TUMOR GROWTH AND TISSUE GROWTH.

By LEO LOEB.

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In the course of the last five years, partly through the aid of their respective governments and partly through private initiative, institutions have been founded in the majority of civilized countries for the investigation of the causes and the conditions of growth of malignant tumors; or, as briefly named, for the investigation of cancer. This fact proves more clearly than anything else could do the widespread interest that has recently been aroused in this part of pathological research. Pathological investigations share with those of other sciences a double nature. On the one hand, their problems are of a practical character. Pathology wants to find the causes of diseases and the conditions that favor and inhibit their progress, in order to lay a firm and scientific basis for their cure. In this respect, pathology is an applied, a technical science. On the other hand, pathology desires to analyze the conditions that ultimately lead to death, in order to recognize some of the phenomena of life. In that sense, pathology is a pure science; its aim is philosophical.

Tempting as it might be to relate something of the first attempts of pathology to find the cause and the cure of cancer, I shall here, rather, turn to the purely theoretical aspects of these investigations and indicate some of the results of tumor investigations that have some bearing upon one of the fundamental characteristics of living matter—the ability to grow. Before entering, however, upon a necessarily very limited discussion of some of the relations between tissue and tumor-growth, it might be well to indicate what a tumor is; and, especially, what a cancer is.

Perhaps I can best approach this delicate task by stating some varieties of growth that are not included under the term tumors.

Our bodies consist of cells (that is small parts of protoplasm with nuclear material), of products of cells of different kinds, of decomposition products of cells and of material used for the building up of cells. Here we are concerned with the two former only, namely, with the cells and their direct products. Now growth is based upon an increase in the number or the size of cells in the locality, where growth takes place. The increase in the number of cells can be brought about in two ways: either through the multiplication of preexisting cells, or through a wandering in of new cells. Cell-growth can take place under various conditions. If toxic substances—the products of bacteria for instance—or even if inert substances foreign to the body are introduced into the organism, a certain proliferation of the neighboring cells and immigration of cells from the blood- and lymph-vessels take place. After a certain period, such reactions come to a standstill, and scar tissue develops. Such a cell-proliferation we do not call a true tumor; but we class it among the inflammatory reactions.

There are other conditions in which an unusual cell-proliferation takes place in the adult organism; in cases of wound healing. If, for instance, a wound is made in the skin, the cells of the epidermis proliferate until the wound is closed; then the additional proliferation ceases. We call this regenerative growth. It lasts only as long as the continuity of the epidermis is interrupted. This is not tumor-growth.

We now come to a third variety of cell-proliferation, distinct from the two former varieties. If a follicle of the ovary ruptures at the time of menstruation, the follicle cells enlarge, and proliferate much more extensively than would be necessary in order to insure wound-healing. There is formed a new growth, which exists for a limited period and then disappears. A still more striking example of this new formation was found in our laboratory in the course of the past year. If, at a certain period after copulation has taken place, or at the period of heat, the inner surface of the uterus is sufficiently exposed and cuts are made in the wall of the uterus, we find that, instead of the ordinary wound-healing, another process takes place, namely: the development of nodules of new tissue, which resembles closely the maternal part of the placenta—without, however, an ovum being in this case responsible for the new formation; but also in this case the experimentally new-formed decidua, as we call this tissue, dies.

The latter variety of growth resembles much more closely the real tumor-growth than do the former; but in this case also the cell-proliferation, and even the life of the newly formed cells, cease, when the cause for the proliferation has disappeared. The cause for the development of an artificial decidua is probably two-fold: in the first place, a general chemical condition exists in the body at that period; and, under these predisposing conditions, a local stimulus suffices to produce the tumor-like growth. These new formations might be called transitory tumors, because they have a definite life-cycle; they grow for some time, and then they disappear.

In real tumors we find a similar but still more marked cell-proliferation; and they do not have such a definite life-cycle. Real tumors do not retrograde usually, and may even grow, more or less, during the lifetime of the bearer. Furthermore, we do not know the cause of their origin, as we do in the case of the transitory tumor. They grow, and we do not know why. If such tumors grow more rapidly, and especially if they grow deep into the surrounding tissue, digesting it, if parts penetrate into the blood- or lymph-vessels and are carried away to distant parts of the body, and here start a new growth, a so-called metastasis, then we call the tumor malignant, or a cancer.

