I. Introduction

Here in Volume I we shall discuss the physical and chemical therapy of the diseased plant; the treatment of the diseased plant as an individual, not the plant as a member of a population. We shall consider the plant as a "patient" not as a public health charge.

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Protection is aimed at the healthy plant. Therapy is aimed at the diseased plant. Protection is aimed at the pathogen as it lives and moves between hosts. Therapy is aimed at the pathogen after it has arrived in and has established housekeeping in the host. Therapy is the cure of a sick plant, the mitigation of its symptoms, or the repair of the damage whether the pathogen be animate or inanimate.

The practicing plant doctor is interminably being presented with sick plants, singly or en masse. He usually gives the disease a name on the basis of symptoms, identifies the fungus on the basis of its structures present, and suggests a preventive measure. The grower too often still has a diseased plant and a confused mind, with the one clear, happy thought that he paid no fee—at least directly.

In the literature written for the advice of growers 50 years ago, “cure” of plant diseases meant to “get ahead of the enemy.” The reader was told that internal fungi, when once they are established, must be treated by removal and burning of diseased parts. This is common advice today, though mortal for the suffering plant. As our knowledge of the biochemical nature and mechanisms of disease increases, there is more concern that the plant patient lives. The next decade or two should see a “break-through” in the therapy of the diseased plant.

This phase of plant pathology is still in the adolescent stage. The framework is outlined, but the ideas and applications that are necessary to reach full maturity are appearing here and there in the writings of many men. An attempt has been made to encompass and clarify today’s concepts on plant therapy with the hope that progress can advance faster in this important field.

A plant is today thought of as a dynamic entity maintained in health by a correlated series of interdependent metabolic processes. Animate or inanimate factors may disturb the usual functional pattern and result in developmental changes. Therapy removes the cause of disease so that the normal mechanism of living can run smoothly.

Combating the causal agent after it has injured the plant is a form of disease control labeled by some as “disinfection.” However, the concept should include not only the neutralizing or stopping of the injurious stimulus, but also the repair of the cellular damage done. Hence, the subject matter concerns the pathogen-host interactions during the time interval between “infection” and death of the plant or its organs—a lifesaving action. Knowledge of the pathogen-host relationship must answer many questions before effective therapy can be carried out. Usually the extensiveness of the infection is first thought of in order to make use of physical means of therapy aimed at confining the zone of injury.
II. PHYSICAL THERAPY

Two courses are open for the therapy of plant diseases, physical therapy and chemotherapy. In the former, the disease is fought with physical means, such as surgery, temperature modification, radiation, and moisture modification. In the latter, the disease is fought with chemicals that act topically or systemically.

A. Surgery

Surgery is the removal of infected tissues to prevent additional damage. Sometimes the plants themselves are able to stop further injury by shedding diseased structures. The "shot hole" symptom in leaves of cherry and poplar is familiar to pathologists. Similarly, leaf cast may avoid infection of the twigs, petal fall may avoid involvement of the fruit, and fruit drop the involvement of the spur or stem. Self-therapy is accomplished by the shedding of infected bark where the growth of suberized tissues exceeds the rate of penetration of the pathogen through the cortex. While expressed physically, the underlying mechanism is biochemical.

An unusual therapeutic measure has been proposed for the American leaf spot ("Ojo de gallo") of coffee by Wellman (1950). Gemmae of Mycena (Omphalia) citricolor serve as the inoculum and are too heavy to be borne by air currents, requiring dissemination by splashing rain. Hence, complete defoliation of the diseased trees rids them of the fungus.

A chemical "pruning" may be effective for ridding tomato plants of the root knot nematode. While evaluating the nematocidal activity of chemicals, Hopper and Tarjan (1954) observed that following chemical treatment of the soil with p-chlorophenyl rhodanine around young infected tomato plants they grew normally. Careful examination revealed that the infected roots were killed, but the plants formed a new root system free of nematodes.

Man uses, in many forms, the principle of mechanical excision of diseased parts as a means of therapy. Removal of localized knots on plums and cherries, and galls on olives and roses are among the more common examples. The systemic wilts are sometimes checked by pruning infected roots or infected branches. Cutting off branches of pear trees several inches below the zone of visible fire blight symptoms is practiced to halt further invasion by the causal bacteria. We have found that removal of the fruits and succulent cane tips of rose bushes stops the advance of Botrytis downward through the pith into the crown. The
bark over diseased areas in tree trunks and branches is removed to permit a drier environment unfavorable to the pathogen, e.g., slime flux. For a similar purpose, bark is excised from diseased areas in the exposed main roots and crown of walnuts and chestnuts. Sometimes it is done to permit better contact of toxicant with the pathogen. Bark tracing or removal has been used to check bleeding canker of hardwoods and stripe canker of *Cinchona*. However, the causal *Phytophthora* spp. remain in the roots and may grow upward to kill new sections of the cambium and adjacent living cells.

