Is Cancer a Communicable Disease?

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Although the mystery of cancer is as yet far from solved, information recently accumulated from extensive studies on this problem has gradually dissipated a number of misunderstandings and introduced a few new facts that suggest theories quite different from those accepted only a few years ago.

Tumors are probably as common in frogs, fish, flies, chickens, mice, rats, rabbits, dogs, or horses, as in man. In animals, as in man, cancer is usually a disease of older age, and is only occasionally observed in young subjects. Tumors may arise in almost any part of the body; some grow rapidly and kill their hosts in a comparatively short time; many others grow slowly; still others may persist for years without much injury to their hosts.

I
THE INOCULATION OF TUMORS IN ANIMALS

Tumors that develop in animals can be excised and reinoculated into the same host, or transplanted from one animal to another. Although tumors can usually be successfully transplanted only within the same species, or even race, as from mouse to mouse, rat to rat, rabbit to rabbit, etc., transplantation between animals of different species is also possible. By implanting into the anterior chamber of the eye instead of subcutaneously tumors can be successfully transferred from one race, species, or even order, of animals to another, for instance from mice to rabbits, rabbits to guinea pigs, etc.

It was first thought that tumors could be transferred only by large particles of undamaged cells, because the first new growths found in rats and mice could not be transmitted by cell-free filtrates. Later it was discovered that malignant neoplasms in chickens, and certain tumors in frogs, rabbits, and dogs are often readily transmissible by cell-free filtrates or by tumor tissue that has been either desiccated or stored in glycerine. Recent studies indicate that mammary cancer in mice also can be transmitted by cell-free filtrates if certain experimental conditions are met.

ACQUIRED SPECIFIC IMMUNITY TO THE IMPLANTATION OF TUMORS

Successful implantation of a malignant growth into a susceptible host is not necessarily fatal for the animal. In certain instances the implanted tumor grows only temporarily and eventually disappears, and even one that is highly malignant for certain races or inbred lines of animals may occasionally regress.

It has long been observed that animals that have exhibited complete, spontaneous regression of successfully implanted tumors usually resist reinoculation with the same neoplasm. On the basis of this observation a method of active immunization was devised by Besredka and the writer a few years ago (11, 12). Susceptible animals were inoculated intradermally with a very small amount of finely ground tumor-cell suspension; under proper control of dosage the resulting intradermal tumors regressed in an appreciable number of instances and animals in which this occurred were found immune to reinoculation of the same neoplasm by any route. This procedure has been applied successfully in mice (11, 12), rabbits (16, 13), and chickens (14). It has also been observed in recent experiments that temporary growth of an intradermally implanted tumor, followed by its spontaneous and complete regression, confers immunity on the host no matter what the origin of the tumor or its genetic relation to the inoculated host (38). This immunity is directed specifically against the tumor used for the immunizing inoculation. Although it is substantial (40) and durable it cannot be transferred passively from one animal to another, even by the injection of large amounts of serum or of ground organs from immunized animals (13, 14).

The immunity acquired by spontaneous recovery from tumors presents a complete analogy with that observed in diseases caused by various microorganisms and viruses. Many centuries ago men observed that persons who had recovered from certain infectious diseases, such as smallpox or measles, usually possessed a lasting immunity. This is most striking in certain virus infections although it exists in other communicable diseases also. Thus observation that susceptible animals can be successfully immunized against the experimental implantation of neoplasms is of considerable significance. At the present time, however, no more than theoretical importance can be attached to these experiments since no proof has yet been furnished that intradermal immunization may also
prevent the development of tumors naturally occurring in animals.¹

THE "SPONTANEOUS" DEVELOPMENT OF TUMORS

Although malignant growths develop frequently in various animals, in most instances no evidence has been found to suggest that a tumor-bearing animal can transmit the disease to another. Whereas neoplasms can be transplanted artificially from one animal to another, no similar transfer seems to occur in nature; for a handful of tumors only, such as the rabbit myxoma or rabbit papilloma, were data at hand to indicate transfer under natural conditions, but since no such evidence could be found for the great majority, it seemed logical to assume that each of these tumors is a separate entity, arising de novo in the afflicted animal without any causal connection with similar neoplasms in other animals. Hence, with few exceptions, each tumor that developed in a normal, untreated animal was considered to be a "spontaneous" new growth.

