

CANCER: CLINICAL AND EXPERIMENTAL ASPECTS

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Since civilized man recorded his opinions on stone, papyrus or in the memories of man, cancer has been mentioned. The early Greeks, Hindus and Egyptians left recognizable descriptions of what they saw. It is probable when the Stone Age man noted his wife dying of something which he could not understand that it was a cancer. Crude surgery developed during the Middle Ages, but presumably no one was ever cured. The invention of the microscope was the next necessary step and then came the discovery of the cellular nature of the tissue structures about one hundred years ago. In the forties and fifties of the last century the classification of human tumors became the main subject of interest. Various hypotheses as to the causation of cancer were produced, the most important being that of Virchow, who believed that the appearance of cancer was usually correlated with chronic irritative processes, and clinical observers began to collect material to support this notion. The betel-nut cancer of the mouth in the East, and the Kangri cancer due to the native custom of carrying a basket of burning charcoal under the clothes for comfort in winter, which frequently burned the abdominal wall, are two examples. Many of these burns were followed by cancer. The Far East also offered the first examples of the parasites in the internal organs which ultimately cause human cancer. About 1875 Cohnheim introduced the idea that many of the more complex growths were the result of remnants of tissue left during embryonic development.

Attempts to transplant tumors occurring in domesticated animals were carried on for many years but failed completely until Loeb and Jensen at about the same time, that is in 1901 to 1903, found that spontaneous tumors in mice and rats were transplantable into the same species only. Shortly after this the Imperial Cancer Research Fund was established in England, with Bashford at its head. He was an aggressive, broadly trained pathologist and gave great impetus to cancer research. Another worker was the famous Paul Ehrlich, the inventor of salvarsan, who after a few years abandoned all attempts at cancer research but made important contributions concerning inoculated tumors during this period. The earliest studies were exploratory in direction and included the transplantation of tumors in animals purchased, in general, in the open market, and the observation of a host of phenomena following grafting, among them the prompt disappearance of a tumor, leaving the animal immune.

This false lead has wasted hundreds of thousands of dollars and literally thousands of years of labor. For thirty years investigators had been struggling to imitate the process of the spontaneous disappearance of tumors. Finally, Little, a geneticist, Tyzzer, a pathologist, and the

workers in the Institute of Cancer Research of Columbia University, began to insist upon the importance of pure strains as a culture medium for the tumors. Immediately all spontaneous cures ceased, no immunity could be produced by the inoculation of tumors, and a host of observations, biologically important but not pointing the way to any fruitful results, have disappeared into the scrap-basket of the forgotten.

It is now generally understood that the cancer cell is an individual in the body of the host and that some tumors may spring from a single cell. More rarely multicentric growths appear. It probably takes an individual cell a long time before it and its descendants make a sufficient mass to produce a noticeable tumor, years in fact in man and more rapidly in the shortlived rodents. The change in the cell is probably a mutation of some type or if the geneticists want to argue about the question of a "somatic mutation," let us leave the phrase to them and call it a change of some sort in the protoplasm and the nucleus of the cell. Once this change has taken place the new race lives as a parasite on the body of the host. There is ample evidence now that this is a permanent and irreversible change. A cancer cell cannot be made to revert to a normal cell, as was believed even a few years ago.

All the morphological and biological qualities of these inoculated tumors remain permanent over thousands of transfers. The Jensen rat sarcoma still looks as it did in 1903. Nevertheless, this new race has the same cell chemistry of the host in which it originated and, therefore, it does not incite reactions of the type induced by bacteria and foreign proteins. Hence, the search for immune reactions has been a continuous failure.

It was hoped that cancer could be diagnosed by serum or chemical reactions, but all efforts have so far failed, with the exception of the Aschheim-Zondek test. This is limited to one type of tumor and is based upon the stimulation of the ovary of the mouse or rabbit to form a hemorrhagic follicle owing to the production of hormones by the tumor. The source of these hormones are the chorionic cells from the placental structures which form in the teratomas of the testicle. The use of the Aschheim-Zondek test is not so much to make a diagnosis of the teratoma as to call attention to recurrences if such take place, as in that event the patient can be treated by x-ray. The seminomas of the testicle, the most frequent type of tumor, do not show any reaction to the Aschheim-Zondek test, as their cells are derived from the testicular tubules. In women with chorio-epithelioma of the uterus, a positive reaction is important if pregnancy can be excluded and if the reaction does not become negative, it shows that extensions of the growth have taken place in other parts of the body where they may be unrecognizable even by x-ray examination.