B. Temperature Modification

A well-known measure for freeing plants of pests is based upon the differential heat inactivation of the pathogen in, or on, the host. Generally the extent of the injury depends upon the physical state of the respective protoplasm, the degree of hydration or solation. The composition of the protoplasm and the containing membranes also affects the action. When possible, the life activities of the microorganism to be eliminated are stimulated and the host is maintained dehydrated and/or dormant.

Occasionally, the curing of diseased plants by growing at above-normal temperatures is reported. Brierley and Smith (1957) observed that White Wonder and Dynamo chrysanthemum plants infected with the flower distortion virus, when grown in a greenhouse maintained at 35° C. for 2 to 3 months, produced tip scions free of the virus. Heat therapy of viruses is considered in detail by Matthews in Chapter 12 of Volume II.

Hot water immersion, with or without antiseptics in solution, has been used to free crucifer seed of viable black rot bacteria, strawberry plants of virus, and bulbs and rhizomes of nematodes. The differential in heat resistance of host and pathogen may be explained on the basis of the heat stability of their respective enzymes. The thermal growth range of organisms reflects the thermal stability of their cellular proteins. These in turn are affected by the cell water content and the physical and chemical state of the cell components.

C. Radiation

Ultraviolet radiation is often proposed as a means of plant disease therapy. The researches of Fulton and Coblentz (1929) sum up its advantages and limitations. The shorter wavelengths (about 240 mμ) exert the greatest germicidal action, which decreases with wavelength until about 365 mμ which is an upper limit. The abiotic effect varies with the time of exposure and the intensity of the light. The principal limita-
tion seems to be the inability of the ultraviolet rays to penetrate sufficiently beneath the surface to destroy the thalli of pathogens.

Infrared energy has been exploited for killing microbes in foodstuffs and materiel, but seemingly is not sufficiently selective to be used in plant therapy. Instances where exposure of plants to the visible light spectrum (313 m\textmu and longer) has suppressed disease, leave in question whether a direct lethal effect, or the indirect change, is responsible. Ultrasonic inactivation of microorganisms in and on inanimate substrates has been shown, but reduction to practice on living plants is, as yet, not practical.

The therapeutic value of radioactivity as well as its harmful effects on animals are well known. Solutions and powders containing alpha particles were distributed for test on plant diseases by one manufacturer, but no beneficial therapy was evident against Dutch elm disease in our tests. Beta and gamma radiation exert potent stimulatory and lethal action on cell protoplasts but, as yet, nonselectivity, cost, and danger to the user militate against their use in plant therapy.

Scientists of the U. S. Department of Agriculture, according to a recent news release, had hoped that nursery stock and other agricultural products could be freed of plant-pathogenic nematodes by exposing them to ionizing radiation. The golden nematode of potato (\textit{Heterodera rostochiensis}) can withstand radiation up to 20,000 roentgens before the females are sterilized and 120,000 roentgens or more are required for complete killing. Man is a "softie" by comparison, since a mere 300 to 650 roentgens are fatal. Other nematodes require between 350,000 and 640,000 roentgens for a lethal dose. So there is little hope that radiation can be used for killing nematodes in living plants, because nematode-killing doses of radiation also injure plants.

The possibility of using ionizing radiation as a therapeutic agent for a bacterial disease has been explored. Crown gall, caused by \textit{Agrobacterium tumefaciens}, is suppressed by irradiating the inoculated plant with X-rays (Waggoner and Dimond, 1952). Irradiation usually does not kill the pathogen but rather destroys the auxin system of the plant, so that it is unable to respond by gall formation. Thus maleic hydrazide, which also prevents growth of the plant, inhibits gall formation in inoculated tomato plants (Waggoner and Dimond, 1955). Generally, the susceptibility of a fungus pathogen to ionizing radiation is much lower than that of the host. Waggoner and Dimond (1952, 1956, 1957) have studied these interrelations together with the changes in resistance to disease undergone by tomato plants on exposure to X and gamma radiation when plants are then inoculated with \textit{Fusarium oxysporum} f. \textit{lycopersici}. The plants were killed with lower doses than the fungus.
Generally speaking, the effect of radiation treatment on susceptibility of the plant is related to the effect of irradiation on the auxin system.