THE "CANCER FAMILIES" IN MICE

During early experiments on the transplantation of tumors several investigators observed that spontaneous neoplasms could be transplanted without difficulty from one sibling to another, but that such transplantations only rarely succeeded in other animals. By successive transplantations a tumor would only gradually acquire sufficient virulence to grow indiscriminately in various animals of the same species, if its virulence were enhanced at all. Since the number of takes in "market" mice, i.e., in animals of promiscuous origin, was wholly irregular, several investigators began inbreeding mice to obtain a sufficient number of siblings or sibling-like animals equally susceptible to implantation. Thus female mice have been mated in each generation to their brothers only, a process that eventually resulted in a high degree of genetic uniformity in all animals of a particular inbred line. For practical purposes these animals were as alike as identical twins, and they proved to be equally susceptible or equally resistant to the implantation of certain tumors.

Several lines of mice have been thus established (74—77), each designated by a letter symbol such as A, C, C3H, and so on. It was soon observed that the animals of some of these lines developed spontaneous tumors when allowed to reach older age, whereas mice of other lines remained free. The comparatively short life-span of these rodents seemed to afford a good opportunity for experimental study of the inheritance of these naturally occurring neoplasms, and interest switched from transplanted to spontaneous tumors.

Mice of some of these lines have been found practically free from neoplasms, no more than 2 or 4 per cent developing them; the C, C57 black, CBA, and other similar lines are therefore called low-tumor lines. On the other hand, certain inbred lines like the A, or the C3H, show a remarkably high incidence of spontaneous tumors in each generation. These are called high-tumor lines.

THE INFLUENCE OF SEX AND AGE ON THE DEVELOPMENT OF SPONTANEOUS TUMORS

A striking influence of sex and age on the development of spontaneous tumors was immediately observed in these strains. Thus practically all females of the C3H line have mammary carcinomas before they reach 1 year of age. Females that have had litters develop mammary tumors earlier (5) than virgin females. Male animals of this line develop neoplasms of the liver or lungs at an average age of 15 months (1); many of them, however, die without tumors, or before they reach the comparatively late tumor age.

The females of the A line differ from those of the C3H line, since there is a striking difference in the incidence of mammary cancers between the breeding and virgin females (74, 17, 19). Practically all breeding females of the A line develop mammary carcinomas at the average age of 12 months; on the other hand, virgin females of this line, with few exceptions, remain free from mammary tumors. They develop, however, lung carcinomas (17) upon reaching the average age of 17 months. Males of this line also develop lung carcinomas at approximately 15 months of age (17).

Males of the high-tumor lines do not normally develop mammary tumors. When castrated early in life, however, and engrafted with ovaries (58), or when injected with estrogenic hormones (48), they have mammary tumors about as often as virgin females of the same line. It should be pointed out, though, that animals of low-tumor lines do not develop mammary cancers from overstimulation with estrogenic hormones.

Thus it seems that hormonal stimuli, coupled with changes that are associated with older age, have only an intermediary influence on the development of certain spontaneous tumors, such as mammary cancer, in mice. It may be that in certain animals old age, together with an alteration in the hormonal balance, may activate a pre-existing but hitherto latent tumor factor, and thus be only indirectly responsible for

¹For bibliography on transplantation of tumors and experimental tumor immunity see (39), and (92).
the development of at least some of the “spontaneous” neoplasms.

Mammary Cancer in Successive Generations under Promiscuous Breeding

The studies on the development of spontaneous tumors in successive generations of “cancer families” of mice have been carried out on genotypically uniform animals of pure inbred lines. Clearly the breeding conditions are artificial, and cannot be compared with those occurring in nature. A similar development of spontaneous tumors in members of successive generations of mice has been observed also, however, under the usual conditions of promiscuous breeding. Thus Dobrovolskaia-Zavadskaia (29) obtained 5 female mice of unknown origin with mammary carcinomas. Two of these were mated to males that had been born to cancerous mothers, and 3 to males of unknown origin. There was a striking incidence of cancer in the resulting progeny. All females of the first generation that lived over 6 months developed mammary tumors, and of the 84 females in the second generation 56, i.e., 67 per cent, died with mammary carcinomas.

In other and similar experiments (28) a cancerous female mouse of unknown origin mated successively to 3 different males had 7 cancerous and 5 noncancerous daughters. One of these cancerous daughters mated to her own brother had noncancerous offspring, but her 2 granddaughters developed mammary tumors.