It was hoped also that in some way we might extract anti-bodies from animals with cured cancer which, when injected into a cancerous animal or a cancerous human being, would result in the destruction of the tumor. All this failed. A large series of experiments was carried on by Hodenpyl, who used the ascites fluid from a case of quiescent human cancer to inject numerous patients, with results which were startling at the time, but unfortunately no cures resulted. The injection of

damaged cancer cells, killed by heat, cold, radiation and chemical agents, was tried in the hope of inducing an immunity similar to that obtained by injecting dead bacteria, but without the slightest result.

It has been known for nearly 200 years that gas tar causes cancer in human beings. For a long period attempts were made to produce cancer in animals by this agent but, curiously enough, the experimenters used either dogs or white rats and the skin of these animals is not susceptible to this agent. If they had used white mice they would have succeeded in the first attempt, because the skin of the mouse is exceedingly sensitive to tar irritation. Yamagiwa, in 1915, showed that cancer could be produced in the ears of rabbits by tar painting. Many of these were only papillomas, but a moderate number of carcinomata can always be produced with an effective tar. The English, who are always interested in tar and the industrial oils because of the large number of cases of carcinoma which occur in their factories, continued these investigations and the most promising were those of Leitch and Kennaway. Kennaway showed, in 1925, that acetylene when heated yielded a cancer-producing tar, hence the substance which causes cancer in tar workers would probably be of that composition, that is carbon and hydrogen.

The spectroscopic study of many of the carcinogenic substances showed a characteristic fluorescent spectrum in the near-ultraviolet, and Hieger showed that 1 : 2 dibenzanthracene gave this same spectrum. Clar in Germany was the first to synthesize 1 : 2 : 5 : 6 dibenzanthracene and Cook, who was working with Kennaway, resynthesized this material and found it to be carcinogenic. A somewhat more powerful carcinogenic substance was obtained from gasworks tar and is known as 3 : 4 benzpyrene. In 1933, another carcinogenic substance, methylcholanthrene, was synthesized by Wieland and Dane. Cook investigated this compound and found it highly carcinogenic. Methylcholanthrene is derived from the cholic acids and this suggests the possibility that such a synthesis may take place in the body. Further studies have shown that beta-naphthylamine given by mouth or subcutaneously will cause tumors of the bladder and Japanese workers have produced tumors of the liver with orthoaminoazotoluene and paradimethylaminoazobenzene. Azotoluene causes cancer of the bladder and it is probable that 3 : 4 : 5 : 6 dibenzcarbazole produces not only cancer of the skin at the site of application but also tumors of the liver.

The method of action of these compounds is unknown and tumors have been produced in a variety of animals: mice, rats, rabbits and guinea pigs. Tests are going on with the longer-lived creatures, but the ape, for instance, which presumably has a life of some twenty or thirty years, would require three or four years' treatment to produce a tumor. For out of all these studies has arisen the fact that the time of appearance of a tumor with the same carcinogenic agent is correlated with the length of life of the animal. If a mouse lives two years, one-twelfth of that would be two months; if a human being lives 72 years, one-twelfth would be six years. It would be expected that if a mouse had a tumor in two months, which is the case, the human being might require six years, and such is also the case in connection with tar workers, x-ray injuries and a number of other cancers the origin of which we can determine.

Another experimental study has been the investigation of the effect of trauma on animal tumors in order to determine the possibility of a single injury causing cancer in human beings, a matter which is frequently discussed in the law courts. All the animal experiments showed that trauma had no effect on a tumor.

The three most important practical investigations which have come out of the laboratory are: (1) The demonstration by Tyzzer and Knox, that the massage distribution of animal tumors with small cells can be easily accomplished, while the fibrous types, such as the fibrosarcomata and some of the sarcomata with large cells could not be dislodged by massage, and the small-cell sarcomata metastasized extensively without massage. (2) It was shown that the incision of a tumor for removal of a specimen for microscopic examination was not injurious in animals when properly carried out. (3) Quantitative experiments using radium and x-rays on tumor particles and tumors in animals showed, twenty or more years ago, that animal tumors required large doses to destroy their cells, an important bit of knowledge which is just beginning to penetrate into human practice and reveals the lag between the laboratory and the clinic.

It is obvious that the laboratory research side has been in general more the laying of foundations and the removal of misconceptions, most of which were derived from bacteriological analogies. The investigation of cancer has really gained nothing from bacteriology. General biology, on the other hand, has greatly benefited by the discoveries of Rous, Gye, Shope and other workers who have studied the cancer problem from the point of view of the viruses. This does not mean that human tumors are with any probability connected with virus infections, but the fact that certain chicken sarcomas are is an important biological point and the recent demonstration by Rous that the Shope rabbit papilloma virus can act as an agent for the production of malignant growths in the rabbit by means of tar or the carcinogenic hydrocarbons was certainly a discovery of prime importance as regards general biology.

