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# PLANT GROWTH AS A CANCER CLUE

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IT is well-known that plants compete with each other for sunlight, nutrients, water, and growing space. The mechanics of such competition involve several patterns. For example, fast-growing trees tend to shade smaller vegetation. Some plants with widespread roots take up ground water and minerals more readily than other plants. An additional mechanism of plant competition has recently been attracting increasing attention from scientists in several fields. Some plants apparently prevent the growth of competing plants by secreting chemical growth inhibitors. These inhibitors appear to be quite different in nature from inhibitors or anti-auxins which tend to regulate the plant's own growth patterns.

Apparently, the phenomenon of chemical warfare between plants is rather widespread. It is not confined to exotic species in far-away lands, but occurs in the common grasses, weeds, and trees of ordinary American gardens and farms. There is increasing recognition of the importance of understanding this phenomenon, not only as a fundamental factor in ecology, but also as a practical matter that affects lawns, orchards, farms, and may also affect the fate of nations and the development of new drugs for the cure of disease.

STUDIES done thus far suggest that most of the chemical warfare agents secreted by plants are not general toxins. Thus, the term "toxic" probably is not a good description of their action. Instead, they appear to be, for the most part, highly selective differential growth inhibitors which exert their effects even when well diluted in soil. The selectivity has two separate facets.

Most of the inhibitors tend to affect one set of plant species but not other species that seem closely related. For example, the black walnut tree (*Juglans nigra*) inhibits the growth of blackberry, among others, but not of black raspberry. Furthermore, a list of plants inhibited by the secretions of a particular species seems to be quite mixed, with no apparent relationship between the plants inhibited. For example, the black walnut is also reported to inhibit the growth of poverty grass, dock, common cinquefoil, red and white pine, apple trees, potatoes, tomatoes, asparagus, alfalfa, hydrangea, lilac, and chrysanthemum. Undoubtedly some biochemical feature is common to the inhibited group and not to other groups, but as yet no information is available on this point, nor am I aware of any current studies on it.

A second aspect of the selectivity of the chemical inhibitors is their effect on different parts of the victim plant. Some of the inhibitors, including those found in tonka bean, sweet clover, and mountain ash inhibit root growth. The tops of the victim plants apparently grow normally for a short time and then die abruptly. When dug up, they are found to have tiny, stunted roots. Other inhibitors apparently affect the leaves primarily, and some inhibiting secretions of grasses affect roots and foliage of other grasses.

THE source of the growth inhibitor differs with different plants. Some apparently are produced in the roots and spread out in the soil. The black walnut is believed to be an example of this type. Some plants such as *Encelia farinosa*, *Bergenia crassifolia*, and *Artemisia absinthium* (wormwood) have an inhibitor in the leaves. When the leaves fall to the ground and decompose, they release the inhibitor, which keeps other plants from growing for a prolonged period. Seeds and fruits are also sources of inhibitors. As the inhibitors leach out into the soil, their action provides a small, safe zone in which the seedling can obtain a vital start in its growth. A few plants of genera *Salvia* and *Artemisia* secrete volatile growth inhibitors. The vapor apparently condenses into dew, and the dew inhibits growth of competing plants.

The actions of the growth inhibiting chemicals fall into two general groups. Some inhibit growth of plants of other species. They are referred to as heterologous inhibitors. Other inhibitors act on plants of the same species and are referred to as homologous. As a general rule, the homologous inhibitors are more likely

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*"A man can really fight for humanity in a place like this."*

to be found in less fertile habitats such as deserts, where lack of crowding has great survival value. The effect of the homologous inhibitors therefore resembles the end effects of territoriality behavior in animals, an interesting example of the breadth of ecological principle.

The chemical structures of growth inhibitors do not follow any consistent pattern. A corresponding lack of similarity in chemical structure is noted in antibiotics, which are also differential growth inhibitors.

To my knowledge there have been no controlled studies to find out whether the inhibitors are produced in equivalent amounts during all phases of a plant's life, or whether they are produced in much greater amounts during certain times, such as budding or flowering. However, some general observations suggest that the production of inhibitors may relate to certain phases of the plant's life cycle.

In some cases, specific ecologic patterns may be explainable on the basis of differential growth inhibitors. The single stand consists of a large number of plants of the same species, growing in the same area, without any plants of different species. In the past, attempts were made to explain this pattern on the basis of superior adaptability to a particular habitat. However, in similar habitats, one may find a single stand of another species, or a mixture of many plants. On the other hand, if the species in a single stand secretes a broad-spectrum growth inhibitor which is heterologous, it could produce a single stand once its density on the land exceeded some critical level which resulted in a concentration of inhibitor greater than that which could be withstood by the hardiest competitors.

A second interesting ecologic pattern, the "fairy ring," has been explained as due to growth inhibitors. The "fairy ring" pattern consists of a central flower, surrounded at a distance by a ring of similar flowers, all separated from each other. At times, the central flower may have disappeared. The most fitting explanation for the "fairy ring" is that the central plant is the oldest, and that it has produced a homologous growth inhibitor which prevents any plants of the same species from growing within a certain radius. Plants outside that radius, however, could grow and flower.