Transmission of Cancer Through Mother’s Milk

For a number of years elaborate genetic theories were advanced to explain the origin of spontaneous tumors, and especially mammary cancer, in mice. A few years ago, however, it became clear that chromosomal factors could not be held exclusively responsible for their development. It was observed by members of the Roscoe B. Jackson Memorial Laboratory (73) that females of a high-tumor line mated to a male of a low-tumor line were able to transmit the tumor factor to their offspring in a high percentage of cases, whereas males of the same high-tumor line mated to females of the low-tumor line had offspring in which few, if any, tumors appeared. It was concluded that some maternal or extrachromosomal influence responsible for the development of spontaneous tumors had been transmitted from the mothers to their progeny.

The Prevention of Breast Cancer by Foster Nursing

The maternal influence could be transferred by cytoplasmic inheritance, during intrauterine development, or by way of the mother’s milk. Suspecting milk transmission, Bittner (18), early in 1934, removed young mice born to high-tumor A line females from their potentially cancerous mothers before they were 24 hours old, and transferred them for foster nursing to lactating females of the low-tumor CBA and C57 black lines. The results were striking (19). Whereas 96 per cent of 376 breeding females of the A line developed spontaneous mammary cancers at the average age of 10 months, no more than 8 per cent of the 127 fostered females did so; 92 per cent of these died at the average age of 17.7 months without tumors.

These dramatic observations have been repeated and confirmed by other investigators, and with various lines of mice. Andervont (2—6) observed that foster nursing of females of the high-tumor C3H line by low-tumor females of the C, Y, or I lines reduced the incidence from 100 to 20 per cent. The appearance of spontaneous mammary cancer could be entirely prevented in C3H females by removing these animals at full term directly from their mothers’ uteri and foster nursing them on females of the low-tumor C57 black line. It has been observed that removing mice from their mothers 24 hours or later after birth had little or no effect on the future development of tumors in these animals; in order to prevent the appearance of neoplasms in such mice they had to be removed immediately after birth.

Thus it was definitely established that the development of breast cancer can be prevented in mice of high-tumor lines by isolating newly born animals from their potentially cancerous mothers and transferring them for nursing to lactating females of low-tumor lines.

In recent experiments Bittner (22) removed C3H females on the day of birth from their potentially cancerous mothers, and transferred them to females of the low-tumor C57 black line. Through 5 successive generations only 1 per cent of 165 descendants of these fostered mice developed tumors; the remainder died at the average age of 16.9 months without neoplasms. Of the 214 control C3H females 97 per cent developed mammary cancers at the average age of 8.9 months.

Hence a high-tumor line changed into a low-tumor line after foster nursing of females from one single generation of a high-tumor line by lactating females of a low-tumor line.

Transmission of Mammary Cancer to Mice of Low-Tumor Lines

A logical sequel was to determine whether mice of a low-tumor line would develop mammary cancer when nursed by females of a high-tumor line.
It was soon observed by Andervont (2) that mice of the low-tumor C line developed mammary cancers in 64 per cent of cases when nursed by females of the high-tumor C3H line. None of the control females of the C line reared by their own mothers developed tumors. In other experiments the incidence of mammary cancer in low-tumor hybrid females, derived from matings of C57 black and 1 lines, was increased from 0 to 80 per cent by transferring the newly born animals to C3H females. The tendency to develop mammary cancer, once acquired, could also be transmitted through successive generations. Thus when acquired by females of the low-tumor C line after foster nursing by females of the high-tumor C3H line it was transmitted to the second and third generations; a low-tumor line changed into a high-tumor line after foster nursing of females of one generation of a low-tumor line by females of a high-tumor line.

The tumor factors carried by various high-tumor lines are probably not identical, since they may have a different affinity for animals of various inbred lines (4). Conversely, animals of a low-tumor line may prove susceptible to a tumor factor carried by one high-tumor line, but may at the same time have a low susceptibility to a tumor factor carried by another high-tumor line.

**Importance of Susceptibility to Cancer Compared with That to Various Infectious Diseases**

According to the generally accepted theory (19, 20), three factors are responsible for the origin of mammary cancer in mice: (a) the transmissible milk "influence," which may, however, according to Bittner (20), arise de novo within the individual; (b) inherited susceptibility; and (c) hormonal stimulus.

