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Dr. Ernest F. Bashford, an English physician, lived from 1873 to 1923. For many years before his untimely death, he was an officer for the Imperial Cancer Research Fund. From articles in the *British Medical Journal* and other publications, Bashford prepared a volume of reprints (1903–1909) concerning problems, growth, and heredity of cancer, and experiments with breast cancer in mice. Cancer had been studied histologically and clinically, with only speculation as to its origin, nature, and cause in man. He suggested cooperative studies by investigators in many different fields. Concerned with why the growth of cancer seemed limitless, and with problems of age dependence, he and his associates studied cancer in a short-lived animal, the mouse, comparing it with man. They transferred cancer cells from infected mice to cancer-free mice and found that sites of cancer were determined by age at maturity, involution of an organ, and chronic irritation or injury to a part; they concluded that surgery for early-stage cancer would save lives. They also studied cancer resistance in mice. Because implanted cancer was rejected by certain mice, Bashford concluded that cancer was sporadic and not hereditary.

INTRODUCTION

Dr. Ernest F. Bashford (Fig. 1), an English physician, lived from 1873 to 1923. For many years before his untimely death at 50, he was an officer for the Imperial Cancer Research Fund. During that time he was much concerned by the meagerness of knowledge about cancer that had so far emanated from clinical observations (such as biological, chemical, and other conditions of growth of cancer cells) that appeared to be purely speculative. The only real advances in the field until 1903 had come from pathologists, who received specimens from surgery and autopsies and analyzed them under the microscope.

THE PROBLEMS OF CANCER
(from Bashford, 1903)

Because of his concern about the problems of cancer, Dr. Bashford proposed that a very extensive biological study be organized to include all races of man and the animal kingdom as well. Only with animals could experiments be made concerning the etiology, pathology, prevention, and cure of cancer. He stated that there seemed to be a general feeling of hopelessness among investigators that the cause of cancer might ever be revealed through studies of any sort. He advocated, instead, more intense studies of the biological and biochemical conditions causing growth of cancer cells rather than concentration only on the problems of their genesis. He hoped to settle questions of the cause of cancer and its influences, such as parasites, heredity, injury, tobacco, and age at occurrence for each species of animal, as well as the approximate age of occurrence of cancer in a specific body organ. This might only be possible by studying the more common domestic animals that are much shorter-lived than man.

Investigations of the incidences of cancer in the animal kingdom could not possibly be carried out by physicians only. It requires cooperation and investigation by biologists, ethnologists, zoologists, and embryologists. He asked if it was too much to hope that workers in all of these fields be willing to share in attempts to ascertain the nature of malignant tumors in both man and animals, because he felt that this combined effort might bring the results needed. (For the past 25 years, Dr. Victor McKusick and his genetics teams at the Johns Hopkins Hospital have collaborated with the staff at the Jackson Laboratory of Bar Harbor, Maine, in research studies of man and small animals such as mice and rabbits.)

THE GROWTH OF CANCER
(from Bashford, 1905)

Dr. Bashford stated that studies of the growth of cancer—as distinct from its genesis—had been avoided by investigators. Earlier hypotheses had been 1) the cells were freed from the constraint of connective tissue; 2) they were freed from the control of other cells; 3) cancer cells were derived from "embryonic rests"; and 4) a parasite caused the cancer cells to multiply. He noted that *all* of the above failed to show how cancer cell multiplication was maintained. However, the previous investigators were unaware of mitosis and meiosis and the growth of normal cells. In addition, studies up to this time were limited to histological studies of fully-developed cancer in man, so that nothing was known about the development of cancer. However, studies had revealed that cancer cells developed from normal tissue.

Therefore, Dr. Bashford, as a member of the Imperial Cancer Research Fund, began a study of cancer growth in many different animals including man, horse, dog, cat, trout, and mouse. First, it was noted that in all animals, both short- and long-lived, the incidence of cancer is related to aging (though immunological influences were not known then). Cancer occurs more frequently in man after 45–50 years and in mouse after two years. It is also related to the age at decline of reproductive activity. Bashford wondered if the factors that determine the size of the body and the length of life in different animals might influence the time when cancer occurs in each species.

