Symbiosis, Antibiosis, and Cancer

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VERY FUNDAMENTAL ARE THE FACTORS of symbiosis and parasitism that condition helpful or harmful associations between living things. They operate at many—perhaps at all—levels in the plant and animal kingdoms and are not without interest in the cancer problem. In human relationships also they play a very large part as has been eloquently outlined by the philosopher, Arthur E. Morgan, of Antioch College.

In symbiosis (which is life together), individuals of two different sorts are to some extent benefited by the partnership. A large number of very striking examples are furnished by Nuttall. The green algae in many aquatic invertebrates, and myriads of *Bacterium radicicola* within clover root nodules, are typical instances of this phenomenon. In some cases the original association started with parasitism, which, by mutual adaptation of host and parasite, became symbiosis.

Consider the leprosy organism. In so-called tuberculoid leprosy of children, the infecting organisms in the tissues are few in number and often very difficult to find, but the reaction of the tissues to them is vigorous and the young patients usually recover. Conversely, in nodular leprosy of adults, a relationship approaching symbiosis is established between these organisms and the most voracious cells of the body, the macrophages, so that the organisms live and multiply within them. It is thought that leprosy organisms, by repeated sojourn in humans through thousands of years, have become far less pathogenic for adults in the process of adaptation already mentioned.

An example of more enduring association is provided by certain little opalinid parasites of the genus *Zelleriella* in tailless amphibians. Metcalf concludes that these arose in South America, probably millions of years ago in the early Tertiary, and spread by a land bridge to Australia, the only other part of the world in which they occur. These host parasitic associations come in the domain of paleogeographers.

Arachnids have lived on this world much longer than have amphibians. Many of them harbor organisms, termed symbionts, which are passed from generation to generation in the eggs. I have been impressed by this occurrence in ticks. The adaptation here is the most intimate of which we have knowledge. When it started we do not know. It may be among the most long-standing cases of symbiosis. Both partners have been world inhabitants up through the ages.

I like to think of the relations between the cells which make up our own bodies as being symbiotic also. There will be objections, of course, to such a concept. The term has thus far only been applied to mutually beneficial associations between two organisms of different kinds. It will be said that I am romancing in regarding body cells as "organisms," but it is not considered bad form to refer to protozoa as "cells." Both have many features in common. They are descendants of other individuals closely resembling them. Some are sessile, or fixed in position, others are motile, and they have the distinguishing features common to their kind. They live, age, and die as individuals. Very significant is the fact that they can be grown as individuals in pure cultures, apart from any other living things, and they seem to carry on their streams of life as long as environmental conditions remain favorable.

If the basic organismal nature of body cells is accepted, it may be further objected that within the body it is not exclusively a case of mutual benefit between two different cells as it is in the classical concept of symbiosis between two different organisms. Against this view the argument could be advanced that the qualification "exclusively" is not justified, because animals live in associations, and some additional species derive benefit from the presence of such others, themselves fortified by symbiosis. But this would be to avoid the issue. In symbiosis it is often a case of benefit between a single larger organism and many others that live in it. Many instances of mutuality of the benefit are seen in the body between two groups of cells. Thus, the spinous cells of the epidermis help to shield the basal ones from the external environment, while the basal cells partly shield the spinous ones from the blood stream. Gland cells produce secretion and are benefited by the duct cells that carry it away, while the duct cells, in so doing, find employment. But the benefit of association is not exclusively felt by any two groups of cells. It extends in ways too numerous to mention to the whole community of cells, often over considerable

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distances, by the blood stream and nervous system. The body is, in effect, a complex of symbiotic relationships recreated with each generation in patterns which have gradually taken form in possibly a billion years of history. Some may prefer to call this partnership "commensalism," in which neither organism harms the other. This term is derived from the Latin words *com* (together) and *mensa* (a table). Our body cells do feed together at the same revolving table of the arterial blood stream. Ordinarily they do not harm each other, and there is benefit to all concerned. But in this paper we concentrate on the opposing phenomenon of antibiosis.