This theory does not sufficiently stress the importance of a transmissible causative agent in the origin of mammary cancer in mice; on the other hand, the importance of inherited susceptibility as well as the influence of hormonal stimuli seems to be overemphasized, and may be misinterpreted. Thus few bacteriologists, if any, would state that anthrax, for instance, is caused by two factors: (a) the transmissible anthrax bacillus, and (b) inherited susceptibility. The anthrax bacillus only would be mentioned, since it goes without saying that this microorganism can act only on a susceptible host. Susceptibility is obviously fundamental in the acquisition of any communicable disease, since pathogenic microorganisms or viruses can act only on susceptible cells within susceptible hosts. Some microorganisms have a wide range of action; others are limited in their pathogenic activity to susceptible races, families, or even individuals. These microorganisms are nevertheless considered the true causative agents of the resulting diseases. Thus Algerian sheep, in contrast to European, are relatively insusceptible to anthrax; field mice are relatively resistant to streptococci or pneumococci, whereas albino mice are very susceptible to these organisms (33). Webster (87) selected susceptible and insusceptible parents for breeding and eventually obtained two lines of mice, one showing 95 per cent mortality and the other only 5 per cent under the same conditions of exposure to *B. enteritidis*.

Hormonal stimuli may also distinctly influence the susceptibility of the host to certain communicable diseases. Thus a higher susceptibility of males, as compared with females, to many infectious diseases has long been observed in human and animal pathology (33). Some diseases, such as ringworm of the scalp (*Tinea tonsurans*), occur in childhood but rather seldom in sexually mature individuals (69).

The susceptibility of the host, fundamentally inherited, but also strongly influenced by hormonal stimuli, age, and various environmental factors, seems, at least in principle, no more important in the origin of cancer than it is in the acquisition of diseases caused by various microorganisms and viruses.

**Mammary Cancer in Mice—A Communicable Disease**

Upon reviewing the problem dispassionately it is difficult to avoid the conclusion that mammary cancer in mice is a communicable disease transmitted through the milk of nursing animals from one generation to another. Animals that transmit the tumor factor and are responsible for the dissemination of the disease do not themselves display any apparent symptoms at the time of transmission; they develop tumors, if at all, later in life. They are carriers of a temporarily latent tumor factor, which is probably a virus (20): they have an asymptomatic neoplastic disease. Young animals that acquire the tumor factor by suckling milk from their potentially cancerous mothers do not have mammary cancer until they reach approximately 1 year of age, and some die without tumors. In the meantime, however, they become carriers, and before displaying any symptoms may again transmit the disease to the next succeeding generation.

Although these observations refer thus far to mammary cancer in mice, there is no reason to believe that this form of tumor has an etiology essentially different from that of other neoplasms.

**The Law of Obligate Communicability Probable Also for Tumors?**

The generally prevailing supposition that cancer is a "spontaneous" disease, caused by various internal
and external factors, is not unlike the ancient conception of "spontaneous tuberculous degeneration" advocated by Pidoux (82) and other believers in "morbid diathesis." At the time of Villemin tuberculosis was thought to be "a common result of a quantity of diverse external and internal causes" (82), and it is worth emphasis that as late as 1885 typhoid fever and diphtheria were believed to originate de novo in filthy surroundings (66). It took many years to demonstrate that the law of obligate communicability still prevails for all infectious diseases. The same may be true for cancer. The conception of the spontaneity of at least certain of its forms seems untenable in view of the experimental evidence suggesting that what was thought to be "spontaneous" mammary cancer in mice is a disease communicable from generation to generation, and that its appearance can be effectively prevented by isolating the potentially cancerous mothers from their newly born progeny.

It is true that while mammary carcinoma in mice has been found to be communicable from one animal to another, no experimental evidence has been obtained as yet for a similar natural transmission of other tumors, such as various sarcomas, etc. It is possible to assume, however, that the mammary carcinoma of mice does not represent a form of cancer fundamentally different from other neoplasms. If this assumption is correct, the law of obligate communicability may sooner or later be established for other tumors also.

Thus far milk has been recognized as the intermediary factor transmitting the disease from generation to generation. Other means of transmission, however, such as ovarian transfer, should also be considered. Cancer is not limited to mammals, and it seems reasonable to assume that tumors can be transmitted by means other than milk, not unlike various microorganisms that are transmitted from one to another. (81, 71, 60, 32).

Occasionally the same animal may simultaneously carry several different tumor factors, such as lung or bone tumor factors, and a mammary carcinoma agent. Although the appearance of mammary cancer may be prevented in the next generation by isolating the potentially cancerous mothers from their newly born progeny, this precaution will not necessarily eliminate the bone or lung tumors, since these may have ways of transmission other than milk.

II

Let us now consider the few available experimental data and observations referring to the transmission of human cancer: (a) in the same person, (b) from one person to another, and (c) from one generation to another.

