuable information about tumor cells.

More important, presumably, was the discovery that primary spontaneous cancer, altogether like cancer of man, can be made to arise in laboratory animals under the influence of chronic irritation of tissues or because of inherited properties. Each of the major contributions in these fields had been foreshadowed by minor observations of the same effect. In 1914 Yamagiwa and Ichikawa in Tokio reported that squamous-cell carcinoma could be produced in rabbits by long-continued application of tar—a method and principle that have since been greatly extended in other laboratories, and of much greater experimental value than the earlier observation of Fibiger that cancer may develop in the stomach of rats from the irritation produced by nematodes coming from cockroaches.

Early observations suggesting that heredity might play a rôle in the occurrence of spontaneous tumors in animals, such as those of Eberth and Spude (1898), Leo Loeb (1904), Tyzzer (1907), and Murray (1911), were followed by the more extensive observations of Loeb and Lathrop on subcutaneous (chiefly mammary gland) tumors, and of Maud Slye, who first showed on a large scale, with mice of known ancestry, how important a rôle heredity plays in producing tumors of various types and in different tissues. This work has established the fact that, by proper breeding, strains of mice and rats may be obtained with a high incidence of tumors, even independent of the application of any unusual stimulus or other factor to cause tumors to appear.

Since modern cancer research is now largely based on these three sets of observations, the question of animal cancer becomes a vital one in a consideration of the present and future developments of cancer pathology, etiology, and treatment. A fundamental question is: What is the relation of the disease or diseases called cancer in animals to cancer in man? Is it the same thing, or merely a similar thing, or even something essentially different? Another question that may well be raised is: Can anything be learned about the nature of cancer in man by the study of neoplastic diseases as they naturally occur in animals?
At the outset of work on experimental cancer not a few objections were raised to considering that carcinoma in mice and sarcoma in rats were the same thing as the human diseases known by the same names. Attention was called to the fact that these tumors showed less tendency to metastasis than human cancer, especially to the lymph nodes; that they reached relatively enormous size in proportion to the body weight of the animal, before causing either cachexia or death; and that the most studied tumor, from the subcutaneous tissues of mice, presented histological differences from the usual types of mammary gland cancer of women. Also, it was argued that this mammary gland cancer of mice was a special disease, since, as it was then believed, these animals did not suffer from any of the other sorts of tumor seen in man.

The intensive study since given to these growths has served to remove all doubts that they represent fundamentally the same disease, cancer, in animals and man, and that the differences observed depend either on anatomical peculiarities of different species, or on other differences between species, for the frequency of each type of cancer varies with each species. The identity of animal neoplasms with those of man is shown by the following facts.

The cells of malignant animal tumors resemble fundamentally those of human cancers, in that they are of embryonal character, showing many mitoses, which are often atypical, forming at times atypical cells differing in appearance from those of normal tissues, arranged atypically, infiltrating the adjacent tissues and destroying them, invading blood and lymph vessels to produce tumor emboli and metastases in remote organs. No infectious agent can be found in them, and they are no more contagious than human neoplasms. Animal carcinomas also exhibit the same characteristic age distribution as human carcinomas, rarely being seen before the middle age period, and increasing in frequency with advancing age. For example, Fröhner never saw carcinoma in a dog under two years of age, and eighty-seven per cent of his cases were in dogs over five years old. Those tumors which exhibit histological malignant characters are as inevitably fatal as human cancers, recurring after removal, and undergoing necrosis with ulceration and secondary infection like carcinoma in man. Especially in Miss Slye's large stock, with vast numbers of animals permitted to live out their natural lives, it has been found that
even in mice, cancer is by no means limited to the readily observed carcinoma of the mammary gland. We have seen many sarcomas of various types, especially osteogenic sarcomas, and lymphosarcomas that seem to be closely related to the abundant cases of pseudoleukemia and leukemia. Squamous-cell carcinomas, especially of the skin and mouth, are not rare, and papillary adenomas and adenocarcinomas of the lung are common in mice. In fact I have seen in Miss Slye's mice most of the forms of tumors that I have seen in men, even rare tumors, such as a papilloma arising in the ependyma of the lateral ventricle, a malignant adenomatous growth of the anterior lobe of the hypophysis infiltrating the meninges and brain, and primary liver-cell carcinomas. Furthermore, each type of growth behaves about the same as it would in man. For example, the solid tumors of the ovary are commonly bilateral, the squamous-cell carcinomas of the mouth arise at points of irritation from broken teeth, etc., and I have seen them infiltrate the skull and invade the meninges. Basal-cell carcinomas, most often seen on the faces of old men, in mice usually are found on the skin of the face of exceptionally old individuals, and, like human basal-cell carcinomas, they do not readily produce metastases. Furthermore, the types of tumors which are histologically like benign tumors in man behave as benign tumors. Uterine fibroids are found in mice as benign growths, prone to calcify; even infiltrating adenomyomatosis is seen in the uterus of mice. Teratomas are seen chiefly in the ovaries, both in mice and women, and typical hypernephromas are found in their kidneys. Thyroid tumors, alike in mice, dogs, and men, have a strange tendency to look as if made up of a mixture of carcinoma and sarcoma, a feature not often seen in tumors from any other tissue.

Cancer is certainly not an exclusively human affliction. Indeed, the more we study comparative pathology the better we realize that there is nothing exceptional about man in respect to cancer, not even its frequency. Our idea that cancer is especially common in man is correct, simply because man is one of the few species of animals that is commonly permitted to reach old age, and cancer is a disease of old age. The few species of animals that often reach old age, as turtles, elephants, and the rhinoceros, seldom have the benefit of clinical study or post-mortem examination to tell us just how often cancer has been present. Systematic study of old dogs shows that neoplasms are extremely
common among them; in fact, it is rare to find a really old dog without some sort of tumor, either benign or malignant, or both. Multiple tumors are especially common in old dogs. It seems safe to say that tumor formation in dogs is as common as, and probably more common than in men of corresponding age. Indeed, it seems probable that if one were to study a large group of mice, cows, dogs, or horses, it would be found that they exhibited much the same frequency of neoplasm formation as a group of human beings in the corresponding part of the life cycle.  

Cancer is undoubtedly a universal disease in multicellular organisms. It has been found in almost all species of animals that come under the observation of people able to recognize and report it. Its range and diversity may be illustrated by citing recorded observations of varied types of tumors in widely separated species, such as the following examples: carcinoma of the ovary with metastasis to the liver in a python (116); sarcoma of the urinary bladder in an ox (15); carcinoma arising at the base of the right horn of cattle in India, at the point where they are attached by a rope to the wagon they draw (13); sarcoma of the heart in a guinea-pig (6); sarcoma of the liver in a "porose crocodile," producing metastasis to the cerebellum and heart, with cerebellar symptoms (87): malignant adenoma of the hypophysis in a baboon (10), an Indian buffalo (10), and a parrakeet (34); teratoma of the testicle in a golden eagle (75); carcinoma of the cervix of the uterus in a rhinoceros (9), together with fibroids, the mass weighing 120 pounds; a fibromyoma uteri in an armadillo (33); fibromyoma of the stomach of a codfish, and chondroma of the humerus of a lizard (10); glioma of the gasserian ganglion of a dog (39); glioma of the eye in a gull (1); fibromyxoma (107) and sarcoma (85) in goldfish; leiomyoma of the uterus in an elephant (101); giant-cell sarcoma of the hand of a baboon (83); seminoma of the testicle in rats (12) and mice (92), although especially frequent in horses (53); carcinoma of the gallbladder in guinea-pigs from experimental gall-stones (51), and of the bile ducts from distomiasis in cats (46); sarcoma of the foot with metastasis to the liver in a frog (106); chorionepithelioma of the uterus in a porcupine (35); carcinoma of the testicle in a salamander (81); sarcoma in the mesentery of an eel (120); thyroid carcinoma in a sea bass (67); and even a neurofibroma in a honey bee (113), to say nothing of multiple melanoma in the larvae of fruit flies (98).  

1st Scientific Report, Imperial Cancer Research Fund, 1904.
The foregoing examples, which might be greatly extended, are selected merely to indicate that the most varied sorts of neoplasms found in man are also found widely distributed throughout pretty much all the animal kingdom. Possibly vegetable tissues also suffer from true neoplasms, although most if not all of those so far studied seem to be merely inflammatory reactions to injury. As yet, as far as I can learn, the presence of true neoplasms has not been demonstrated in any invertebrates (27), except possibly the insects, but it is to be expected that they will be found as more examples of lower animal forms come before persons competent to recognize neoplasms in them.\(^4\) Metcalf (71) has even suggested that irregular and atypical nuclear division observed in protozoa may be equivalent to tumors in multicellular forms. The growing number of observations on cancer in animals adds strength to the statement of Bashford (4) in 1904 that “the great diversity of food, habit, and conditions of life generally in animals in which cancer occurs, shows that such external agencies have no causative influence.” In Miss Slye’s mice, kept under identical conditions of nourishment, temperature, and environment, the incidence of cancer in different strains varies from zero to practically 100 per cent in mice of sufficiently advanced age. Certainly comparative pathology offers no support to the hypothesis, often advanced, that cancer depends on diet, and that it may be controlled by diet, especially vegetarianism. Most of Miss Slye’s mice are on a vegetarian diet, and the vegetarian carp seem to offer as many tumors as carnivorous fish. Old cows and horses frequently develop malignant neoplasms, these being the chief examples of herbivorous animals permitted to reach old age under conditions in which tumors are likely to be detected. Elephants and hippopotami also live to old age, but the percentage of necropsies is low.

Between different species there is, however, a marked difference in the frequency of different types of neoplasm, which presumably is of significance, but for which we still lack any explanation. For example, in man cancer of the stomach undoubtedly takes first place in frequency, but in every other species, as far as is now known, it is extremely rare. Why this should be is an interesting problem. Dogs, with their high incidence of cancer in

\(^4\) The early reports of a tumor of the pericardium of an oyster, observed by Leidy and reported by Ryder (57), and of an “adenomyoma” arising in a fresh water mussel (115) are not adequately described to permit us to know whether they were true neoplasms or not.
general, eating much the same food as their masters, do not have 
gastric cancer. There are but one or two reasonably authentic 
reports of cancer of the stomach in dogs. Possibly this depends 
on the fact that man is the only animal who eats hot and spiced 
foods. Many things can be cited in favor of this theory, but an 
attempt made in my laboratory, by Julian Lewis, to produce 
cancer of the stomach in dogs by feeding hot food was unsuccessful, 
though this negative result, of course, proves nothing.