In antibiosis the association between two different organisms is detrimental to one of them. It is Greek *anti* (against) *biōsis* (life). When the injury is caused by a substance produced by the offending organisms, that substance is said to be an antibiotic. We are here concerned with such organismal (organic or biological) antibiotics, and we set aside other substances not produced from organisms, though these may be equally powerful antibiotics. The offending organism is an "antagonist" of the injured one.

This antagonism, whether brought about by some antibiotic substance produced by the antagonist, or by some other mechanisms, is an occurrence almost as widespread in Nature as is symbiosis. It is found, as knowledge expands, with increasing frequency between different types of viruses and between different kinds of bacteria. There is marked antagonism between invading organisms and the cellular defenders, leucocytes and macrophages, without which we would soon die. We know that there is mass antagonism between the cells of different species. Those of one create conditions incompatible with the continued life of others offered to them in transplants.

Before we come to malignant cells, we ask ourselves about normally-occurring antibiotic phenomena and cellular antagonisms in multicellular animals. If one interprets these terms broadly, they cover every influence exercised by cells of one type upon cells of another type which is antagonistic to the lives of those of the other type. The factors that can adversely influence cell life are legion. One wonders about the mechanism of what zoologists call "determinate growth." Rotifers, and several other kinds of invertebrates, are limited to a fairly definite number of cells. When this number is attained, cell division abruptly stops. The number of cells is counted by enumerating the nuclei. In the normal organs of the rotifer the number is constant. Van Cleave examined 435 gastric glands and invariably found the number to be 6, never 5 or 7. Is this because of mass antagonism of the cells already present to more of the same sort, expressed by cellular birth control brought about by some contraceptive substance? Or, is it due to the cells being endowed with some vital elixir, the supply of which is only sufficient for a given number of cells? We do not know, but it would be interesting to discover whether extracts of these multicellular communities made when mitosis stops contain any substance inhibitive of mitosis.

Within a single growing mammal, which is higher up the scale and more complex, but about which we have more information, cell division of certain cell types is arrested at a definite age and never resumed, while for other replaceable cells it continues. And in compensatory regeneration, when multiplication of cells follows a loss of cells, mitosis is halted, as in the lowly rotifer, at the moment that the normal complement of cells is attained. An influence, or influences, antagonistic to the vital act of cell division swings into action. The nature of this influence is a mystery, as is its source; it may emanate from the hard-pressed cells which no longer must work harder because of the loss of their fellows, or from cells of other sorts which also felt the loss because they depend on adequate service by the tissue called into regeneration.

Within the body one has to look closely to see signs of antagonism. In the placenta, cells of fetal origin invade maternal tissue. During development, bone replaces cartilage. Bone is built by osteogenic cells, and osteoclasts appear to be involved in breaking it down. The cells may be less active than the fluids about them which they help to create. The association between different types of cells within the body is not wholly free and complete. There are some limitations. Walter Cannon spoke of homeostasis—the maintenance of like states in the blood. But the tissue cells are shielded from the blood stream by an endothelial barrier; were it not so, specialization and division of labor could not have been developed, because equal exposure to the blood stream would tend to perpetuate uniformity. In fact, the condition of organized symbiosis is heterostasis—the maintenance of different or special states in tissue fluids adjusted to the functional needs of certain cell groups. This I have discussed in detail elsewhere. The point is that a mesenchymatous cell does not become an osteocyte until its fluid environment is limited by the maintenance of a special state characterized by many fibers and much mineral material. Cartilage cells, when they lose their natural special fluid environments by growth in tissue cultures, change their whole appearance. Some cells in avascular tissues like the cornea can function only when tissue fluid is restricted. Heterostasis, evolved during development and continued during life, is essential.

One reason why so little is known about cellular antagonism in the body is that most cell types do not have an opportunity to exhibit it.

When cells are removed from the body and grown in tissue cultures, they are released from special tissue fluid environments and from controls of many kinds. In mixed cultures of fibroblasts and epithelial cells, the former survive and the latter die. The obvious explanation is that the fibroblasts are a tougher race of individuals than are the epithelial cells. Apparently search has not been made for the generation by them of some antibiotic active against epithelial cells. But tissue culture is a fine art, and its devotees may be able to cite instances of true cellular antagonism of which I am ignorant.