We distinguish different varieties of cancer, according to the tissue or variety of cells from which these cancers originate. The malignant tumors derived from epithelial surfaces or gland cells, we call carcinomata and the malignant tumors derived from the connective-tissue cells, which unite the functionally more highly developed cells, we call sarcomata. But from whatever tissue these malignant tumors are derived, their main characteristics are identical.

During the second half of the last century, pathologists studied very carefully the microscopical character of the different tumors; and they determined quite accurately the genesis of these tumors from normal tissues. They observed how cells began to grow down into the adjoining tissues in cancer; they described the general spreading out of the new formation, and the character of the secondary growth; they also determined that a certain number of tumors apparently originate in tissue that has been misplaced during embryonic development. In other cases, long irritation, and occasionally a traumatism, may be held responsible for the origin of cancer. Apparently, however, no further progress could be made by these means of observation. The investigations seemed to have arrived at a dead point.

After a few isolated previous attempts, mainly since the year 1899, the attention of the investigators was directed to the occurrence of tumors in animals; to the fact that cancer in animals frequently occurs endemically. This means that a number of animals are affected with cancer simultaneously in a certain locality. Furthermore, they observed that certain kinds of tumors are characteristic for certain species of animals; and that the tumors occurring endemically in a species of animals are all of the same type.

The most important fact, however, which was fully developed only within the last eight years, is that it is possible to transplant a certain number of cancers into other animals of the same species. Many attempts have been made to transplant cancers into animals of other species and make them grow in these animals, but without any success. A certain kind of cancer found in the dog can be made to grow in some related species, as, for instance, in the fox. Other tumors found in white rats may be transplanted into hybrids between white and gray rats, and the cancer of white mice can occasionally be made to grow in gray mice. The cancer of a Japanese mouse could not be successfully transplanted into white mice, however, but only into the Japanese mice. No such tumors can be transplanted into more distantly related animals, nor can the cancer of man be transplanted into lower animals. A very malignant tumor from a mouse can occasionally be made to grow for a few days in a rat, but the growth soon stops. In a similar way, normal tissues of the body, for instance the epithelium, may be transplanted into other animals of the same species, and kept there alive after an initial growth; but if transplanted into an animal of another species, it grows for a short period and then it dies.

Some tumors, and probably the majority of them, can be transplanted only into the same animal in which they have originated.

Here they live, and even grow; while in other animals of the same species, they die very soon after transplantation. This probably applies to most of human tumors. The same holds good of certain animal tissues and organs; as, for instance, the ovary. They can much more easily be transplanted into the animal of which they have formed an integral part, than into other animals of the same species.

There exists another point of similarity between the transplantation of normal tissues and organs, on the one hand, and of tumors, on the other: in both cases, after transplantation, only the peripheral parts of the transplanted piece usually remain alive; the central part, which is not well supplied with lymph or blood from the host, soon dying. This similarity between the behavior of normal tissues and of tumors after transplantation can be easily explained, if we consider that in both cases we have equally to deal with the inoculation of cells or tissues from an animal organism; and that the transplanted tumor, as can be readily shown by microscopic examination, grows merely from the transferred tumor-cells themselves, and not from the tissues of the receiving host-animal.

On the other hand, however, there exist also some very interesting differences between the growth of normal tissues and of tumor-tissues after transplantation, the former always growing only very slowly for a time, and then ceasing to grow, or merely remaining alive after transplantation; and the latter continuing to grow rapidly, and sometimes continuing to infiltrate the surrounding host-tissue and to make metastases. Their character is not markedly modified through transplantation. Eight years ago I transplanted a sarcoma of a white rat into more than forty generations, without an appreciable decrease in the energy of growth of the tumor cells. The fact that it is possible to propagate tissues of the animal body through years and years in other animals of the same species, without any loss of vitality and power of propagation of the tumor-cells, while they would long since have died if they had remained in the animal to which they originally belonged—suggests, it seems to me, a consideration of great biological significance, namely, the question whether our own body-cells are all equally mortal, or whether their death does depend upon their accidental connection with other cells and with an organism that dies, and because a certain number of cells, especially of nervous character, cannot survive.