Cancer of the cervix uteri is also relatively infrequent in other 
animals than man, although cancer of the corpus uteri is not so 
infrequent as cancer of the stomach; especially is it found in cows 
and rabbits, but even with these species it is a rare condition (93). 
Uterine carcinoma is seen more often in multiparous than in 
nulliparous women, but most other mammals are much more 
multiparous than women.

These facts suggest that the differences in occurrence of 
different neoplasms in different species depend not so much on 
the amount or character of traumatism to which their tissues are 
subjected as on the properties of the tissues themselves, as deter­ 
mined by heredity. Supporting this view is the species distribu­ 
tion of cancer of the breast. Among mammals in general the 
mammary gland is one of the common sites of cancer, possibly 
because it is a highly specialized organ developed relatively 
recently in animal evolution. But of all the mammals the one 
with the most traumatized, overworked, and specialized mammary 
gland, the dairy cow, seems freest from mammary cancer. I 
cannot find a single record of a cancer in a domestic cow's mam­ 
mary gland, despite the fact that milk cows are commonly kept 
until they have reached sufficiently advanced years to be subject 
to carcinoma. 5 None has ever been seen in the vast material 
coming to the Union Stock Yards in Chicago, according to the 
statement of the government pathologist, Dr. L. E. Day. Carci­ 
noma is not particularly uncommon in the less-used mammary 
gland of mares.

Only on the basis of hereditary species susceptibility can we 
explain the facts that in mice the malignant tumors, especially of 
the mammary gland, are predominatingly carcinomas, whereas in 
rats the tumors are mostly sarcomas (12), and that in dogs the 
tumors especially seen are mixed epithelial and cartilaginous

5 Dibble (23) has reported a few cases of squamous-cell carcinoma of the mammary 
gland in wild Australian cows.
growths in the breast, thyroid tumors (94) (often of mixed structure), and lymphomatous growths. So, too, we note that swine are especially prone to exhibit embryonal adenosarcomatous tumors of the kidneys, that horses show a high incidence of testicle tumors considering how few old horses there are with testicles, that fowls are especially likely to have ovarian tumors, that gray horses are particularly subject to melanotic tumors of the skin, and that sheep and cows have tumors of the liver most frequently.

Another striking fact is that gliomas of the brain, so common in man, are unknown in other species, only one reasonably satisfactory report of a cerebral glioma, this in a dog, having been found in the literature (95).

These pronounced variations in susceptibility to cancer of different tissues in different species seem most readily explained as a difference in the inherent properties of the tissues, which suggests their dependence on inherited qualities that determine species differences. For example, mice very frequently suffer damage to the liver from parasites and from infections, but I have never seen or heard of a primary sarcoma of the liver in mice. Yet rats of certain families very frequently develop sarcoma in the liver at the site of parasitic invasion. Other families of rats do not exhibit sarcoma of the liver when infested with parasites (18), thus resembling the mice. Furthermore, certain strains of mice develop epithelial tumors of the liver independent of parasitic invasion, whereas most other strains of mice never develop liver tumors under any circumstances (91). That is to say, the facts brought out by consideration of the comparative pathology support the view that the inherited constitutional make-up of the species is an important factor in determining what sort of tumor will occur in that species. A human analogy is furnished by the markedly greater tendency of negroes to develop fibroid tumors and keloids than whites.

Comparative pathology promises to throw light, also, upon leukemia, pseudoleukemia, and related conditions, which are widely distributed throughout the animal kingdom, and which seem to correspond closely to the corresponding diseases in man. In Miss Slye’s experience (90) the chronic leukemias and true pseudoleukemia behave like malignant neoplasms, shading off by imperceptible degrees into local lymphosarcoma with metastases, an observation in agreement with the view of many pathologists.

*See full discussion by Simonds (88).*
that chronic leukemia and pseudoleukemia in man are true neoplastic processes. They commonly occur in strains of mice that bear other tumors, not infrequently being found in a mouse that also has carcinoma or sarcoma at the same time. The fact that leukemia with its related diseases can now be obtained readily for experimental purposes in laboratory animals, and that it can be studied both as a spontaneous disease and as an inoculated or transplanted process (65), opens the way to a greatly improved knowledge of these important, and at present baffling conditions.

Transplanted Tumors

Accepting as conclusive the evidence that human and animal tumors are essentially the same, what has been learned from the vast number of experiments so far carried out by means of transplantation of a tumor from one animal to another? The chief result seems to be the demonstration that tumor cells are essentially the same things as the tissue cells from which they arose. Transplantation of tumors is no different from transplantation of normal tissue cells, and the same requirements are found to be necessary in each case. That is to say, transplantation is most likely to be successful when made into the same animal as the one which furnished the grafted tissue; grafts into members of the same family, i.e. brothers, sisters, or parents, have a much better chance of success than grafts into unrelated members of the same species, and grafts into other species are usually impossible. Such a striking dependence on close genetic relationship is entirely in disharmony with the hypothesis that cancer depends on a specific cancer parasite, for we know of no infectious disease transmissible from one animal to another that requires any such close relationship of the donor and the recipient of the infection.

The old suggestion that the cancer parasite is the cancer cell itself has received strong support from the study of transplantable tumors. Any procedure that destroys or devitalizes the cancer cell interferes with its transplantability, just as is the case with the transplantation of normal cells. No one has yet succeeded in separating from a mammalian carcinoma any agent that will produce a cancer in other animals, except viable cancer cells.

The so-called "Rous sarcoma" of chickens, which is trans-

7 A few exceptions have been observed. Rat or mouse tumors can be grafted into early chicken embryos (Murphy), and mouse tumors can be grafted into the brain substance of rats under certain conditions (Shirai, corroborated by Murphy and Sturm, 73).
mitted by some agent passing through filters fine enough to hold back bacterial cells, presents unsolved problems that I have not the space to discuss here. It exhibits all the characters of a true sarcoma, as far as morphology and general properties are concerned, but is exceptional in that drying, long preservation in glycerine, and other drastic procedures do not destroy its ability to incite new growths. I confess that I am impressed with the fact that when a chondrosarcoma is transmitted from fowl to fowl by filtered extracts the new tumors are cartilage-forming tumors, even when arising in tissues that normally contain no cartilage (102). This is difficult to harmonize with the hypothesis of a filtrable virus being responsible for the new tumor, but more in favor of the possibility that fragments of cells, or even whole cells, small enough to pass through coarse filters, may regenerate to form viable cells possessing the properties of their ancestors. 8

The fowl tumor “virus” does not pass through the finest filters.

Somewhat similar in respect to their doubtful nature are the round-cell tumors not rarely observed arising in the genitalia of dogs. Being readily transmitted by coitus or direct inoculation, and sometimes failing to recur after not too thorough extirpation, they seem like an infective granuloma of distinctly contagious character. But in histologic structure, tendency to generalize and metastasize, and in respect to the behavior of transplants (Ewing and Beebe), they have all the appearance of a true sarcoma. 9

Transplanted tumors have furnished much material for the study of immunity, specific serological diagnosis of cancer, and treatment, with results that sum up to nothing encouraging when only the best controlled experiments are considered. 10 Unfortunately many incautious and inexpert experimenters have aroused unwarranted excitement concerning supposed curative measures based on a small number of experiments, disregarding the common tendency for many sorts of transplanted tumors to disappear spontaneously. In evaluating the results of experiments with transplanted tumors, it is necessary to bear in mind that an inoculated tumor is something quite different from a spontaneous tumor. A transplanted tumor differs from a spontaneous tumor fundamentally in that it is never a growth of the cells of the

8 Nakahara (76) believes that he has found minute ameboid cells in the Rous chicken sarcoma which can pass through filters that hold back bacteria.
9 See review by Novak and Craig (77).
10 See review on Immunity to Transplantable Tumors by W. H. Woglom (119).
inoculated animal, but it is a growth of the cells descended from
the animal that furnished the original spontaneous tumor from
which the transplanted growth was obtained. For example, a
mouse inoculated with a strain of the Jensen carcinoma, which
has been carried through myriads of generations of transplants
during the thirty years since Jensen first started the transplanta-
tion, is growing a tumor composed of cells derived from Jensen’s
original tumor mouse and not from its own tissues. The mouse
bearing an engrafted tumor is merely furnishing the soil on which
some grafted tissue is growing, much as a culture tube furnishes a
soil on which bacteria are growing.

That the inoculated cancer is fundamentally different from the
spontaneous cancer is shown by the fact that successfully inocu-
lated growths often disappear spontaneously, and that protection
may be furnished by various procedures of immunization, phe-
nomena which are never seen in spontaneous tumors. Further-
more, animals that are immune to tumor inoculation may develop
spontaneous tumors, and by painting the skin with tar, true
carcinomas may be produced in mice immune to grafts of the same
sort of tumors. Therefore, observations on the influence of
heredity on the susceptibility of animals to transplanted tumors,
or methods of treatment using transplanted tumors as the indi-
cator, can have no direct bearing on the question of susceptibility
to or healing of spontaneous tumors, since the resistance to one
bears no direct relation to the resistance against the other. Only
the behavior of true spontaneous tumors arising in animals from
their own tissues can give final information in respect to the
behavior of cancer in man.

Experimental Production of Tumors in Animals

What seems to be the most useful step yet made in the study
of cancer is the demonstration that laboratory animals can at
will be made to develop cancer of their own tissues, just as human
cancer is produced. To be sure, it has long been known that
laboratory animals do develop cancer, but until recently this was
seen only as a rare occurrence, not possibly furnishing material
for systematic study of the problems of cancer. Now we have two
methods that permit us to secure large numbers of animals with
true autogenous neoplasms. One is by selective breeding, de-
pending upon the demonstrated influence of heredity upon the
occurrence of cancer, a matter that will be discussed more fully
It is gratifying to find that research workers are now beginning to test proposed therapeutic procedures on natural spontaneous cancers secured by selective breeding, as reported in the recent paper by Itami and McDonald (48) on the treatment, with negative results, of mouse cancer by means of an active extract of adrenal cortex (Swingle and Pfiffner).