AUTOINOCULATION OF HUMAN CANCER

Accidental contact transplantations of tumors in the same patient, as from one lip to another, from tongue to gum, from one vocal cord to another, from breast to the adjacent chest skin, etc., have long been observed by various authors (10, 23, 30, 50). Accidental transplantations of tumors during laparotomy, abdominal paracentesis, or débridement of a tumor through the vagina, have been described by numerous surgeons (50). An accidental transplantation of an adenocarcinoma from the breast to the skin of the thigh in a 43 year old white female was observed by Spies and his colleagues (72); 2 months after the plastic transplantation of Reverdin grafts from the patient's right thigh to the granulating wound surface of the left chest wall a nodule developed in the skin of the right thigh where the autografts had been excised. The microscopic report on this nodule (Ewing) was "a very cellular infiltrating carcinoma of mammary gland type." A similar case of accidental transplantation of a breast tumor to the skin of the arm was observed by Hubard (44).

Cornil reported (26) that an "anonymous surgeon" transplanted in 1887 a breast sarcoma and a breast carcinoma, each into the patient from whom it had been excised. The implants grew after incubation periods of 2 months and a few weeks, respectively. The sarcomatous implant was excised and found to be histologically identical with the original breast sarcoma. The carcinomatous implant grew, but was not excised. Similar cases of successful, intentional autotransplantation of human cancer were reported by Delbet (cited by Kurtzahn) and Hahn (41).

More recently de Martel (54) transplanted carcinoma of the breast (3 patients) and carcinoma of the bowel (1 patient) under the skin of the abdomen, and each into the patient in whom it had originated. A latent period of approximately 5 months was observed in all 4 instances; after this had elapsed the implants began to grow very rapidly. They were destroyed in all patients without difficulty by x-rays.

On two occasions Besredka and Gross (15) implanted intradermally a carcinoma excised from the breast into the patient in whom it had originated; both already had metastases at the time. The intradermal implants grew in both cases after an incubation period varying from 6 weeks to several months; they were later removed and proved to be microscopically identical with the original tumors used for inoculation.

A melanosarcomatous metastasis was excised and immediately reinoculated intradermally in a 53 year old woman by Gross, Zinninger, and Ulin (37). The implant grew after an incubation period of 10 weeks.
and proved to be microscopically identical with the original tumor used for inoculation.

Transplantation of Cancer from Man to Man

A few dramatic observations of accidental transplantation of malignant tumors from man to man have been recorded by competent observers. According to Tross (79) a man developed a carcinoma of the glans penis presenting a structure histologically identical with the cervical carcinoma from which his wife suffered. A patient reported by Martin (55) suffered from a recurrent epithelioma of the external ear and neck. This patient "was most free from pain when resting his head on the breast of his wife, the stained dressing often being in contact with her bare skin." A few weeks after the patient's death Martin was called to attend the widow, and found her suffering from an epithelioma of the chest wall, just above the left breast, in the exact place where her husband's head most often had lain. A similar case of probable transplantation of cancer from a woman's breast to her husband's gum was reported by Peyriche (63). Balacesco and Tovaru (7) reported the case of a young woman who had a small nodule in her right breast. The woman delivered a baby and at this time the nodule in her breast ulcerated. Nevertheless, she nursed her baby. After 11 months the child developed a tumor on its lower lip. Both mother and child were at this time operated upon, and the breast tumor as well as the lip tumor were excised. The mother proved to have an adenocarcinoma of the breast, the child had a spindle cell sarcoma of the lip. In spite of the microscopic difference in appearance of these tumors, there is a strong possibility that the tumor was transmitted from mother to child by contact inoculation.

Weber and his associates (86) reported the case of a melanosarcoma most probably transmitted from a 27 year old mother to her child. The full term child had been delivered by cesarean section in apparently good health 3 months before the woman died of generalized melanosarcoma; the physician (E. Holland) who delivered the child remarked that "the lower uterine segment of the mother was during the Caesarean section occupied by a huge black placenta proved to be infiltrated with masses of tumor" (86). He thought it probable that tumor cells might have been carried in the placental blood stream from the mother to the liver of the fetus. The child died after 8 months from generalized melanosarcoma with large tumors in the liver.