The inevitable fate of all metazoan organisms is death; and this conception deeply influenced all our valuations and directions of thought, as Metchnikoff only recently pointed out in his book on the "Nature of Man." Weismann added one consoling idea: not all of our cells must necessarily die, but only the so-called somatic cells; the germ-cells, ova and the sperm-cells, of each individual may propagate forever, may be immortal. The results of the tumor investigations just mentioned may, perhaps, enlarge the number of cells that may remain alive for so long a period that we cannot see the end at present; ordinary somatic cells may propagate through many generations, long after their brother cells that remained in the original organism have been transformed into simple chemical substances, and who can at present deny the possibility that they may have the potentiality of immortality, as well as the germ cells? Thus the work on tumors leads us into different realms of general biology, and opens up new fields that are not without interest.

The experimental work on tumors has given some other results of an unexpected nature. One of the great achievements of the last century was the development of bacteriological technique by which it is possible for us not only to cultivate bacteria on artificial culture-media, but also to influence markedly their behavior, functions, vitality, and virulence. It has been found to be possible to raise the virulence of certain bacteria by inoculating them into animals through several generations; on the other hand, it is possible to decrease their virulence by subjecting them to certain injurious chemical or physical agencies. Such a bacterial culture with artificially decreased virulence has been used as a vaccine; that means, as a substance that, when inoculated into human beings or animals, without causing the disease, confers immunity against the virulent bacilli.

In experimenting with tumor cells, the surprising result was obtained that, through successive transplantations, by cutting out pieces of tumor, an artificial stimulus is given to the tumor cells, so that they begin to grow more rapidly and more extensively. In other words, their virulence has been increased. This is due to a direct stimulating action upon the tumor cells, and not to secondary conditions. This explains a fact very familiar to surgeons; namely, that after an operation a recurrent tumor is frequently more malignant than the original tumor.

But it is also possible to decrease the power of propagation of tumor cells without killing them by exposing the cells to chemical and physical injurious influences, in a way similar to that pursued in the case of bacteria. Here, also, we may, not without some hope, look forward to the preparation of some vaccine that may, some day in the future, help us to combat the dreaded disease. Even in this case, however, tumor tissue probably differs only in degree, and not in principle, from normal tissue. At least, this conclusion is indicated by the fact that such an organ as the normal thyroid gland may, without being entirely destroyed, be markedly weakened in its power of growth through a short exposure to the air before transplantation.

There exist, however, some interesting differences of another kind between tumor tissue and normal tissues or organs. Normal organs have a specific metabolism and, in connection with or as a part of this metabolism, they exert distinct specific functions. We understand by functions those physical and chemical processes which attract our attention by their real or apparent significance for the organism as a whole. The normal female mammary gland, for instance, secretes milk under the influence of certain chemical stimuli which are present in the circulation at the end of pregnancy; and it also grows during pregnancy, under the influence of similar stimuli. If we now transplant the mammary gland of a nonpregnant animal into a pregnant animal, the foreign transplanted gland may secrete milk at the end of pregnancy in a similar way to that of the animal's own gland. The circulating chemical substance exerts the same stimulus upon the transplanted as upon the autochthonous gland, and the transplanted gland responds to the stimulus in the normal way.

There exist certain conditions in which a tumor-like hypertrophy of the mammary gland is found in the white rat. The structure of the gland is slightly modified, but the tumor is not infiltrating. We do not call it a cancer, but a benign tumor—an adenoma. If we transplant such a tumor to another place in the original animal, it heals, and if the animal becomes pregnant, it begins to grow in the same way as the normal gland, but is no longer able to produce milk. It responds, therefore, only to certain stimuli, but not to others.

If we persist still further and transplant a malignant tumor, a cancer, of the mammary gland, we find that it no longer responds to the stimuli of pregnancy. Such tumors do not seem to assume a more rapid growth, nor do they ever secrete milk. The metabolism of tumors differs, however, only in a greater or less degree from that of the corresponding normal tissues; and the tumor tissue can even still continue to secrete certain substances in a similar way to the normal tissues. This has been observed, for instance, in the case of the tumors of the liver and of the thyroid gland, which latter provides a so-called internal secretion, without which widespread changes would take place in our body. It seems, therefore, in the case of the tumor tissues that there exists a parallelism between its loss of function and its capability to respond to chemical stimuli in the body that normally excite and regulate function and growth.