The other method of getting cancer animals, more popular because easier and less time-consuming, is by using the recognized factor of long-continued irritation in the production of cancer. This irritation may be produced by animal parasites, as in the production by Fibiger of cancer of the stomach in rats infested with the nematode, Spiroptera; or of sarcoma of the liver in rats infested with a cestode (Cysticercus fasciolaris), as observed in the Crocker Laboratory, New York (12, 18). These methods are of limited applicability because they introduce an unusual, special, and not readily controlled factor, a specific animal parasite.

The experimental production of cancer by x-ray irritation, following the clue furnished by x-ray cancer in man, has so far produced neoplasms in too small a proportion of tested animals to be of much value as a method, although of significance in the study of the disease. By far the best method yet devised was described in 1914 by Yamagiwa and Ichikawa, who succeeded, where others had failed, in producing cancer of the skin of rabbits by the repeated application of tar, analogous to the tar cancers observed on the skin of man.11

This ready method was tested in many laboratories as soon as war activities permitted, with complete confirmation and much extension of the original observations. So readily are skin tumors produced in mice with tar that the Tworts (104) have been able to report on four thousand such growths. Although this line of study is only in its infancy, and much is expected of it with time, certain results seem already to have come from it.

One important result is added support for the now widely accepted view that cancer does not depend on a specific parasite. This opinion, deduced from careful observations on the biology of human cancer, and held by most thorough students of tumor pathology, receives confirmation from the work on tar cancers. Advocates of the theory of a cancer parasite have always argued that the reason trauma and chronic irritation predispose to cancer is that they open the way for the supposed infectious agent to

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11 A full review to 1926 is given by Woglom (118).
enter the tissues. But Yamagiwa produced carcinoma on the ears of rabbits by the application of a strongly antiseptic tar, and no one had ever before seen a carcinoma arise on the ear of a rabbit, despite the vast numbers of these animals under observation in laboratories, nearly all with plenty of openings in the skin of their ears to permit the entrance of cancer germs, due to needle punctures, ear tags, identification notches, and rough handling.

The fact that an antiseptic agent, characterized by its stimulating cells through mild irritation to repeated multiplication, produces cancer, is in full harmony with the long widespread impression that cancer does not depend on any specific cancer parasite, but that it may be the result of any condition that repeatedly stimulates cell proliferation until the proliferative activity dominates the life processes of the cell, which acquires an exaggerated "habit of growth." The fact that the growth always appears at points irritated by the tar, whether this be the skin, the lungs, or the stomach, also confirms the long prevailing view that cancer is essentially a local disease and not a constitutional disease with local manifestations.

The importance of heredity in the genesis of cancer is also confirmed by the tar experiments, for there is a vast difference in the susceptibility of different species of animals to the production of tar cancer. While the skin of rabbits, and especially of mice, will often develop cancer after sufficient tar painting, it seems to be practically impossible to produce skin carcinoma in rats, guinea-pigs, dogs, or fowls, with tar. Nevertheless, carcinoma has been produced by tar in the uterus, urinary bladder, and stomach in rats, and in the gallbladder in guinea-pigs. Furthermore, sarcomas have been produced in rats and fowls by subcutaneous tar injection. These facts indicate an inherited species-characteristic difference in the susceptibility of different tissues to malignant transformation by a common agent. The fact that some animals of a susceptible species develop tar cancers quickly, some slowly, and some not at all, indicates that there are also individual differences in susceptibility. This is of course quite the same as the differences in susceptibility of x-ray workers or dye workers to cancer produced by the agents involved in their occupations.

The observation that the same agent may produce either sarcoma or carcinoma also affords evidence that these diseases are essentially the same. The apparent shading off of sarcomatous
proliferation into inflammatory proliferation is so confusing that we have felt far from certain that we might not some day learn that all sarcomas were inflammatory processes and essentially different from carcinomas. The experimental results point in the other direction.

The experimental production of cancer by tar has thrown much light on the relation of age to cancer. It has been found that young animals are fully as susceptible to the action of tar as older animals, and perhaps more so, but at any age considerable time is required to produce a cancer with tar. Some animals will develop carcinoma in a few weeks, but some require a year or even more. As Murray points out, if a population of mice, six months old, is started on a tar painting course, one obtains a cancer incidence curve similar to that in man, beginning at zero and continuing at that point for about four months, increasing rapidly in middle age, and then continuing to rise more gradually toward the end of life. Obviously, since young mice can develop cancer as well as old mice, senility of the tissues is not the reason why cancer affects mice and man chiefly in middle or old age, as we have commonly assumed. The explanation, as shown by the experimental work, is that a prolonged period of chronic irritation is usually necessary to produce cancer. It requires about one sixth of the normal span of a mouse's life to produce tar cancer, which would correspond to ten to fifteen years of a human life. This fits perfectly with the experience with occupational cancer from dyes, x-rays, tar, and other cancerogenic agents, for the cancer rarely appears until seven or more years have elapsed after the occupation has been begun; more often fifteen years are required, and it makes little difference at what age the victim began his disastrous occupation. These facts suggest that cancer of the stomach, breast, or uterus arising in a woman at the age of forty-five years, owes its origin to a slow, continued process which began ten, fifteen, or even more years before, and not usually to some event immediately preceding the growth. Cancer is, then, not essentially a disease of old age, dependent on senescence of tissues, but a disease of long irritated tissues, the necessary duration of irritation being seldom reached in the first half of life. This also seems to explain why authenticated cases of cancer following a single trauma are so rare.

The period of time that must elapse before cancer develops in mice subjected to tar painting varies greatly; it varies from three
months to a year or more, corresponding to variations in man of from seven years to thirty years. This indicates that among different individuals of the same species considerable differences in the susceptibility to cancer exist, and has its counterpart in the clinical experience that occupational cancer appears only in a fraction of the individuals following a given occupation. It is to be noted in this connection that the types of malignant neoplasms that seem to depend on protracted stimulation by mild injury, as skin cancer and gastric cancer, rarely appear in the first half of life. The malignant tumors that are seen in childhood, such as the retinal neuroblastomas, cerebellar gliomas, mixed renal tumors, and suprarenal neurocytomas, are largely those that seem to arise independent of chronic injury, perhaps owing their occurrence to developmental defects or hereditary factors. The trend of these results of recent cancer research is in support of the old view that cancer is usually the result of protracted stimulation of tissue growth by non-specific agents, acting on tissues the susceptibility of which is determined by their hereditary background.

II

Evidence Furnished by Statistics

Probably in no other field of medicine has the use of statistics in an attempt to answer problems been so general as with cancer, or so unsatisfactory. Presumably light on cancer has been largely sought from statistics because there are so few sources of light. Furthermore, statistical compilation and analysis is something anyone can do, without the necessity for employing ideas, originality, equipment, or even a knowledge of either cancer or statistics. That is why there are so many papers on cancer statistics, and why most of them are so useless. To those who take them seriously, they are also misleading. Perhaps the magic of numbers adds to the size of the group who are thus misled; conclusions presented in the form of exact percentages are so much more convincing than statements of impressions. If the mathematical conclusions can be supported by a statement of "probable error," the figures are overwhelmingly convincing to some.

Unfortunately I am such a poor mathematician that I get no thrill from medical statistics, at least not enough to enable me to be satisfied with the beauty of the mathematics for its own sake. As a very unmathematical pathologist, when I see figures
relating to diseases with which I am familiar, I am inclined to
think more about the disease than about the figures. It seems to
me that some of my statistically minded and trained friends are
thinking only about the figures and the mathematics, and for­
getting all about the disease. I have previously expressed my
lack of conviction as to the value of most of the cancer statistics
available (112), and as nothing I have been able to learn since has
served to change my views, I shall be compelled to restate much that
I have formerly said, with the introduction of such further evidence
as seems fitting.

It may be that my attitude is in large part due to the pictures
that are in my mind as I read the tables of cancer statistics. I see
more than the columns of figures; I see their origin. I see
some old grandfather lying in bed in the home of a working man,
complaining, as he has complained off and on for years, that
his food doesn’t agree with him any more, that his rheumatism is
worse than ever, and that he doesn’t feel like getting up in the
morning. After he has stayed in bed, complaining a few days,
the daughter-in-law says that grandpa has been failing lately,
and perhaps they had better get a doctor; but probably it’s just
old age and a doctor couldn’t do any good. Then one morning
they find the old man evidently much worse, coughing and com­
plaining of a pain in the chest. So the doctor over the neighboring
drug store is called in, finds the old man’s lungs full of râles over
the bases, the bronchi gurgling with mucus, and the pulse irregular
and feeble. He shakes his head, says the old man has heart
trouble and pneumonia, and things do not look very good, but
perhaps some of this anodyne expectorant mixture will ease the
cough, and they better keep his chest warm. So when two or
three days later the old man cannot longer keep his bronchi open,
and strangles slowly out of life, a death certificate is unhesitatingly
prepared which gives, as the cause of death, pneumonia with
myocarditis as a contributing cause.

As a pathologist I puzzle about what lay back of all this, for
sometimes such old men are taken to the hospital to breathe their
last, and if they reach the necropsy table, unexpected things may
be found, as a large ulcerating cancer of the stomach that did not
produce obstruction symptoms, or a diffuse bronchogenic carci­
noma of the lung, or a prostatic carcinoma with bone involvement
and profound anemia. I wonder, therefore, what all these columns
of figures mean that they should be taken so seriously—for I
know the way they had their birth, in laboring men's homes, in lodging houses, in hall bedrooms, in undertakers' "parlors," as well as in the homes of the relatively few who have good and adequate medical service for their old people, and in hospitals and institutions of all sorts and qualities.

And after thinking about what the figures may mean, and what they really do mean, and what others think they mean, I match up the impressions so obtained with those other impressions obtained from thirty-five years' observation of cancer in living people and in dead bodies, under the microscope, and in animals of many species, and I find myself able to accept little, if anything, about cancer as finally established by statistics.