The real advances, however, which have been made in the last forty years on the cancer problem have not been made by the laboratory investigators. They have rather been due to mass attack on the problem and two vital discoveries in physics, that of the x-rays by Roentgen and of radium by Marie Curie. They have added immensely not only to diagnosis but to the treatment of cancer as well. It is scarcely necessary to mention before this audience what enormous facilities have been placed in our diagnostic armamentarium by the development of the x-ray technic. No one procedure in diagnosis has been so valuable in every phase of medicine and surgery as this.

Other improvements have taken place, all of them practically within the last forty years. Firstly, the development of asepsis, which was really concluded with the adoption of the rubber glove, in about 1895. Then there is anesthesia, which, of course, is always necessary for the prolonged surgery of cancer. Not only general anesthesia with ether, but also a host of modern anesthetics, both general and local, greatly facilitated the handling of the disease in surgery. Forty years ago the treatment of cancer was in the rudimentary stage and very few patients

were ever permanently cured or relieved of the disease. Today with the introduction of improved instruments, such as the gastroscope, bronchoscope, cystoscope, peritoneoscope, etc., the various internal organs of the body can be inspected and tumors can be seen and fragments removed for microscopic examination. While it is not always possible to see every carcinoma of the stomach or every bronchial carcinoma, nevertheless most of the tumors of these regions, even of small size, can be demonstrated.

Since 1895, a matter of only forty-five years, the whole development of an effective attack on cancer has taken place. This is due largely to experimental work on animals and the efforts of leading surgeons in this country and Europe. What we have learned from experimental physiology and pathology has in many ways directly helped in the treatment of cancer and added to our ability to attack the disease in parts of the body where no one had thought of attempting to do so with successful results ten years ago, yet such operations are now being done quite frequently, as in the case of carcinoma of the lung. Obviously, many of the internal cancers are seen so late that despite modern diagnostic efficiency nothing can be done because metastases have occurred throughout the body. But with the improvement in and extension of education which, of course, must go hand in hand with diagnosis, patients are coming earlier for examination and many are having annual or semi-annual studies made in order to eliminate the possibility of an inaccessible growth.

A good deal of this effort owes its success to the publication of large series of cases operated upon or treated by radiation which have survived for a five or ten year period. The American College of Surgeons has contributed much to this by the collection of some 30,000 recorded cases of cancer well for five years or more. This was done very easily, the figures coming mostly from the large hospitals in this country, and such a demonstration cannot help but be impressive and of value in aiding education. No one will listen with pleasure to a recital of the number of deaths from cancer. On the other hand, now that the profession is in a position to say that as a result of the last forty-five years' work and scientific study a real step forward has been made, people will listen eagerly.

An example of the change which has come has just been published by Schinz from the Radiation Clinic in Zurich, giving a complete review of their material as observed from 1919 to 1935, with no selection whatever. In this period 2529 patients were treated. In January, 1937, 15 per cent of the total were alive and apparently well. There could be added to this 2 per cent more who died from intercurrent disease during the period without symptoms of cancer, but they and the untraced cases, amounting to another 2 per cent, were rejected. Also, favorable palliative results were obtained in 54 per cent of the total. The patients referred to this Clinic are most of them inoperable and, therefore, represent a more or less hopeless group and the fact that 15 per cent of these hopeless cases can be cured now by radiation, when twenty years ago the effective use of x-ray was just beginning and probably all these patients would have died, shows what can be accomplished.

Another field in which there has been great improvement is that of cancer of the cervix. The League of Nations figures are astounding. Studies of many thousands of cases have been made from all over the world and about one-fourth of such patients are cured for five years or more. The interesting point in this is that the conditions are not very favorable for early diagnosis and in those cases in which the diagnosis was made early, there was a 40 to 50 per cent of five-year cures. But more important still is the fact that there were 5 per cent of cures in the hopeless and advanced types which have never been cured by surgery.

On the other hand, from a purely surgical standpoint, cancer of the breast is now being cured in about 30 to 35 per cent of all patients coming to the hospital for treatment and the early types are being cured in 75 to 80 per cent. This means that the tumor has been diagnosed microscopically and the patient has been followed for the elapsed five years.

This is an astonishing thing to one who like myself has watched the whole period of development of cancer surgery and radiation. During the time of my internship, for instance, from 1894 to 1897, only the very smallest and earliest superficial tumors were cured and no attempt was made to cure a cancer of the stomach, for example, of which the Mayo Clinic now reports a 5 per cent salvage. Most of our patients came so late that the operations today would not be undertaken. Now when a patient is considered inoperable, he is treated palliatively with radiation or surgery, or both, to prolong life as much as possible in comfort.