These observations bring us also nearer to an understanding of tissue growth and tumor growth in general. Just now we mentioned substances of various kinds circulating in the body that regulate the growth of normal tissues and of tumors; but there probably exist a number of such substances. How else could we explain the fact that the majority of tumors may be successfully transplanted into the organism in which the tumor had originated, but not into other individuals of the same species? Evidently there must exist some difference between the chemical composition of the blood and lymph of each individual of one species; and each tissue of one individual is more or less adapted to its own body fluid. Furthermore, we have seen that tissues do not grow in animals belonging to different species; there must, therefore, exist substances regulating growth, which are the same in the same species, but differ in different species. Sometimes, however, certain families of white mice differ among one another to a higher degree than the white mice differ from gray mice.

Such substances, however, can merely regulate the growth of normal tissue and of tumor tissue; they are not able to transform normal tissue into tumor tissue. How the latter transformation is brought about, we do not yet know; and this is one of the problems that remain before us. Of one fact we may be reasonably certain; namely, that the growth-regulating substances to which we referred just now are, in all likelihood, not the primary factors in the production of tumors. We draw this conclusion because the action of such substances has so far not been shown to be hereditary. They influence the growth as long as they are present. If we liberate tissues or tumors from their influence these substances lose their effect at once or relatively soon. If, however, we are able to transplant certain tumors through forty generations of animals and if the tumors preserve their character as tumors, notwithstanding the individual differences of the different animals into which they are transplanted, then there must be present some factor in or near the tumor cells themselves that constantly stimulates their growth and stirs them restlessly to new activity, until through their activity they destroy their host, and thus prepare their own end. What the character of this local stimulus is, we do not yet know. All the discoveries of organisms that have been announced from time to time were found to be based upon erroneous observations; but that does not exclude the possibility that, after all, a microörganism in intimate relation with the tumor cell is the local stimulus acting on the tumor cell.

There are two discoveries that, in themselves of interest, promise to give us a foothold from which to attack successfully this problem: In the first place the endemic occurrence of tumors among animals, to which we alluded above. Here we can determine whether it is caused by hereditary conditions, or whether it is due to microörganisms or environmental factors. Secondly, the surprising fact we learned three years ago, that if we inoculate one kind of tumor, an epithelial tumor, a carcinoma, into animals, the carcinoma, in a certain number of cases, causes the surrounding connective tissue to assume, likewise, a cancerous growth. We have here, therefore, actually succeeded in producing a new tumor, a sarcoma. Such a fact was entirely unforeseen. It could be discovered only through the experimental method of investigation. The more unexpected a new fact, the more welcome it is; the more it promises to change existing conceptions and to open up new roads, where before no way out could be seen.

Lastly, the first steps have already been taken to find a rational way of curing cancer by procuring immunity in a similar way to that by which we are able to cure a certain number of infectious diseases. Protective sera can not only be prepared against bacteria, against toxins, but also against cells; and probably also against tumor cells. The beginning has been made. Certain tumors in animals have been made to disappear in such a way. Let us hope that the future holds still better results, and that we shall be able to alleviate suffering and to gain a deeper insight into conditions that determine the fate of living matter.

Stated Meeting February 7, 1908.

Councillor ROSENGARTEN in the Chair.

A letter was read from the Fourth International Congress of Mathematics, announcing that the Congress will be held at Rome, April 6–11, 1908.

PROFESSOR EDGAR ODELL LOVETT presented a report on the "Leçon sur l'intégration des Equations différentielles aux dérivées partielles professées, a Stockholm (Février-Mars 1906) Sur l'invitation de S. M. le Roi de Suède par M. V. Volterra, Senateur du Royaume d'Italie, Professeur de Physique Mathématique à l'Université de Rome." He also presented a paper on "Integrable Oases of the Problem of those Bodies in which the Force Function is a Function only of the Mutual Distances."

PROFESSOR HORACE C. RICHARDS and PROFESSOR ARTHUR W. GOODSPEED read a paper on "Recent Advances in Color Photography."

Photographs by the Lumière process were exhibited by Dr. Hartzell and Dr. W. P. Wilson.

Stated Meeting February 21, 1908.

Treasurer JAYNE in the Chair.

DR. J. H. HART read a paper on "Artificial Refrigeration."