The composition of plant communities, another area of considerable ecologic interest, is also probably influenced by the differential growth inhibitors, as well as by the usual environmental factors.

There are important agricultural consequences of the actions of the differential growth inhibitors. The deleterious effect of weeds on crops has been known from the beginnings of farming. However, the conventional explanations have not been satisfactory. It has been stated that weeds remove from the soil water and essential nutrients, and thus inhibit the growth of the desired plants. However, some reflection on this explanation indicates its deficiency. Weeds tend to be quite efficient in their usage of nutrients and water; otherwise they could not survive in the poor quality soil in which they are frequently found. The net mass of a weed is seldom as great as the mass of the desirable plant with which it competes. Nevertheless, a scattering of weeds in an area can reduce the yield of a crop considerably.

AN explanation that fits all the known facts is that the weed secretes a differential growth inhibitor that slows the growth of the desirable plant.

It should be noted that crop plants may themselves produce heterologous growth inhibitors. In some cases, the inhibitors are rapidly destroyed by soil bacteria. However, several inhibitors are known to persist in the soil for many years. This may explain why a change from one crop to another may at times result in poor yields. A residue of inhibitor from the first crop may affect growth of a subsequent different species.

The composition of lawns probably depends to a large extent on the effects of growth inhibitors. The relationships are complex. It is reported that Kentucky bluegrass inhibits growth of Canada bluegrass, but in turn is inhibited by redtop. Timothy is also reported to be inhibited by redtop, but is not inhibited by clover which does inhibit Kentucky bluegrass. Commercial mixtures of lawn seeds do not apparently take these factors into account, so that the eventual composition of a lawn may have quite different proportions to the initial seed mixture.

The differential plant growth inhibitors are of great actual and potential importance in medicine. Some of our most useful medications (the antibiotics) are differential growth inhibitors produced by one species of single-celled plant which inhibit the growth of other single-celled forms of life – that is, bacteria. Although all antibiotics in chemical use come from single-celled plants, there is good reason to believe that the higher plants also produce antibiotics. However, since the single-celled plants can be grown so much more rapidly in culture media, they are the most practical sources of the large amounts of antibiotics needed in clinical medicine.

It is noteworthy that although some medical antibiotics actually kill bacteria, most do not. Instead, they inhibit the growth, metabolism, or multiplication of the bacteria. As a result, the ecologic balance between host and bacterial invader is altered in favor of the host, and the latter's basic defense mechanisms are then able to destroy the invaders.

There has been considerable interest in the possibility of finding among the differential plant growth inhibitors one or more which will inhibit the growth of cancer. There are both theoretical and observational reasons to support such a hope. The fundamental biochemistry of animal cells is based on the biochemistry of the plants on which all animals live, directly or indirectly. Many plant materials are known to have profound effects on animal cell functioning even in tiny doses, and such effects are usually quite specific. Examples are atropine, digitalis glycosides, tubocurarine, and ergotamine. Atropine in a dose of 1 milligram will exert specific actions on some parts of the body of a seventy kilogram person—a final dilution of 1-to-70,000,000.

This is not to imply that the medications mentioned above are differential growth inhibitors. They probably are not, and indeed we do not know what function they serve in the plant. However, they are examples of the potency and selectivity of plant materials in relation to effects on animal cells.

Only a few of the plant growth inhibitors have been studied for effects on the growth of animal cells, but these studies have been most encouraging. Some plant growth inhibitors have a rather broad spectrum of action against animal cells. Protoanemonin from *Anemone pulsatilla* has been reported to inhibit rapidly multiplying cells of all sorts—plant and animal—but not resting cells. It might seem that such a material would be a good anticancer agent, but it probably is not, because cancer cells are not predominately rapidly multiplying.

THIS brings up a fundamental point about cancer which should be clarified if the search for an anticancer medicine is to be understood clearly. Cancer has, in the past, been widely considered by both physicians and laymen as a disease in which cells multiply at very rapid rates. To be sure, the rate of multiplication of cancer cells does seem exceedingly rapid to the unfortunate victim and his family. However, by comparison to the multiplication rate of certain normal, vital cells, cancer multiplication rates are not rapid at all.

Some illustrations may be helpful. The cells of the bone marrow in normal persons multiply at a rate sufficient to produce 2,500,000 red blood cells *every second* for a life time. After hemorrhage, this rate may increase five to seven times. In the course of a year, the bone marrow of a normal person will produce approximately eighteen pounds of red blood cells. Other cells essential to life also multiply at rapid rates. Most of the lining of the gastrointestinal tract replaces

itself in a period of less than a day. Even the cells lining the mouth multiply at faster rates than most cancers. It is a fairly common experience to cut or scrape the mouth lining while chewing, and then to discover advanced healing in less than a day.