Experiments on mice then included transplanting a cancer from one mouse to another and from one organ to another within a mouse. It was found that cells proliferating in the new mouse or organ were the

FIGURE 1. Dr. Ernest F. Bashford.

same as those from the original one; they did not resemble the hosts' cells. The host merely provided the blood supply to the new cells that continued to grow independently. Only cells from the same species could be transplanted to another animal, a phenomenon now known as rejection of a transplant when attempts are made at interspecific transfer.

Transplanting efforts were sometimes completely successful and sometimes not. Therefore, "chromatin rods" (chromosomes) were studied and aneuploidy was discovered, some cells having fewer than half the normal number of chromosomes and some having "too many." In many cases, regular mitosis also occurred, which could not be explained.

From various observations, Dr. Bashford thought that cancer occurrence also seemed to be related to organ age and its time of involution, such as chorion epithelioma that occurs after the short life of the chorion; breast and uterine cancers that occur more frequently after menopause in women; and skin cancer that occurs much later in life because the skin remains active long after middle age. Therefore, Dr. Bashford hypothesized that the "limitless growth of cancer cells appears to follow the terminal phases of normal cell multiplication in the body." He realized that much more study and experimentation were required.

THE NATURAL AND INDUCED RESISTANCE OF MICE TO THE GROWTH OF CANCER

(from Bashford, 1907)

In this paper, Dr. Bashford described a number of experiments with mice to demonstrate how resistance to the injection of carcinomatous tumors can be built up, using mostly breast cancers that were implanted in both axillae of mice.

Injections of small amounts of mouse tumor tissue into normal young mice resulted in active tumor growth. In those mice that survived, a second injected tumor was rejected. Young mice were more susceptible to tumor injection than older ones. Exposure to radium caused "absorption," or regression and disappearance of the tumor. Good blood supply in the host was necessary for tumor growth. When spontaneous regression of a tumor occurred in a mouse, it was not possible for another transplanted tumor to grow; instead, the tumor regressed and disappeared. Mice that have been inoculated with a rapidly- growing tumor reject the injection of a second rapidly-growing tumor. It was thought that this was because the first tumor was using up all the nutritive powers of the host. Repeated inoculation of other tumors in negative mice caused increased resistance so that they never developed tumors. (This procedure—developing a tumor vaccine—is still being tried today at various institutions, including Massachusetts General Hospital.) The protection induced in mice can only be acquired by the induction of mouse tumors, not tumors from other species. It can also be induced by the inoculation of blood corpuscles but not by serum of the mouse.

Dr. Bashford prolonged the lives of 13 mice that had exhibited spontaneous tumors by removing the tumors in whole or in part. Thus he was able to transplant their own and other spontaneous tumors into these mice. Two of the mice were successfully inoculated with their own tumors, and in one of them the tumor that was removed did not grow in 94 of 97 normal mice.

The tumor of the second mouse gave negative results in 140 normal animals. One mouse that had rejected tumor inoculation a number of times later developed a tumor of a different histological type. The transplantation of a mouse's own tumor back into that mouse was not nearly as successful as inoculation into a normal mouse. Such tumors rarely grew in other mice that had spontaneous tumors.

Two factors that influence the growth of transplanted cancer cells were considered to be the varying natural susceptibility of the mice and the varying "energy of growth" of the tumor cells. The tumor dose was measured in each case, and cancer resistance could be measured by the dose necessary to cause a tumor in a normal mouse in ten days that did not cause a tumor in a tumor- resistant one. If a tumor did develop in a cancer-resistant mouse, it was smaller than the tumor in a normal mouse, and young normal mice were more susceptible to tumor inoculation than older mice. The axillae of the mouse accepted a transplant more readily than the dorsal subcutaneous tissue due, it was thought, to the increased supply of connective tissue in the mammary region.