This attitude is not uncommon among pathologists who are familiar with the large amount of error that occurs in the registration of causes of death, which serve as the basis of most statistical studies on cancer. For example, one of the leading German pathologists, Professor Lubarsch (63), after an analysis of practically all the autopsies performed in all Germany for a year (amounting to but 5 per cent of the deaths), estimated that about 50 per cent more cancer deaths occurred than were shown by the death records. In this great series of 8,301 cancer cases observed at necropsy, the diagnostic error for the internal carcinomas was 32.44 per cent, of which 17.35 per cent were failures to recognize the cancers; internal sarcomas showed a diagnostic error of 43.23 per cent, and even external carcinoma an error of 8.26 per cent.

I once checked up my own autopsy records of cancer cases (111), many of them from a large charity hospital where most of the cancer deaths are in persons brought into the hospital in extremis, dying usually from terminal infections and too ill for thorough examination, and found much the same thing as did Lubarsch. In a total of 578 cases, there were 211 incorrect diagnoses (178 omissions, and 33 erroneously called cancer), or a diagnostic error of 36.5 per cent. Such a high ratio of incorrect diagnoses in a great hospital might seem to be evidence of something wrong with the hospital, but we find that other institutions dealing with a similar class of cases, in which most of the cancers coming to necropsy are of the internal organs, exhibit not dissimilar figures. For example, the statistics collected by Bashford (4) from a number of London hospitals showed 112 internal cancers erroneously diagnosed, as against 284 correctly diagnosed, or 28.2 per cent erroneous diagnoses.
Many similar observations have been made by other pathologists in different parts of the world, indicating that vital statistics of cancer universally contain large and undeterminable errors, chiefly errors of omission of cancers of the internal organs. Conditions vary so much in different communities that it would be purely guess work to estimate the actual cancer incidence from the death certificates. And if the diagnostic error is large in the great city hospitals, it is presumably larger in the greater part of the population who die under conditions much less favorable for accurate diagnosis or recording of death.

I will even venture the suggestion that the frequency of diagnosis of chronic myocarditis in vital statistics varies inversely with the accuracy of the statistics, so commonly is it a refuge of ignorance; a safe retreat, since most people do die from cessation of myocardial activity, and it provides, furthermore, a diagnosis not likely to cause dissatisfaction or give rise to questions. It will be found the favorite diagnosis placed on the death certificates of old people who have not been subjected to careful study before death. For example, I have recently examined necropsy records from an institution where paupers die under conditions not usually permitting much medical study. Of 138 cases coming to the post-mortem table, 32 had been recorded on the death certificate as chronic myocarditis, and so entered in the vital statistics of the community. Of these, there were but six in which it seemed fair to consider that death was due to chronic myocardial disease, whether myocarditis or even general arteriosclerosis with terminal bronchopneumonia, in which cardiac inefficiency was perhaps a major factor. Four of the remaining 26 exhibited cancer.

Besides statistics based on death records there are cancer statistics based on hospital clinical records and on autopsy records. Are the latter any more satisfactory sources of information about cancer than vital statistics? Not a bit, for hospital and autopsy records always represent a selected material. If the records from a general surgical service are considered, it will be found that the cancers seen here are predominantly those so located that they may be attacked by surgery, cancers of the breast, uterus, and large bowel predominating; but if the institution is one with good facilities for radiotherapy the cases of cancer will be especially those of the skin, mouth, and uterus; whereas the autopsy records from a general hospital, especially the large charity hospitals, will seem to indicate that cancers of the skin, mouth, breast,
and uterus are relatively rare conditions, while more than half the cancers affect the alimentary canal, especially the stomach.

From the foregoing statements, it is at once evident that hospital statistics are bound to be misleading as to the frequency of cancer in different organs. Clinical observations indicate that cancers of the external tissues form a much larger proportion of the total incidence of cancer than they really do. Necropsy statistics deviate just as far in the other direction from the true relations, for they represent a selected group of cases, especially in respect to cancer. Consideration must be given to the fact that in relatively few hospitals are more than 20 per cent of the deaths followed by post-mortem examination, and that the cases that are so examined are preponderantly the cases that offered difficulty in diagnosis during life. There is much less incentive to secure a permit for a necropsy in a case that is of obvious character, and permission, if requested, is not so readily secured as in the cases that have been clinical mysteries. If a man dies of cancer of the tongue, or a woman of cancer of the breast, it is not easy to convince the relatives that a post-mortem examination is necessary to learn the cause of death. But a primary carcinoma of the liver, or one of the other less readily recognized internal cancers, will have offered diagnostic difficulties that stimulate the physician to make every possible effort to secure a necropsy permit, while the disease has often been mysterious enough to arouse the cooperative curiosity of the relatives. Hence rare internal growths appear more frequently in autopsy statistics than their actual incidence, and common external cancers less frequently.

In view of these and other facts that might be brought forward, it seems to me that we must admit that at the present time we have no available cancer statistics that give an even approximately accurate indication of how frequently cancer is the cause of death, how many people die of other conditions with undiscovered cancers not responsible for death, or even of the relative frequency of attack of different organs by cancer. We cannot have really reliable records until they are furnished by a large community in which, for a period of several years, all deaths are followed by post-mortem examinations, and as yet there is not a community that has reached anything like this degree of enlightenment. And even these figures, when obtained, will be valid only for the particular community.

We can use such statistics as we have, therefore, only with
great discretion, keeping before us always their source, their probable errors, and their probable relation to the whole cancer picture. With these facts in mind, we may try for ourselves to ascertain what information may be obtained as to the problems in which the solution is most sought by the use of statistics, especially these five:

1. What is the relative frequency of cancer in different organs or tissues?
2. What is the relation of cancer to other coexisting diseases?
3. What is the influence of heredity in determining the occurrence of cancer?
4. Is cancer a growing menace?
5. Is cancer a disease of civilization?

The Relative Frequency of Cancer in Different Organs and Tissues: As indicated in previous paragraphs, there is such a discrepancy in figures from different sources, and so large an error in both vital statistics and autopsy statistics, that it is not possible to answer the questions so often raised as to how frequently cancer affects various parts of the body. I think it is safe to assume that cancer of the stomach ranks first, affecting as it does both sexes, and ranking first, so far as I have ever seen, in all autopsy statistics on general hospital populations and in most statistics based on death certificates.\(^\text{12}\) Unquestionably the stomach is the commonest site of carcinoma in men, and there seems to be no doubt that gastric cancer is more common in men than in women. But whether in women it outranks cancer of the breast or uterus, or which of these last two leads the other, cannot be ascertained from any statistical material that is critically considered. Presumably if we did have satisfactory figures for any one part of the world’s population it would not hold for the rest of the world. For example, in the recent attempt on the part of the League of Nations to get some reliable cancer statistics, cancers of the uterus and breast were selected for consideration as offering types of cancer with a good percentage of correct diagnosis\(^\text{13}\) and recording. Nevertheless, there were found to be such wide

\(^{12}\) See, for example, the statistics of Norway, with gastric cancer accounting for 51.66 per cent of all cancer deaths; cancer of all parts of the alimentary apparatus for 66.59 per cent; of the uterus for 6.19 per cent; of the breast, for 4.94 per cent; of the skin for 1.43 per cent (Gade, 38); or the recent figures from Kiel: digestive tract, 65.49 per cent; stomach, 39.2 per cent (Harms, 43).

\(^{13}\) Although a surprisingly large number of cases of uterine cancer are missed, e.g. 10.2 per cent in the statistics of Berencsy and Wolff (8).
differences for the frequency of carcinoma of the uterus and the breast in England and in Holland as to defy explanation. There is fairly general agreement that Jewish women have cancer of the uterus much less frequently than Gentile woman (103)—3.9 per cent as compared with 16.5 per cent in the Mayo Clinic according to Horwitz (47)—and that Japanese women escape cancer of the breast much more than either Jewesses or Gentiles (45, 37, 54).

Even when we compare sex with sex in published general hospital autopsy figures we do not get useful information, because the recorders almost invariably fail to mention the relative proportion of the two sexes in the entire hospital population or in the necropsy material, despite which they usually write confidently of the relative frequency of various diseases in the sexes. But despite these deficiencies there seems to be no room to doubt that, outside of the generative tract, the bile tract, and the thyroid, neoplasms of all sorts are generally more common in men than in women, especially in respect to the skin, mouth, esophagus, stomach, and bladder. Beyond this it does not seem safe to go.

The Relation of Cancer to Coexisting Diseases: The relation of cancer to other diseases has recently been considered by statistical methods by Raymond Pearl (78), with particular reference to the reputed antagonism of tuberculosis and cancer. It is evident, of course, that much of the long observed lack of coexistence of cancer and tuberculosis depends on the difference in the ages at which each of these diseases occurs most frequently. Pearl thought that there was also an actual antagonism between the two at the cancer age level, and even undertook the treatment of cancer with tuberculin. The fundamental errors of such a conclusion are evident enough if one considers the natural history of disease rather than statistical cards. There would also be found a low incidence of active tuberculosis in a series of fatal automobile accidents, and a low incidence of acute appendicitis in a series of cancer cases, just as Carlson and Bell (14) found a low rate of coexistence of cancer in cases of heart disease. Fortune (32) found that the cancer cases observed on the autopsy table at the University of Michigan exhibited either active or healed tuberculosis neither more nor less frequently than cases in which death was due to any other major cause.
The Influence of Heredity In Determining The Occurrence of Cancer: In attempting to learn anything about the hereditary aspects of cancer, existing statistics are worthless. Such attempts as have been made are usually based on ascertaining the number of cancerous relatives possessed by a group of cancer patients, and comparing this figure with the number of cancerous relatives of patients who do not exhibit cancer. The sources of error in such a proceeding are many and some are obvious. In the first place, the material is a selected material. The statistics are usually compiled from hospital history sheets, the records having been made by interns in routine questioning of the patient at the time of admission. A large proportion of the patients who come to a hospital with cancer know this fact at the time the intern examines them. They have come to the hospital for relief from the cancer, if possible, and expect to be submitted to operation or other therapeutic procedure. Before taking this step they have usually talked over the matter with their families, and the family history of cancer has almost surely been discussed, often to a consideration of the most remote relatives. Therefore, when the intern asks these patients as to the occurrence of cancer in the family they can at once give him much information on the topic, although how accurate it may be there is no way of knowing. How many of their relatives who are supposed to have died of pneumonia or peritonitis, for example, really died of these conditions as terminations of a cancer, cannot possibly be ascertained.