Since many normal cells multiply at such rapid rates, it follows that a broad-spectrum growth inhibitor that affects all rapidly multiplying cells would affect these normal cells, too. Since at least two types, those in the bone marrow and those lining the gastrointestinal tract, are essential to life, a broad-spectrum inhibitor of any origin would kill the patient at a smaller dose than that needed to completely control the cancer. This principle accounts for the undesirable side effects of gastrointestinal bleeding found with many of the anticancer drugs in use today.

PARENTHETICALLY, we may consider whether or not cancer cells multiply more rapidly than the normal tissues from which they are derived. Often they do, but not always. For example, a skin carcinoma may grow more slowly than normal skin. The distinguishing feature of cancer is not its rate of growth but its ability to invade normal tissues and to metastasize.

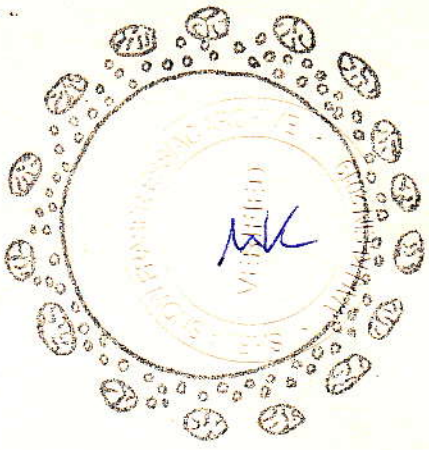
A material which selectively slows the growth and multiplication of cancer cells might not "cure" cancer in the sense that surgery cures appendicitis, but it could arrest the disease sufficiently to allow the patient to live normally for a full life span as insulin does for diabetics. Accordingly, a differential growth inhibitor, which exerts a much greater effect on some cells than on others, appears to be a promising target for cancer research.

There is already some evidence of the existence of plant growth inhibitors that exert a differential effect on animal cells. Parasorbic acid obtained from the ripe berries of the mountain ash inhibits multiplication of animal cells of fibroblastic origin in concentrations much lower than those needed to inhibit multiplication of epithelial cells.

There have also been reports of several plant growth inhibitors that cured transplantable tumors in mice and rats. Such reports must be considered most cautiously for several reasons. The transplantable tumors of rodents, despite their widespread use in cancer research, are not exact duplicates of human cancers. Spontaneous animal cancers, which are much closer to the human disease, are unfortunately seldom used in cancer research because of the expense and difficulty they entail. Furthermore, it is not uncommon to read a report describing the excellent effects which a plant extract has had on a group of transplantable rodent cancers, and then to find no further reports of follow-up studies. We don't know if the follow-up studies were unreported because they turned out badly, or whether they were never performed because the investigator was unable to obtain sufficient research funds to follow up his original observation.

Several groups of investigators have been studying the effects of plant extracts on cancer without reference to any possible relationship to plant growth inhibition. The reports of their initial experiments indicate that a substantial proportion of the plant extracts studied had some inhibiting effect on tumor growth. It seems significant that several of the plants found to inhibit tumors also are known to secrete plant growth inhibitors. *Euphorbia* and *Trifolium* are examples. In several additional cases, one species of a genus was reported to inhibit cancer growth, but wasn't tested for plant growth inhibition effects, while another species of the same genus was reported by other investigators to produce a differential plant growth inhibitor but wasn't tested for effects on cancer. Examples are the genera *Anemone* and *Prosopis*. We do not yet know whether the proportion of differential growth inhibitors among the plants which also affect cancer in animals is higher than could be expected on the basis of chance alone, but I strongly suspect that it is.

The overall research effort on the effects of plant extracts on cancer deserves considerable attention. A number of investigators both here and abroad have studied the effects of plant extracts on tumor growth, and their reports have, in general, been encouraging. In general, investigators screening plant extracts for antitumor activity find a higher proportion of positive leads than are found in the screening of synthetic chemicals.



THERE has been a vigorous national screening program of synthetic chemicals for anticancer activities, with over 40,000 different chemicals screened, and very few, if any promising leads developed. Less than 10 per cent as many plants have been studied. It is difficult to understand why the study of plant materials for anticancer activity has not been better supported by government agencies. It cannot be argued that the plant materials would be synthesized anyway. Many medications of plant origin, whose structural formulae are known, cannot be synthesized with our available techniques. The digitalis glycosides are excellent examples. The study of plant extracts for anticancer activity is one of several aspects of cancer research severely handicapped by a chronic shortage of funds. This is difficult to understand when two extracts from the common periwinkle plant, vincristine and vinblastine, have already been shown to be helpful in some human malignancies.

The number of trained investigators in the nation today is sufficient to increase our national research effort on plant extracts in cancer by a factor of ten to thirty times without handicapping any other vital programs. The potential role of botanists in cancer research is much greater than their current participation would suggest.

In the search for a satisfactory treatment for cancer, it will be helpful to think, not in terms of a magic bullet which will kill all cancer cells without killing the patient, but in terms of agents which can modify the complex ecologic balance between tumor and host in favor of the host.