Lecène and Lacassagne (49), and later Katz (45), described the dramatic case of a fatal accidental inoculation of human cancer into the hand of a medical student, Henri Vadon. The unfortunate Vadon aspirated serum from a wound following radical mastectomy in a woman suffering from an adenocarcinoma of the breast. The syringe slipped, however, and while falling accidentally punctured his left hand, injecting some of the fluid deep into the tissues of the palm. This happened on the 13th of February, 1923, in a ward of the Cochon hospital in Paris. In February 1925, i.e., two years later, an irregular induration appeared at the site, with a distinct prolongation toward the old scar remaining after the puncture, and tuberculous synovitis was suspected. The induration increased slowly in size. It was removed in August, 1925, and sent for histological examination. This revealed a fusiform sarcoma. The tumor recurred in the scar and metastases rapidly appeared under the skin of the internal surface of the arm. On September 23rd the whole arm was disarticulated by Lecène; 2 months later, however, metastases appeared above the clavicle and in the neck. Vadon died on December 12th, 1926, one year after the metastases appeared. Thus he inoculated himself with a mammary epithelioma, and developed a fusiform sarcoma at the site of inoculation. There had been no tumors in Vadon's family for 3 preceding generations on his paternal side; on the maternal side, one grandfather died of a suspected tumor of the kidney.

It should be emphasized that striking histological changes occurring in tumors in the course of experimental transplantation from one animal to another have been repeatedly observed by numerous competent observers. Thus during serial transplantation of a carcinoma a sarcoma may eventually develop. Such transformation may occur more or less rapidly following successive transfer of the neoplasm. Whether the transformation is genuine, i.e., whether the carcinoma actually changes into a sarcoma, or whether the transformation is due to a sarcomatous change in the stroma that gradually overgrows the carcinoma is of considerable theoretical importance, and has been fully discussed by Woglom in his review of experimental cancer (91). From a practical point of view, however, the fact remains unchallenged that following transplantation of a carcinoma from one subject to another, a sarcoma may develop. Thus it is possible to assume that a similar histological transformation may occur also in human neoplasms accidentally transplanted from one person to another. This would perhaps explain the case of Vadon (45, 49), and also that described by Balacesco and Tovaru (7).

Transplantation of Cancer from Man to Animals

Human sarcoma or carcinoma can be transplanted without difficulty into the anterior chamber of the eye of various species of animals, such as rabbits,
guinea pigs, etc. After an incubation period varying from 3 weeks to 4 months the implanted tumors begin to grow rapidly, and can then be transferred by serial passage in the new hosts. Thus a human fibrosarcoma could be transferred for 14 consecutive passages in guinea pigs (36). The incubation period may rapidly diminish during successive transfers so that eventually tumors will grow within 7 days following implantation. After several ocular transfers the tumor may be successfully inoculated by other routes, for instance into the testicle.

Thus examples of either accidental or intentional inoculation of human cancer in the same subject, or of unintentional transplantation of a tumor from one person to another, are comparatively rare; not all such observations have been published. Yet the available experimental data, however scarce, suggest that the analogy between neoplasms in animals and in man is not limited to the microscopic appearance of tumors and to their clinical evolution. Like tumors observed in animals, human cancer is unquestionably inoculable in the same person, or from man to various species of animals. Although no sufficient experimental data are as yet available, it seems logical to assume that under certain conditions human cancer can be transplanted also from one human subject to another.

**Appearance of Cancer in Families and Successive Generations in Man**

It has been observed repeatedly that tumors may develop in several members of the same family. Although cancer is a comparatively common disease, and the accidental occurrence of tumors in more than one member of the same family must be considered, a number of "cancer families" has been observed with such a striking incidence of tumors (62, 85) that mere chance can reasonably be excluded. Broca observed breast cancer in a woman whose 4 daughters had cancerous tumors (24); of the 16 grandchildren, 8 died with neoplasms. Finney (31) reported a family in which the mother, 4 daughters, and 3 nieces had all been operated upon for cancer at the Mayo Clinic; all but one had cancer of the breast. Graham's (35) patient had cancer of the rectum; her 3 daughters and 1 son all died of cancer of the rectum. Handley (42) reported 4 sisters with breast cancer; their mother and grandmother also died of tumors.

Körbler (46) reported that by questioning 426 patients treated for tumors he was able to find 4 cancer families. In one case both parents and their 3 children died of cancer. In another case a mother, 4 daughters, and a son died of tumors. Most interesting was the third case, where 5 of 7 children of apparently healthy parents developed tumors. One of the tumors was a daughter had 3 daughters, all of whom developed cancer of the breast. Two granddaughters of this patient also developed breast carcinomas. Thus cancer appeared in members of 3 successive generations of this family. Körbler cited another in which both parents and their 3 children developed carcinoma. Wood and Darling (93) reported a family in which bilateral carcinoma of the breast, or other tumors, developed in numerous members of 4 successive generations. Three sisters of the third generation all developed cancer of the breast.