The patients admitted to the hospital for some other disease than cancer have not made this preliminary survey of the cancer history of their families, and consequently their records are bound to show fewer cases of cancer in relatives than the records of the cancer patients, even if the number really is exactly alike in both series. Another inherent error lies in the fact that of the control material (the patients with other diseases than cancer), a certain proportion are going to develop cancer at some later date, and yet are being used as non-cancer material.

Furthermore, this method of statistical study of heredity is based on the assumption that each individual inherits a certain fraction of each feature of his make-up alike from each of his ancestors, an assumption now known to be incorrect. If we attempt to work out the heredity of cancer with human statistical material, using the mendelian principles of inheritance, we find that this is impossible, for a single error of diagnosis could invali-
date an entire family record, and there are probably no existing families with complete necropsy records of all the deceased members for any considerable period. At present we can secure direct evidence of the influence of heredity on the occurrence of cancer in man only by the intensive study of compact families that have been under good medical observation for a long period of years, as has been done especially by Warthin. Further information on the influence of heredity on the occurrence of cancer must be obtained by application of the results of heredity studies on lower mammals.

Is Cancer Increasing in Frequency: This problem has been attacked from the statistical side with far more enthusiasm than critique. All statistics agree in indicating that the proportion of deaths recorded in civilized communities as the result of cancer has been increasing for several years, but the exact significance of this fact is not yet agreed on. It is perfectly evident that the average age of the people of these communities has also been increasing during the same period, partly from lowered birth rate, partly from reduction in the mortality from tuberculosis, typhoid, diphtheria, and numerous other infectious diseases that attack the young, especially the infantile diseases. Obviously, every person saved from death in youth becomes a potential victim of cancer in later years, and consequently every improvement in public health leads to an increased cancer mortality. Should a means be found to cure or prevent effectively the last remaining large group of infectious diseases, the acute respiratory infections, there would result a marked augmentation of cancer mortality in the following years, just as during the influenza epidemic the cancer rate was low. A high crude cancer death rate is evidence of a good state of public health, being in direct proportion to the degree of control of preventable diseases. We find, therefore, high cancer rates in Switzerland, Denmark, Holland, and other such well governed, well educated communities; the low rates are in Serbia, Jamaica, and other countries occupied by less advanced populations.

Likewise, every forward step in diagnosis, hospitalization, and medical observation adds to the number of recorded cases of cancer. The roentgen rays have undoubtedly added far more cancer diagnoses to the vital statistics than they have kept from the death records by their therapeutic effects. The motor car, by shortening the distance between patient and physician, un-
questionably increases the number of recognized cases of cancer. The growing frequency of post-mortem examinations is also adding many cases of cancer to the records that otherwise would have been unrecognized.

Furthermore, even in the ages past forty, the improvement in diagnosis, hospital care, and therapeutics are undoubtedly saving some lives from diseases other than cancer that would have been lost under the conditions of from twenty to thirty years ago, and the prolongation of life by these means is undoubtedly even more marked. Many of these persons are saved from other deaths to die of cancer. The introduction of insulin, for example, will undoubtedly permit not a few persons to die of cancer rather than of diabetic coma; the earlier recognition and better management of hypertension will also unquestionably increase the cancer death rate in persons past forty.

Another important factor in the increasing cancer rate is the improved recording of vital statistics. In many countries the older rates are based on death records a large proportion of which were filed by non-medical persons, in some places the parish priest, in others the undertaker, often by friends and relatives. Laymen rarely report deaths as due to cancer, and in some communities a large proportion of the death certificates have been filed by laymen. The great influence of this sort of certification on cancer statistics has been well discussed by Willcox (114).

A large error in earlier statistics also lay in the recording of deaths of old people as resulting from "senility," "old age," and "causes unknown." The refusal of authorities during recent years to accept this sort of diagnosis has been responsible for transferring many cases to the list of deaths from cancer. The trouble is that there is no possible way to learn how many such transferred cases there are in any set of vital statistics.

We cannot disregard the great error introduced into the vital statistics in many places by wilful falsification of death certificates, in deference to a popular sentiment that there is something discreditable or disgraceful in cancer—perhaps a relic of theories that cancer is a form of syphilis or an evidence of decadence. There is no doubt that in some communities this has been an important factor in keeping down the figures of cancer mortality. To illustrate its importance I quote part of a speech by Delbet (22): "In France it is impossible to prepare accurate statistics of cancer. In many small towns practitioners never record a
diagnosis of cancer upon the death certificate. Some have told me that if they did so they would lose all their patients because of the stigma that widespread and incorrect ideas as to the inheritance of cancer would cast upon a family a member of which had died of cancer. The cancer committee appointed by M. Strauss, the Minister of Hygiene, has discussed this matter and failed to find a solution. The law relating to professional secrecy is still in force; it is a violation of that law to enter a diagnosis of cancer upon the death certificate. The Minister of Hygiene cannot expect medical men to do something which his colleague, the Minister of Justice, will penalize."

Similar conditions also obtain, to a less degree I hope, in some parts of America. Of course, with advance in popular education and medical efficiency these intentional erroneous diagnoses will be replaced by honest ones, with an apparent rise in the cancer rate.

If we take the statistical studies that have been published during the last decade on this topic of cancer increase, there seems to be a certain line that can be drawn, depending on what sort of cases is being considered. Those who take the entire mass of cancer statistics are impressed with the vast increase in the crude rate, and consider that the subtractions they feel required to make on account of the various factors previously mentioned cannot account for all the increase. On the other hand, those who select for consideration only the external cancers, which are less likely to be incorrectly diagnosed or recorded, usually fail to find any tendency for these types of cancer to increase. For example, Willcox finds that the corrected rates for accessible and inaccessible cancer in Frankfort for the period from 1860 to 1913 show that the increase was limited to inaccessible cancer, the rate for accessible cancers remaining stationary. Therefore, the increase was probably due to improved diagnosis. An analysis of the cancer deaths in Stuttgart from 1873 to 1902 by Weinberg and Gastpar (109) indicated an increase in cancer of the stomach and other internal organs, but a decrease in cancer of the breast and uterus. These writers remark that "the mortality of neoplasms of the uterus has fallen in Berlin quite as much in half the time (fifteen years) as in Stuttgart; in Hamburg it has increased little or not at all, and the same is probably true for Frankfort-on-the Main."

Renaud (84) likewise reports that in recent years the number of visible cancers is stationary or declining, except for mammary
cancer in Switzerland. Peller (80) has studied the statistics for several countries, and finds that in men over thirty-five years of age there is little if any increase in cancer of the skin; in England and Wales, for example, the rate for 1909 was 43.5, in 1868 it was 45.7. In the same countries cancer of the female generative organs and breast shows little change in frequency, the rate being 117 in 1888, 127 in 1909, and 121 in 1919.

Dublin reports that in the enormous number of people coming under the industrial department of the Metropolitan Life Insurance Company, a large proportion of whom were in the ten registration states, the records of cancer "show no decisive upward or downward tendency for all age classes combined" in the period from 1911 to 1916 inclusive.

More and more, recent discussions of cancer statistics have come to take into consideration the various sources of error and deception, so that in the last few years the greater number of papers have ended with the conclusion that, in proportion to the population of cancer age, the death rate from cancer shows little or no actual increase. Among those arriving at this conclusion, I may refer to Dr. Georg Wolff (121) of Berlin, who concludes that between 1910 and 1925 there has been no actual increase in cancer mortality in Berlin; to Faulds (29), who found no marked increase in cancer in his English statistics; to Stage (97), who compared the figures in Copenhagen for 1890 to 1894 with those for 1915 to 1919, and concluded that the recorded increase of 23.3 per cent is for the most part only an apparent increase due to a shifting of the population to the older age groups; to Junghanns (49), who analyzed 36,408 necropsies performed in Dresden between 1893 and 1927 and found a decrease in many common types of cancer, and an increase chiefly in pulmonary cancer; to Gruber (40), in Innsbruck, who found the autopsy records from 1869 to 1927, 17,164 in all, to indicate but little change in the percentage of malignant disease of males and a decrease for female cancer. Hadda (41) observed no change in the cancer death rate for the last twenty years in Breslau, when correction was made for age; Heiberg (44) states that during the years 1905 to 1924 there was no change in the death rate from cancer of the stomach in persons between the ages of fifty-five and sixty-four years in Copenhagen, and Dunlop's careful study of the cancer deaths of Scotland (26) led to the conclusion that there had been no true increase, except possibly for mammary cancer.
If I were to take of the statistics the only ones that seem to me, as a pathologist, likely to be reasonably accurate, namely, the data on external or accessible cancers, corrected for age and sex, I should have to conclude that in all probability cancer is increasing to just about the extent that people are kept from dying of something else. It seems to me that the improvements in diagnosis, the increased age level, and the many new means of prolonging life even in people who have reached cancer age (a

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factor that is, by the way, largely unconsidered) are fully sufficient to account for all the observed changes. And in support of this is the fact, also too little emphasized, that the increase in the cancer rate is just about the same as the increase of the other three common causes of death in those who have passed the prime of life, namely, cerebral hemorrhage, nephritis, and heart disease. Diabetes, which is chiefly an old age disease, shows the same trend. Witness the figures on the percentage change in death rates from the vital statistics of Chicago (Table I). The rising tendencies are shown more graphically in the accompanying chart.

An analysis of the same records, to bring out the rate of change of the death rate according to age groups, shows that for heart disease, nephritis, cancer, and cerebral hemorrhage the death rates have been increasing about as rapidly for one as for another in the periods 1910 to 1920, 1920 to 1925, and 1910 to 1925. Evidently, all the diseases of old age are increasing because old age is becoming a more common condition. Why, then, the particular excitement about cancer?