All observers are agreed that differentiation is antagonistic to mitosis, but in this case the basis of comparison is different. It is not the influence of cells of one kind on another but rather that of advancing age and specialization on the ability of the same cells, losing their youth, to divide. In exploring possible means of influencing cell division it would be interesting to see whether the multiplicative rate can be reduced by administering to young cells extracts of their older and highly differentiated fellows of the same strain.

Cancer cells are developed from normal cells by what is termed a malignant transformation. Previously living in symbiosis with their fellows, they suddenly become redoubtable antagonists for them. They invade territories not their own, crowd out the proper cellular inhabitants, and live as parasites at the expense of the whole cellular community, which undergoes slow starvation. Witness the loss of weight and emaciation in victims of advanced cancer.

These malignant cells are in some respects less differentiated than their normal prototypes—that is, they have lost certain properties, but they have acquired other properties that condition their malignant behavior. On the whole, they are said to resemble comparatively undifferentiated embryonic cells, especially in their power of multiplication, though in this they exhibit wildness and lack of restraint. Yet in speed of multiplication they are still second best. No cancer grows at the rate of the fetus *in utero* in some stages of gestation. Hope is found in the fact that the rate is subject to variation. Sometimes a cancer patient, expected to die in 6 months, survives much longer than that, and the reverse—death coming sooner than was expected—may happen. The same type of cancer may spread like wildfire in one person and, in another, extend very slowly. A large primary cancer may metastasize slightly, and a small one extensively. Occasionally, a cancer remains more or less dormant for a considerable length of time, only to become active later. In extremely rare cases cancers have been known to disappear completely for no obvious reason. It would appear that such differences in behavior must be occasioned by changes in the cancer cells themselves or by alterations somewhere in the cellular community in which the cancer cells are living as antagonists. Some cancer cells have not altogether lost the regulative control usually exercised by other cells on their normal prototypes—that is, on the kinds of cells from which they arose when the malignant transformation took place. For instance, prostatic cancer cells are partly curbed by estrogenic hormone; therefore, experiments designed to intensify the influence of other body cells and fluids on cancer cells are indicated.

On the basis of some similarities between cancer cells and embryonic cells, it would seem logical to try to bring to bear on the cancer cells influences that promote differentiation of embryonic cells in the hope that the cancer cells likewise would undergo some measure of differentiation. One of the most fascinating lines of research in experimental embryology relates to the so-called "activators." When a piece of tissue is implanted under embryonic ectoderm, an activator is (or activators are) given off by it which very greatly enhances the differentiation of the ectoderm. It makes little difference whether the implanted tissue is dead or alive. It can be boiled without destroying the activators. Many tissues and materials will act in this fashion, and we may have to wait on the embryologists for more data; but there is urgency in the cancer problem, and if it were possible only very slightly to promote differentiation in a cancer, this might be helpful, since, as every biologist knows, differentiation is antagonistic to mitosis.

Many have been the attempts to treat cancer by the injection of tissue extracts and to intensify the action by purification and concentration of substances in extracts antibiotic for the cancer cells. Some guiding principles seem to take form even from this elementary discussion of symbiotic and antibiotic relationships normally existing in the cellular community and from what is known of the heterostatic maintenance of different tissue fluid environments.

Returning to the antagonism between differentiation and cell division, there are, of course, as many lines of differentiation as there are kinds of highly specialized cells in the body, each conditioned by a particular complex of factors. Consequently, it might be the part of wisdom to expose malignant cells to extracts of more differentiated cells of the types from which they themselves developed when the malignant transformation took place—epidermal cancers to extracts of pure epidermis, neuroblastomas to extracts of nerve cells, and so on down the list. The specificity

of the cellular birth control mechanisms, already alluded to, which cut short compensatory regeneration at the point when the loss of cells has been made good, provides a further argument for this kind of search for possibly antibiotic extracts.