Williams (90) treated a woman with uterine cancer whose maternal grandmother, mother, and mother's sister all died of cancer of the uterus; two sisters of the patient also had cancer of the uterus. Manson (53) treated a 27 year old woman who developed a fatal sarcoma on the left side of her neck; two of her 3 sons died of identical sarcomas at the same site. Power (65) reported a cancer family in which the father, 2 sons, and 6 daughters all died of cancer.

Silcock (70) reported melanosarcoma of the eyeball in 3 successive generations. Another highly malignant tumor of the eye that affects infants, the retinoblastoma, is a very rare disease, 1 case being observed in 34,000 births; in many families, however, half of all the children are afflicted (89). "Only recently," stated Weller (89), "has it been appreciated that the disease may exhibit also a vertical familial distribution appearing in successive generations, or in collateral lines." Thirty families giving evidence of the appearance of retinoblastoma in successive generations have been collected (88, 89).

Instances of the concurrent development of cancer of the stomach in brothers (59) or twins (57), or of the appearance of tumors of the breast (25) or ovaries (80) in twin sisters, or of the concurrent development of osteogenic sarcoma in brother and sisters (67), or sisters (64), have been compiled (51). Numerous statistical studies on cancer families and on hereditary factors in patients suffering from tumors have been conducted (8, 27, 43, 46, 51, 52, 56, 61, 84, 85, 88), leaving little doubt that cancer is definitely more frequent in the families of cancer patients than in the average population. Although most cancer patients seem to represent sporadic cases, the number of these cancer families is impressive.

Studies on cancer families have been limited to 2 or 3 successive generations with few exceptions, and it has been established that the disease can follow members of certain families for the number of generations observed. There is no reason to doubt that a similarly high incidence of tumors may occur in both preceding and succeeding generations. Other families,
on the contrary, are essentially exempt, practically no cancer having appeared in several generations.

Analysis of the available data does not suggest that any hereditary mendelian factor, either recessive or dominant, determines the development of cancer in animals or in man. The late Prof. A. S. Warthin, in a statement to his class in pathology in 1929, summarized the work completed to that time thus: "Heredity may show itself in some cases as recessive, in others as dominant, and in still others in a hit-or-miss fashion" (19). The genetic explanation of cancer thus proved clearly inadequate. On the other hand, recent studies have demonstrated that mammary cancer in mice can be either prevented, or acquired in early infancy, through the ingestion of milk from tumor-free but potentially cancerous mothers. Although it is true that inherited susceptibility is essential for the development of tumors, cancer does not differ in this respect from other communicable diseases. Susceptibility is indeed of paramount importance in the development of all infectious diseases; the infecting microorganism or virus is, however, ultimately responsible for the disease.

III

Theoretical Implications of the New Approach to the Cancer Problem

The observations discussed above suggest the possible existence of external factors transmitted from generation to generation, and responsible for the appearance of tumors in animals and man. Transmission of various infectious diseases from one generation to another has been observed (81, 71, 60, 32), and cancer would not be the first disease known to be communicable from one member to another in 2 successive generations. Although it can be artificially or accidentally transplanted from one subject to another within the same generation, a natural or spontaneous communicability of cancer seems to take place between individuals of successive generations. This may be true at least for certain forms of the disease, such as the mammary carcinoma of mice. This fact contributed to the difficulty in understanding the nature of cancer as a communicable disease, especially since a long interval of time may intervene between the development of the initially observed and the transmitted neoplasm.

Thus individual instances of the development of tumors should be viewed in their proper perspective, i.e., as single links only in a continuous chain of a disease that is being transmitted from one generation to another. In order to appreciate the communicability of tumors, the time factor should be disregarded; their communicability may then be compared in principle with that of various infections, except that diseases thus far recognized as being contagious spread, as a rule, among members of the same generation. One is almost tempted to admit the possibility of an "epidemic in the fourth dimension." Human life may well be too short to permit any one investigator to grasp the concept of the communicability of cancer in man; the time factor may prove to be one of the most formidable obstacles in further research on the epidemiology of tumors.

The Vertical Epidemic of Cancer

In a normal or "horizontal" epidemic, that of smallpox or common cold, for instance, the chain of infection spreads among individuals of the same generation, and the whole picture of a communicable disease, as such, is clearly discernible to anyone; thus several hundred consecutive cases of transmission of the disease from one individual to another may occur within a comparatively short time, and certainly within the lifetime of the human observer. In a "vertical" epidemic of tumors, however, one human observer can see but a very few scattered links in the chain of communication. The comparatively short life span of the investigator does not permit him to follow the spread of the disease for more than a few consecutive transmissions, and the communicable nature of the disease may therefore entirely escape the individual observer. One single physician, driving his car, could visit during one day a dozen patients who contracted smallpox, or common cold, one from another. A human observer, however, could visit several persons who had contracted breast tumors one from the other only if he were able to travel in the fourth dimension, i.e., if he were able to travel in both space and time.