I would not have it thought that I am denying the possibility that there is a real increase in cancer in people of cancer age. All that I am willing to say is that, as far as the statistical evidence goes, it seems fully as justifiable to conclude that there is no real
increase, except to the extent that all diseases of advanced life are increasing because a larger proportion of the population reaches advanced life. It is, nevertheless, perfectly possible that changes in the cancer rate are really taking place; I believe they are, but the errors in our statistical material do not permit us to determine them. For example, a smaller proportion of the population are now engaged in outdoor occupations, which theoretically favor the development of cancer of the skin of the face. Chimney sweeps' cancer is decreasing or vanishing with modern house construction and heating in the countries where it once occurred. Bladder cancer may be increased as an industrial disease through the development of dye factories. Perhaps changes of diet or culinary technic may influence the occurrence of cancer of the stomach—but in which direction there is no reliable evidence. There seems to be little doubt that primary cancer of the lung is now a more common disease both in Europe
and America (96, 7, 52, 36) than it was even ten or fifteen years ago.\textsuperscript{16}  

My object is not to deny the existence of an increased frequency of cancer, but merely to indicate how unconvincing the evidence appears to one whose daily observation impresses him with the inaccuracy of the recorded statistical data.

Cancer as a Disease of Civilization: The current statement that cancer is relatively rare in what many are pleased to call uncivilized races, despite their including in this group races of vastly older civilization than our own, rests on the most worthless of evidence. For the most part it is not even supported by statistics, but rests merely on the statement of one or a few physicians practising in remote countries that they have seen few cases of cancer; or the remarks of a medical traveler that he found few or no cases of cancer among the members of some primitive tribe. But for primitive peoples vital statistics do not exist.

Any conclusions are unwarranted on the basis of the evidence presented, because this evidence lacks information as to the age of the population under consideration. We know that, except under conditions of civilization, old age is an untoward and unusual occurrence, and hence there are relatively few who reach cancer age in uncivilized or backward countries. The expectation of life for males in India is said to be 26.6 years as against 54 years in the United States. What, then, is the chance of a native Hindu reaching cancer age as compared to an American? Again, among

\textsuperscript{16}As explanation of this increase in the frequency of pulmonary cancer the most favored factors have been: (1) irritation by gas from automobiles and industries; (2) dust from tarred roads; (3) influenza. It seems to me that the first two theories are eliminated by the fact that the same increase has been observed in countries where these factors are not important, e.g., Russia. In favor of the third is the striking epithelial proliferation seen in healing influenza, often resembling carcinoma. I quote herewith a prophetic statement published by Winternitz in 1920 (117): "It is rare to see such activity on the part of the epithelium as that frequently encountered in influenza. The alveoli may be lined by newly formed cubical cells, and mitotic figures in the injured bronchiolar lining occur in abundance. This might lead to the supposition that, if the epithelium were restricted in its path of development, it would pile up to form a typical nest, just as the epithelium at the edge of a healing chronic ulcer of the skin may pile up and extend fairly deep into the tissue. In a number of cases, epithelial proliferation has been so extensive that it could not be differentiated histologically from an invasive, malignant neoplasm. There is no reason to believe that malignancy might not result from the continuous stimulation of the epithelium to proliferate, in the chronic inflammatory process of the lung in influenza, just as chronic infection in the lung of a mouse results in a much higher percentage of spontaneous neoplasms of the respiratory tract in this species than in those animals where chronic pulmonary inflammatory processes are uncommon. It will be interesting, indeed, to see whether, as a late manifestation, there is an increase in the number of now relatively rare epithelial new growths in the respiratory tract of man." (Italics mine, H. G. W.)
primitive people it is especially the old persons, of cancer age, that the foreign physician does not see. They stay back in the hills, dreading the foreigner and his innovations, relying on the native medicine man. Only the young people are likely to visit the missionary doctor or other foreign physician.

Looking over the literature on malignant disease among the uncivilized races or among peoples of backward culture, the pathologist is struck with the fact that so large a proportion of the reported cases are sarcoma; in fact, sarcoma is often said to be more common than carcinoma in such people. This fact at once indicates that the physician making the report is seeing chiefly young people, for until about thirty years of age, sarcoma is more common than carcinoma, according to the best evidence we have for our own people (110, 86).

Of course, in undeveloped countries the chance of internal cancers being recognized is small, and of the cancers described in such places most are of accessible parts of the body. Rogers found that the rate of malignant tumors in the Calcutta necropsies was only one third as high as in London, but when the age of the patients was taken into account it was found that in the subjects over forty, cancer is quite as frequent in Bengal. Every sort of cancer known in America or Europe has been found in members of black, yellow, and brown races, and it has been repeatedly observed that, as Rogers said, "where the exciting cause is present, there will cancer result in primitive tropical people of the cancerous age at least as readily, if not more so, than in the civilized races of temperate climate." Even the highly primitive Australian aborigines show various types of cancer, and some physicians have reported cancer as common among them (Cleland, 17).

The supposed increase in cancer among primitive peoples when they are in contact with modern civilization, as in the American negroes, may well be only a matter of civilization revealing the cancers, not causing them. It will be found that in places where negroes and white people have the same sort of medical attention, the supposed discrepancy in the frequency of cancer among them is greatly reduced. Only a relatively short time ago cancer was supposed to be uncommon in the Japanese, even as it is now said to be in China. But when Japan developed an educated medical profession to recognize and report diseases, it was found that cancer was about as common there as in Europe, and presumably it always had been (100, 42), unless one is prepared to accept
the idea that Western education has caused a sudden manifold increase of cancer in the people of an old established civilization. It is to be expected that a similar story will be repeated for China, with the new educational movement now going on in that great country (69).

Again, on the basis of the statements of occasional travelers and physicians, cancer has been commonly reported as rare among the Eskimos; but when a systematic inquiry was conducted in Greenland by the Danish Medical Association, it was found that cancer is quite as common as in Europe if proper correction is made for age (31). In the natives of South Africa cancer, formerly thought to be rare or non-existent, was found to increase rapidly as hospitals and dispensaries were opened for the natives (2). The incidence of malignant disease among the Annamites of Cochin-China was found to be approximately the same as in Europeans, when investigated by French physicians (3).

On the other hand, it is biologically reasonable to assume that there really are racial differences in cancer susceptibility, just as we find a marked difference in the susceptibility of different animal species. These differences may concern the constitutional susceptibility to cancer as a disease, or the susceptibility of different organs to cancer, just as we find the mammary gland of dogs and mice highly susceptible to cancer, while in the cow this organ is immune. For example, it seems probable that negroes are more prone to develop fibrous tissue overgrowths, especially keloids and uterine fibroids, than most groups of white people, and there is good evidence that the negro skin is relatively unlikely to develop cancer, perhaps because of the protection against light afforded by the melanin. It is also quite within reason to expect to find that certain customs will introduce an amount of stimulation leading to cancer formation in certain tissues, as in the cases of kangri cancer and betel nut cancer. In China, for example, carcinoma seems to attack the penis with great frequency (25), while many dark skinned races show a high incidence of cancer of the liver (89, 5), probably associated with parasitic infestation and cirrhosis of the liver.

In view of the results of experimental studies by Maud Slye and others on the influence of heredity on the occurrence of cancer, variations in susceptibility may be expected to occur among different races and tribes of men, just as they unquestionably are exhibited in different species of animals. Especially with primitive
people, there is relatively close breeding as compared with the promiscuous matings in civilized lands. Hence, it is to be expected that certain tribes or races may have developed cancer-resistant or cancer-susceptible strains, which would show a distinct difference from one another if we could have them under observation long enough and closely enough to learn just what the cancer incidence really is. Unfortunately, at the present time such information is completely lacking.

**Tumors in Children**

A statistical study of tumors in young children brings out interesting facts when compared with figures for adults. Epstein (28) has recently analyzed 1000 autopsies on children dying before puberty at the Children's Memorial Hospital in Chicago, in which 16 malignant tumors were found, namely six gliomas of the cerebellum, one retinal glioma or neuroblastoma, one neurocytoma of the adrenal, one malignant ovarian tumor, two embryonal adenomyosarcomas and one round-cell sarcoma of the kidney, one multiple chloroma, one multiple myeloma, and two retroperitoneal sarcomas. There were two ganglioneuromas, one mediastinal and one renal. Particularly striking was the fact that in these thousand children there was but one instance of an ordinary benign tumor, such as is so common in adults, this being a single polyp in the cecum of a three-year-old girl. In the autopsy records of a thousand Filipino children Mendoza-Guazon (70) found one adenoma of the intestine, one case of "fibromata" of the liver capsule, and one of adenoma of the intestine associated with a myxoma of the heart. The only malignant tumors in this series were two cases of retinal glioma and one of adenomatosis of the adrenal.

These autopsy statistics bring out not only the well known infrequency of carcinoma in the young, but also indicate that ordinary sarcomas are rare in childhood, most of the malignant tumors in the young being derived from the nervous tissues. A less appreciated fact also brought out is that the common benign neoplasms require years for their development, quite like carcinomas and sarcomas. In order to get more light on this, I have examined one thousand of our autopsy records from adults of all ages, finding 208 benign "tumors" that had been listed on the anatomical diagnosis. This does not include so-called adenomas of the thyroid, or adenomatous hyperplasia of the prostate,
the neoplastic nature of which condition is even more dubious than that of most of the rest of the local overgrowths that by courtesy are called benign tumors. The "tumors" listed were: adenomas, 49; carcinoid of the appendix, 1; fibromas, 10; uterine fibroids, 74; hemangiomas, chiefly of liver and skin, 23; lipomas, 10; neurofibromas, 4; papillomas, 5; polyps, chiefly intestinal, 32.

III
EVIDENCE FURNISHED BY GENETICS

In seeking to learn whether the occurrence of cancer in man is in any way dependent upon his heredity, the usual method, until recent years, has been to compile statistics on the number of relations of cancer patients who exhibit cancer, as compared with the relations of control subjects who did not have cancer at the time they furnished the information for the statistical study. Many such studies have been published, clinical histories of the patients of large hospitals generally having furnished the material used for analysis. Critical consideration of such contributions at once shows that they must be worthless because of the numerous sources of error in the material furnished for statistical study. The usual casual clinical histories are extremely unreliable, not checked by adequate investigation or cross examination. Even if the facts were more carefully gathered, the results would probably be quite as unreliable, because, as has been pointed out above, the average cancer patient before coming to hospital has discussed the matter with members of the family and is quick to answer questions as to cancer in the family, whereas the control subjects, who have entered the hospital for some other condition have much less information to impart. It is not strange, in view of these facts, that almost invariably such statistical studies have indicated that cancer patients have more relatives with cancer than patients who do not have cancer and, therefore, that the impression long prevailed that heredity did play a part in determining the occurrence of cancer, although apparently not a very important part, since many persons with cancer knew of no relatives with cancer, and many persons with cancer had children who did not develop this disease.