Mice in which tumors have been successfully transplanted and the tumors regressed are resistant to further inoculations of tumor tissue. An experiment was as follows: Eight transplanted tumors developed

in 12 normal young mice (67%). The same tumor was inoculated into 36 mice that had been previously successfully inoculated but in which the tumors regressed and disappeared after ten days. Two small tumors developed in the 33 mice that had survived ten days (6%). Thirteen days later, 15 of the 33 mice were reinoculated. No tumors developed, while 13 of the 15 normal mice developed tumors after ten days. The protected mice were then used to test tumor-resistant qualities of the blood.

Larger doses of tumor material caused tumor resistance in a much shorter time that when smaller doses were used. Mice that have been unsuccessfully inoculated with large doses of one spontaneous tumor are less apt to accept another type of tumor than are normal mice. This was thought to be due to blood supply because a number of hemorrhagic tumors had regressed in mice and it was thought that injections of normal-mouse blood corpuscles into transplanted tumors were the reason, whereas normal-mouse serum did not cause regression of the tumors.

Dr. Bashford concluded the paper this way: "We are as yet unable to determine the extent to which agencies directed against tumor cells, themselves, may assist in determining their early death in protected (cancer-resistant) animals. Other experiments still in progress may be expected to clear up the relative importance of the parts played by the hypothetical inhibition of the specific stroma reactions, or of an equally hypothetical direct lethal action on tumor cells."

HEREDITY AND CANCER
(from Bashford, 1909)

At the outset Dr. Bashford wrote, "A general discussion of the part played by heredity in causing cancer in families or individuals must at the present time be imperfect and hugely hypothetical." This is an interesting statement at a time when a few other investigators, such as Dr. Aldred Warthin at the University of Michigan, were compiling medical genetic records of families in which cancer was found definitely to be inherited through several generations.

We would all agree with Dr. Bashford that there was evidence that some etiological factors were external and some internal to the body, although investigators did not understand the etiology of cancer then. He thought that an explanation of the etiology of cancer might be forthcoming when the nature of the transformation from normal to cancerous cells was discovered. A possibility that a predisposition to cancer might exist, rather than hereditary factors, was entertained. He stated that a malignant neoplasm contains nothing foreign to its host, citing that it can grow only in the same species of animal and retains the tissue characteristics of that species.

One argument against the inheritance of cancer was statistical. Dr. Bashford produced numbers concerning the sporadic incidence of cancer among men and women in England in 1906: a man over age 35 had a 1-in-11 chance of developing cancer and a woman the same age a 1-in-8 chance. Then he worked out what the incidence might be for families of six, eight, and ten members, finding that the odds of developing "sporadic" cancer in those families would be so great that few families would escape having some members die of the disease. However, Dr. Bashford did not undertake family studies of cancer because he felt that in most cases family members would be unaware of the cause of death of their more distant relatives (such as aunts, uncles, and cousins), whom he termed "collaterals." In most cases, recorders of medical histories neglected to obtain a family history of their patients (as is true in many cases to this day). Dr. Bashford also felt that family histories should be obtained concerning families with *no* history of cancer, to be compared with those with such a history.

Dr. Bashford thought that family histories of hereditary cancer were extremely rare, comparing the few that had been reported in the literature with the large number of sporadic cancer cases. He concluded, then, that there was no evidence that cancer is hereditary, but rather that it is an "acquired" disease. However, he did point out that cancer can be hereditary in the mice with which he experimented, and that there are constitutional conditions which are favorable and others which are unfavorable to the growth of cancer in these animals. He concluded that "with nothing but negative evidence of the part played by inherited constitutional conditions, and with positive evidence of the important part acquired constitutional conditions can play in furthering the growth, and perhaps the development of cancer, we shall more profitably spend our time if we frankly seek to ascertain how they are acquired than if we continue to preach the doctrine that they are inherited and that it is hopeless to contend against them." He did not seem to realize that finding solutions to the hereditary factors in cancer was just as important as learning about the environmental factors.

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