If more could be learned about cellular and tissue antagonisms within the body, it might be feasible to try the influence on cancer of extracts of cells normally most antagonistic to those from which the cancer developed, the idea being that the cancer cells may not be sufficiently dedifferentiated to have lost susceptibility to the antagonists. The principle of sex hormone antagonism in cancer therapy does not require elaboration. Other equally clear-cut cases are difficult to cite. In the excavation of the marrow cavity in bones it is just conceivable that materials antagonistic to osteoblasts are formed. Consequently, extracts of young bone marrow might conceivably have some deleterious effect on osteogenic sarcomata. The point is that in the focusing of possible domestic, or internal, antibiotics on malignant cells normal cellular antagonisms should be borne in mind. A survey of the behavior of body cells in tissue cultures for such antagonisms is much needed.

Another lead to tissues worthy of special attention is the frequency of acceptance by them of cancer metastases. It would be natural to choose those tissues in which spreading cancers seldom lodge and develop. Skeletal muscle and kidney are at or near the head of this list, presumably because the conditions of cell life therein are not favorable for malignant cells. Why this is so is not known; but it would be logical to try the effect of extracts of these tissues on experimental cancers on the chance that they contain some antibiotics for the cancer cells which would be "domestic," since they are formed in the same cellular community. Already extracts of spleen have been carefully examined. One would try to focus the extract on the cancer by treating the cancer with the extract of the tissue least subject to invasion by that particular brand of cancer.

Many sorts of cancer cells have for various reasons been grown in tissue cultures. Usually efforts are made to eliminate all other cells and to obtain "pure" cultures. Cultures of the cells of special interest, contaminated with other cells, are often discarded, as were, initially, bacterial cultures contaminated with penicillium. It would be interesting to make a survey of malignant cells, intentionally planting two sorts of cancer cells in each culture in a systematic search for antagonisms between different kinds of malignant cells. The word "cancer" in this discussion is used to include all kinds of malignant tumors, whether of epithelial or mesenchymatous origin. Cancer cells are by nature antagonists par excellence. They are harmful to the entire community made up of many cell types, the territories of which they invade and which they almost eat out of house and home. The working hypothesis is that some sorts of cancer cells may be antagonistic also to other types. If this should prove to be the case, the road would be open to the employment of extracts of the antagonist cancers against those for which the said cancers provide antibiotics. One would "set a thief to catch a thief."

There is still a fourth line of exploration which is likewise self-evident. Much attention has been paid to species and even to strain susceptibility and resistance to cancer. The refractory animals may owe their special resistance to many factors. Among these, we think at once of especially effective protection against carcinogens and of particular means of invalidating or eliminating them. It is common knowledge also that the tissue fluids of one species are destructive to the transplanted normal and malignant cells of another species except to a limited degree in some sites, as in embryos and in the anterior chamber of the eye. To capitalize upon these circumstances it is not impossible that something helpful might be accomplished by preparing tissue extracts of animals of a species in which spontaneous cancers are rare and in which it is most difficult to induce cancers by carcinogens, and to expose experimental cancers in another species to them. By the same token higher multicellular plants are extraordinarily resistant to many microorganisms. As R. R. Bensley has told me, their tissues have been consistently neglected in the search for antibiotics, some of which may occur and may even be helpful in cancer therapy.

Probably one of the most significant observations to date is the discovery by T. M. Sonneborn, described elsewhere at this meeting, of the production of an antibiotic poison, kappa, by paramecia against other paramecia. The antagonist paramecia are called by Sonneborn "killers."

In this brief account, emphasis has been placed on the normal symbiosis and antibiosis exhibited by the cells of our bodies without which we could not have evolved and without which we could not exist as human beings. One of the many approaches to the cancer problem is purposefully to discover, enhance, and direct the antibiotic phenomena of cellular and tissue antagonisms. This would supplement the haphazard and usually chance discovery of entirely foreign antibiotics produced by organisms far removed from body cells. The fact that some of these foreign antibiotics have been found to be remarkably antagonistic to experimental cancers also supports this idea of looking for antibiotics for cancer cells in the body itself, where the cancers originate and sometimes display quite unexplained alterations in rate of growth.