A statistical study published in 1904 by Karl Pearson (79) indicated that there was very little difference in the frequency of cancer among the relatives of cancerous and non-cancerous patients in the Middlesex Hospital of London, and as the mathematical
study had been made most carefully by an expert, it was widely accepted as conclusively settling a long vexed problem. It was commonly referred to as proving that heredity had nothing to do with human cancer, and has ever since its publication exerted a great influence on medical opinion as to this important matter. But if we go back to the original papers, we find that Pearson's meticulous studies were made upon about as worthless a material as it is possible to find, namely, the brief replies of the ignorant patients of a great public charity hospital to examining physicians filling out blanks. This non-committal result, therefore, is not of as much significance as was formerly believed.

In an attempt to secure more reliable family histories in respect to cancer, Little (59) has used the family history records of the Eugenics Record Office of the Carnegie Institution, which have been furnished by persons of intelligence, conscientiously endeavoring to provide accurate family histories for scientific purposes. Analysis of these records suggests that cancer occurs much more frequently among the descendants of cancerous parents, or in persons with cancerous relatives, than is to be expected from the general cancer mortality figures. However, we have here the usual defect in that the occurrence or absence of cancer is based on only the layman's belief concerning the cause of death of relatives, and the vital statistics used for comparison are of no more accuracy than any statistics not based on necropsy records, and probably give too low a cancer rate. We know from numerous studies that a very large proportion of cases of cancer are never recorded in the vital statistics, the deficit apparently being from 20 to 35 per cent even at the present time. Undoubtedly it was even higher in the days of the ancestors whose cancer incidence is being sought. Still another error lies in the fact that the controls in most of these studies consist merely of persons selected as not having cancer at the time the history is taken, without regard to the fact that presumably 10 per cent or more of them will develop cancer at some later date. Family history records can have no value in the study of mendelian inheritance if they contain even a single error in an entire family tree, since this would lead to entirely erroneous conclusions as to the method of inheritance. Hence existing human cancer statistics and records with their vast inherent error cannot possibly serve to solve the problem of whether and how heredity influences the occurrence of cancer.
Familial Cancer

But if statistical studies cannot furnish useful information, other sorts of evidence are offered by human material that are at least suggestive. One of these is the recognized occurrence of cancer families. Some of these families have become classical in cancer literature. Such is the Bonaparte family, for Napoleon I, his father, his brother Lucien, and two of his sisters, Pauline and Caroline, all were believed to have died of cancer of the stomach. One of the most remarkable is the family of Madame Z, reported by Broca in 1866, and mentioned in virtually every discussion of heredity in cancer since that time. Many more such families might be described. The chief trouble with most of these reports is that they do not include all the non-cancerous members of the family, and hence we cannot always be sure that the incidence is really as exceptional as it appears. Furthermore, they have, of course, the defect of depending only on family traditions and belief as to the cause of death. Also, we must consider that in family records with a high incidence of cancer, no matter how high the proportion is, the possibility that the heaping up of cases in these families may depend on chance cannot be evaded. Granted that of the entire population past forty, about 10 per cent will have cancer, the laws of probability would determine the occurrence of occasional families in which a high proportion of cancer cases would occur if heredity had no influence at all.

But when we find families that have many cases of a certain sort of tumor which is not common, or a tendency to frequent location of a certain tumor in a certain place, the hypothesis of coincidence becomes inadequate. The retinal glioma families afford outstanding examples of such unquestionable hereditary influence. Glioma of the retina is a rare neoplasm, which is remarkable in that it often occurs in infants or even at birth. Its familial occurrence is equally striking, and we have numerous records of families in which several individuals have been destroyed by this growth.

Another tumor of markedly familial occurrence is multiple neurofibromatosis, which often affects many members of a family for many generations. Davenport (20) thought he found evidence, from an analysis of 243 cases, that the hereditary factor behaves as a dominant, coming down equally well in either male or female lines, and affecting the two sexes alike. Sometimes, however, there is a failure of dominance and generations are skipped.
Another form of benign neoplasm with an extremely marked hereditary character is multiple cartilaginous exostosis. Here the behavior suggests a mendelian dominant character, as in the family reported by Pokrovsky (82). Multiple subcutaneous lipomatosis also appears as a familial condition, occurring, in some families at least, in a way to suggest a sex-linked recessive (58). Multiple benign cystic epithelioma is another growth that has a distinctly familial distribution. These growths, which usually more or less resemble carcinoma histologically, sometimes become malignant. Adenomatous polyposis of the large intestine, with a marked tendency to carcinomatous transformation, often exhibits a familial occurrence, as in the family histories reported by Lockhart-Mummery (60) and the family reported by Jüngling (50), with 15 recognized cases in three generations, with an inheritance suggesting a dominant character. Melanotic neoplasms of the choroid coat of the eye, themselves rare tumors, have in several instances attacked several members of the same family. Davenport (20) has reported one family in which this disease was observed in four generations.

Warthin (108) particularly called attention to the fact, mentioned also by Pearson, that not only are there cancer families, but also families that seem to be highly resistant to cancer. He cited his own family, with some 9,000 blood descendants from an eighth great grandfather, among whom cancer has been uncommon. He said that cross lines had brought in very little cancer, and these had made little or no impression on the family stock, the disease quickly disappearing when introduced. This suggested to him that in some human strains there is a marked resistance to cancer, behaving like a dominant character.

Some writers have looked upon the fact that cancers occur at such a nearly constant level, at least in those communities that furnish the best vital statistics, as indicating that heredity must play a rôle in producing human strains with a fairly uniform cancer susceptibility and resistance. Thus Miche (72) of Geneva, comparing statistics of malignant and benign tumors with the predictions that can be derived from mendelian rules, concluded that the etiology of these tumors is purely hereditary and mendelian.

Another item of evidence is furnished by those cases in which identical tumors occur in identical twins. Several such cases have been reported. I have personal knowledge of two pairs of
identical twins, all four dying of malignant tumors arising in the
testicle. In one pair of twins the tumors appeared within a few
months, but in the other pair the interval was of a few years (16).
But in each pair the corresponding testicle was affected and the
histology of the tumors was the same. Particularly striking is
the report of Leavitt (56) of the occurrence of identical cerebellar
tumors in identical twins, one at six and one-half and the other
at eight and one-half years. It must be admitted, however, that
the evidence furnished by tumors in identical twins is not large,
for relatively few such cases have been reported, and we have no
information as to how frequently it happens that one of a pair of
identical twins has a neoplasm without a similar tumor in the other.
But since many different sorts of tumors have been found duplic­
cating one another in the corresponding sites in both of pairs of
twins, they at least furnish evidence that the site of tumor occur­
rence may be determined by heredity, as do also the families with
adenomatous and cancerous growths in the colon.

Evidence from Animal Cancer

Satisfactory evidence in respect to most inheritable qualities is
usually difficult to get from human material, and unsatisfactory
because of the fundamental facts that the human life cycle is
long, the families small, the matings unselected and perhaps
uncertain. We therefore are forced to seek for evidence from the
domestic and laboratory animals, which offer larger and better
controlled genetic material. In order that such evidence may be
valid, it has first to be established that the principles of inheritance
are the same in man as in the other animals, and that the tumors
of man and other mammals represent fundamentally identical
conditions.

In respect to the first point, it is accepted by biologists that the
fundamental principles of genetics apply for all multicellular
organisms; otherwise there could be no orderly reproduction of
species. We have only to recall that these fundamental principles
were first established by botanists working with such things as
peas and corn, that the zoologists found that the laws governing
heredity in plants applied to birds, mammals, and insects, and
that in those human diseases in which the genetics can be studied,
such as color blindness or hemophilia, the same principles are seen
to be governing the hereditary manifestations.

As to the identity of the human and animal tumors, that
question has been thoroughly settled to the satisfaction of pathologists. As previously stated, tumors in all mammals represent essentially the same conditions, the differences having to do merely with the frequency of involvement of different tissues in different species.

Assuming, then, that the evidence in respect to both the genetics and the neoplasms of the laboratory animals may be utilized in studying the influence of heredity on the occurrence of cancer in man, we turn to that evidence and find that it unequivocally indicates that there is such an influence. As far back as 1864 Virchow pointed out the hereditary nature of the pigmented tumors which occur in the skin of gray horses. In more modern times Tyzzer (105) made observations suggesting that “one of the factors in the development of tumors is to be found in an inherited character or peculiarity.” Still earlier, Leo Loeb (61) had suggested heredity as an explanation of so-called cage epidemics in laboratory animals and the occurrence of “epidemic” conjunctival carcinoma in cattle. Murray (74) and others made early suggestive observations, and a much more extensive study was reported by Leo Loeb and Abbie Lathrop (55, 62), showing that heredity undoubtedly is an important factor in determining the incidence of mammary cancer, for strains were established which ran an almost constant proportion of subcutaneous cancer for several generations, with rates as high as from 58 to 65 per cent.

Furthermore, as pointed out previously, comparative pathology strongly indicates an influence of heredity on the occurrence of cancer, in that certain types of tumors occur more commonly in one species than in another. Possibly the recognized susceptibility of negro women to fibroid tumors in the uterus, and the apparent low incidence of breast cancer in Japanese women and of uterine cancers in Jewish women, may depend on hereditary factors.

The experimental studies on the occurrence of spontaneous tumors in mice reported from the Otho S. A. Sprague Memorial Institute by Maude Slye differ from those reported by others, not only in the period of time and magnitude of the material, since over 90,000 pedigreed mice have been closely studied more than twenty years, but in the fact that not one of these mice has been subjected to any artificial influences that might modify its life, which is prolonged by careful hygiene as much as possible.

Out of this work many facts have come, and much has been
learned concerning the influence of heredity not only on the occurrence of cancer, but also on its behavior. A vast number and a great variety of tumors, from mice of long-established pedigrees, have come under observation, and Miss Slye seems fully justified in her conclusion that her results prove clearly that heredity is a most important factor in determining not only the occurrence, but also the site, character, and in some respects the behavior of cancer.