Another reason apparently responsible for the difficulty in understanding the problem of cancer is the fact that most of those who spread the disease are latent carriers; they do not themselves display any apparent symptoms, but many of them develop tumors upon reaching old age, or under the influence of certain hormonal, or as yet obscure, stimuli. Some die before they reach the tumor age, and some remain free from tumors even though they do reach old age. They transmit the disease, however, not unlike apparently healthy carriers of various infectious diseases in animals and in man. The carriers of typhus rickettsias, for instance, may remain asymptomatic yet spread the disease, and may, for obscure reasons, themselves develop clinical symptoms later in life (Nicolle).

It may well be that at least certain forms of malignant tumors are caused by an invisible virus, whose existence depends upon close association with the cells of a living host. Such a tumor virus would be highly adapted to certain hosts, and probably also to
certain cells within the host, a fact repeatedly observed in various virus diseases. As a rule the tumor virus would be frugal and moderate in its requirements and would not, apparently, injure the host; it would behave like a really "efficient parasite" (78). For obscure reasons the pathogenicity of this virus may sometimes change during the later life of the host, and a tumor would then develop. In most instances the fate of the host would thus be sealed, the neoplasm growing progressively and eventually killing him. Occasionally, however, a tumor may grow only temporarily and then spontaneously regress. Cases of spontaneous regression of human cancer, though unusual, have been repeatedly recorded by competent observers (34, 68), suggesting that similar regression of small and unrecognized tumors may perhaps occur more often than is generally assumed. In any event the survival of the virus would have been secured by transmission to the next generation of the host.

There may exist a group of fundamentally similar but individually distinct tumor viruses causing various neoplasms, not unlike the array of rickettsial microorganisms responsible for the various forms of typhus. It is probable that persons with demonstrable tumors represent but a fraction of those actually carrying the disease. Thus Theobald Smith's statement that "pathological manifestations are only incidents in a developing parasitism" may be true not only for the currently recognized contagious diseases but also for tumors.

In Cancer Families Breast Feeding Should Be Abandoned at Least for One Generation

Speaking with all reserve, there is reason to anticipate that the incidence of certain tumors at least, such as breast cancer in man, could be substantially reduced if the women of families with any tumors in their ancestry were to refrain entirely from nursing their progeny. A similar conclusion has been reached by Bittner (21).

Since no more than a few hours of breast feeding may suffice to transfer the tumor factor, the conclusion seems justified that breast feeding in such families should be abandoned from birth, and that artificial feeding should be substituted. It should be emphasized that many instances are known in experimental cancer research where females of tumor families of mice have been capable of transmitting the tumor factor without themselves displaying symptoms of the disease at any time.

Experiments previously reviewed suggest that it might suffice to omit breast nursing for one single generation. This simple preventive measure may bring substantial rewards in the fight against cancer, although results will not become evident until the next generation reaches the tumor age. Accurate records should be kept of persons, especially women, who have been artificially fed from birth, so that the incidence of tumors in them can be compared with either that of their ancestry or of the average population.

Probably all would agree that further research should be encouraged in the epidemiology of cancer and immunization against tumors.

SUMMARY AND CONCLUSIONS

Recent experiments demonstrate clearly that mammary cancer in mice is communicable from one generation to another. Animals transmitting the disease are, as a rule, carriers of a latent tumor factor and do not themselves display symptoms until they reach the "tumor age." The development of mammary cancer can be entirely avoided in susceptible mice by preventing newly born animals from nursing their potentially cancerous mothers.

The available data on accidental or intentional inoculation of human cancer are reviewed and the appearance of tumors in several members of the same or successive generations in man is discussed. The conclusion is suggested that human cancer may be similar to that observed in mice and may also, perhaps, be communicable from one generation to another.

Since milk seems mainly responsible for the transmission of certain tumors such as mammary carcinoma, it is suggested that the women of families with any malignant tumors in their ancestry refrain entirely from nursing their progeny. Artificial feeding should be substituted from birth, at least for one generation.

This simple preventive measure may bring substantial rewards in the fight against cancer, although results will not become evident until the next generation reaches the tumor age.

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