Whether or not she has completely established the hereditary mechanism of cancer as a simple mendelian inheritance, as her observations indicate, she has unquestionably shown more conclusively than had previously been done that heredity is an essentially important factor in determining whether cancer will or will not appear under ordinary conditions of life, and in particular she has demonstrated that heredity determines in large measure, perhaps entirely, in what site and with what type of structure cancer will appear. For example, in certain strains, sarcoma is very common; in others it is seen rarely or never. In some strains one seldom sees any form of malignancy except mammary gland cancer. Miss Slye has developed one strain of mice whose inbred and hybrid derivatives have yielded more than a hundred primary liver tumors, although in all the other mice examined post mortem in her laboratory not a single liver tumor has been found, and only two other cases have been reported from the thousands of mice examined in other laboratories. Another strain has yielded a considerable number of tumors of the testis, although not a single case has ever been reported from other laboratories. A single small strain of mice has yielded numerous primary tumors of the thyroid, although no thyroid tumors have ever been reported in mice outside of Miss Slye's laboratory.

Miss Slye reports that the resistance to cancer in her mice behaves in breeding like a typical mendelian dominant character. The susceptibility to cancer behaves as a mendelian recessive. She says that when a cancer mouse, derived from the crossing of cancer mice, is crossed with a mouse free from cancer and derived from ancestors that never have shown cancer for many generations, the resulting hybrids of the first generation never show cancer. If such hybrids are bred together or with other hybrids of similar ancestry, cancer will appear in the offspring in mendelian proportions, and strains of (1) pure cancer mice, (2) pure cancer resistant strains, and (3) heterozygous strains, can be extracted
exactly as with any other inheritable "unit character." This fact has been observed by her so many times and with such constancy that she feels certain that her work has established her conclusions.

While we have no similar material to compare with Miss Slye's, in which the complete ancestry for many generations is known, all animals permitted to reach a maximum age, and every dead animal for from twenty to fifty generations submitted to careful post mortem study, yet such study as others have made of the influence of heredity on spontaneous cancer serves to corroborate at least the fundamental point—that heredity is a most important factor in determining the absence or occurrence of cancer. For example, in the Crocker Laboratory at Columbia University, numerous experiments have been carried out with rats infested with a certain tapeworm, *Taenia crassicollis*, which passes its encysted stage in the liver. In some of the infested rats sarcomas develop in the liver as a result of the irritation or growth stimulation. It has been found that different strains of rats differ greatly in their tendency to develop sarcomas in response to this common stimulation of the tissues, some giving a high percentage and some a low percentage of positive results. Wood has reported that when rats that developed sarcoma were bred together, much higher rates were obtained in the offspring, such families sometimes giving 100 per cent of positive results. From the same laboratory there have been reported a large number of cases of spontaneous tumors of the thymus occurring only in a single strain of rats, while certain other tumors predominated in other strains (19), independent of known stimulating agencies.

Another piece of work which may bear on the subject of heredity and tumor formation is that of Stark (98), on a lethal neoplastic process resembling melanoma, discovered by Bridges in a fruit fly, *Drosophila melanogaster* (*amelophila*). If this growth of the fruit fly larvae is a true tumor, it furnishes a remarkably clear instance of a neoplasm that occurs solely on a basis of heredity, which has been worked out conclusively. In the affected strains it is found that one-fourth of the larvae die, and these are all males; i.e., one-half of all the males die. Therefore, this inherited lethal growth behaves in inheritance as a sex-linked recessive factor. Miss Stark (99) has also described what seems to be a benign tumor of the fruit fly which has a more complicated genetic background.
Miss Lynch (64) has reported strains of mice with a high incidence of lung tumors, although, unlike Miss Slye and Miss Stark, she considers the susceptibility of these tumors to be dominant. More recently Dobrovolskaia-Zavadaskaia (24) has reported a limited study of the inheritance of mammary cancer in mice with results agreeing with the assumption that, at least in this strain, the occurrence of cancer resembled that of a recessive mendelian character. But Marsh’s study (66) of two strains of mice with mammary cancer led him to the conclusion that, while the influence of heredity was clear, the behavior on crossing with wild mice (obviously of unknown pedigree and cancer history) showed “inconclusive evidence of simple mendelian inheritance with dominance.” On the other hand, Mathews and Walkey (68), in discussing lymphadenomas of fowls, say that the “bulk of the evidence supports the theory that the lymphoid neoplasms are inherited as a mendelian recessive characteristic.”

Obviously the genetic mechanism of the inheritance of susceptibility to cancer is still an unsettled problem, but data are now being accumulated in many places which should soon clear up many of the now apparently contradictory contributions.

**Mechanism of the Hereditary Influence**

In view of all the experimental evidence cited above, and the absence of any experimental evidence that contradicts it, the conclusion seems inevitable that the incidence, character, location, and behavior of tumors depend, to some extent at least, on the inherited qualities of the animal and of its tissues. This being granted, the next question is: How does heredity determine susceptibility or resistance to tumor formation?

Apparently this may be answered as follows: Tumor formation is the result of stimulation of the tissues to growth, the stimuli being of various sorts and non-specific. Some stimuli produce marked proliferative effects in proportion to the regressive effects, and such stimuli are particularly capable of leading to neoplastic proliferation, e.g., roentgen rays, coal tar. The same amount of stimulation does not produce equal amounts of proliferative reaction in all individuals, even when of the same species; e.g., negroes are more likely to develop excessive amounts of connective-tissue growth (keloids) in response to cutaneous injuries than are white men, and some white men develop more scar tissue than others from similar wounds. Not all roentgen-ray workers
develop the same degree of hyperkeratosis from the same amounts of exposure, and some develop roentgen-ray cancer much sooner than others. Hence there are individual variations in both amount and character of proliferative reaction to a common stimulus, and these variations undoubtedly rest on the hereditary basis, in part if not wholly.

Evidently, then, heredity may determine whether the proliferative reaction that follows injury assumes a neoplastic character or not, just as the Crocker Laboratory rats do or do not develop sarcoma in the liver about the encysted taenia, according to their ancestry. This has been pointed out especially in connection with the study of the lung tumors in Miss Slye's mice, which show that mice with cancer heredity react to non-specific inflammatory conditions in the lungs more often with excessive proliferation which leads to malignancy than do mice of non-cancerous ancestry. All mice of tumor age have suffered more or less from inflammatory conditions in the lungs, with proliferative reactions. In some of the mice of cancer ancestry the proliferation assumes a definitely neoplastic character. On the other hand, mice not of cancer ancestry subjected to corresponding lung injury very rarely, if ever, react with proliferation to a degree even suggesting tumor formation. Since the susceptible animals are not born with cancer, but develop it only later in response to certain environmental conditions, it is evident that only the potentiality, or lack of resistance, is inherited.

_Heredity and Cancer in Man_

Taking all the evidence, whether from clinical experience or laboratory observation, it seems impossible to escape the conclusion that the occurrence of cancer in both animals and in man, is influenced by heredity, and it seems most probable that the hereditary influence is an extremely important one. Admittedly the occurrence of cancer depends often upon the existence of a chronic irritation, whether physical or chemical. How readily such irritation will lead to the development of cancer apparently depends largely upon the inherited capacity or lack of capacity to prevent the reactive proliferation from passing from normal to neoplastic character. The fact that many but not all mice of unselected ancestry may develop cancer after painting with tar, and that the duration and amount of this irritation required to produce cancer vary greatly in different animals, indicates the
existence of different individual capacities to resist cancerogenic stimuli. The fact that so many of the pioneer x-ray workers have developed cancer indicates the possibility that an adequate stimulation may overcome the resistance of almost any human being. On the other hand, the fact that in cancer families, and in experimental cancer strains, the ordinary amount of stimulation common to all the species leads to cancer in most members of the family or strain, whereas a similar amount of stimulation rarely produces similar tumors in the rest of the species, indicates the possibility of inheritance of minimal capacity to resist the appearance of the malignant type of cell proliferation. For example, no particular irritation seems to be required to cause retinal gliomas to form in the young children of glioma families. And what particular irritation could there have been in the roof of the fourth ventricle of each of the identical twins described by Leavitt, who developed tumors at this well-protected point? A particularly illuminating history is given by Warthin (108) of four brothers with cancer ancestry on both sides of the family. Three, who were smokers, died in middle life of cancer of the lip; the fourth did not smoke, but nevertheless developed cancer of the lip at a much later age than his brothers. Here the susceptibility to cancer of the lip was present in all four, but the greater irritation of the lip in three caused an earlier development of the malignancy.

So far, the human material fails to furnish satisfactory evidence as to the genetics of cancer inheritance in man. Some forms of neoplasm, such as retinal gliomas, multiple neurofibromatosis, adenomatous polyposis of the intestine, and multiple cartilaginous exostoses, seem to behave much as if susceptibility were dominant. On the other hand, the large family groups which resist more ordinary types of cancer suggest a dominant resistance to these. The fact that the offspring of the great majority of individuals who have died of cancer do not themselves exhibit cancer, is not in favor of the theory that cancer susceptibility for ordinary types of cancer is a simple dominant. As Miss Slye points out, the way in which cancer crops out in families, often with intervals of several generations, resembles closely the behavior of a recessive character suppressed by dominant with heterozygote matings, which type of cancer incidence she has observed in her experimental breeding. 15

15 The fact that mules so rarely have cancer as compared with the species from which they arise (Feldman, 30) may perhaps offer support to the view that cancer susceptibility is usually recessive, for the ancestors of the mules cannot possibly be
At the present time it seems safe to maintain that the existence of an hereditary influence on the susceptibility and resistance to cancer has been established both for man and animals. The exact mechanism of the hereditary influence has yet to be determined. The evidence offered by human material is conflicting, and inadequate both in amount and character to permit of satisfactory analysis. The studies so far made with spontaneous tumors occurring in laboratory animals show the possibility of modifying the occurrence of cancer in these animals in marked degree, and of determining by experimental genetics the site and character of the tumors that will arise. Therefore, we may reasonably look forward to the eventual finding of a definite explanation of the genetic mechanism which determines susceptibility and resistance to human cancer.

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related, and hence there is much less probability of similar hidden recessive characters being present in both to appear in the offspring, than in the case of breeding of horse with horse and ass with ass.
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