Potato tubers, irradiated to delay sprouting are more subject than control tubers to rotting by *Erwinia atroseptica* and *E. carotovora* because the treatment delays or prevents periderm formation (Waggoner, 1955).

D. Moisture Modification

Intercellular humidity is a factor concerned with disease in a large number of plants. This is most likely where the pathogens are primarily intercellular invaders. Hence, the extent of spread of such diseases within a plant, may be limited, when controllable, by the amount of moisture made available in the environment. This effect of intercellular humidity was demonstrated by Shaw (1935) to exert a definite influence on the degree of fire blight susceptibility in plants of pear and apple. Data indicate, that when 99.5–100% intercellular humidity occurs, maximum host damage results. Conversely, when a turgor deficit, or intercellular humidities of 96% or less obtain, no disease develops. This idea has been validated by Clayton (1937) with another bacterial disease, blackfire of tobacco.

The modification of the moisture-oxygen content of woody stems acts in the therapy of *Verticillium*-infected maple trees by mitigating the symptoms (Caroselli, 1957). Caroselli's data indicate that the degree of injury caused by the fungus is dependent upon the relative amount of moisture and air within the tissues of the tree. When the tree is in full foliage, the water content is least and the air content greatest. Presumably, the additional oxygen favors growth of the systemic fungus so that the wilt symptoms are exhibited after the next rain.

A modern, large-scale commercial application of this measure is the “vacuum cooling” of lettuce and other food crops. The plants are exposed to a partial vacuum. This converts the interior liquid water films to intercellular water vapor which is then withdrawn from the plant structure. This vaporization cools and dries the intercellular spaces. Although thought of as prophylaxis by cooling, a sufficient intercellular drying results to retard the development of bacterial soft rot and other diseases. Thus, Shaw’s (1935) hypothesis is reduced to commercial practice.

Intracellular moisture may be manipulated in plants to minimize the extent of disease. Powdery mildew diseases are prevalent in sites where water deficits due to transpiration exceeding absorption often occur daily or for short periods. A possible explanation is that the haustoria of the extramatrical mycelium are unable to invaginate protoplasts exerting a positive pressure. Thus, by consistently making adequate water available...
and reducing water loss by one of several means, the spread of mildew can be checked.

A further example of moisture modification and attendant disease damage is the case of golf-green turf and Curvularia blight. This may be as much prevention as therapy. On hot, mid-summer afternoons, the close-cut grass (¼-inch) wilts due to a water deficit in the leaf blades. This predisposes them to attack by the fungus, which is a common black mold growing on turf debris. Maintaining the turgidity and vigor of the leaf cells by applying a light watering in early afternoon appears to check the advance of the facultative parasite into the healthy tissues.

Endoxerosis or internal decline of lemon fruit was found by Bartholomew (1928) to be caused by exposure of the trees to high temperatures with consequent rapid leaf transpiration when relative humidity of the surrounding air is low. Water is lost from the leaves and in turn withdrawn from the fruit to the point where cellular damage and gum formation occurs. Endoxerosis is most prevalent when growth activities are greatest. Hence, therapy is aimed at maintaining an intermediate rate of growth by manipulation of contributing environmental factors. Blossom-end rot of tomatoes is a similar disease. Likewise, any practice which tends to conserve moisture and provide a uniform supply to the foliage and fruit reduces losses.

Aging celery seed for 3 years often results in “die-out” of Septoria. This may well be due to the drying of the seed.

III. TOPICAL CHEMOTHERAPY

Chemotherapy is one of the exciting new frontiers of plant pathology. Chemotherapy may be topical or systemic.

Ever since Prévost (1807) treated wheat seed with copper sulfate, research on chemical protection of plants against invasion has been going on. Success has been nothing short of fantastic. We have had Bordeaux mixture, wettable sulfur, “fixed” copper fungicides, chloranil, ferbam, nabam, zineb, dichlone, glyodin, captan. The list lengthens daily. Theses have been written, reputations made. Similarly, we have pursued the microbes in the soil with formaldehyde, carbon disulfide, chloropicrin, ethylene dibromide, and 1,2-dibromo-3-chloropropane. This list is shorter, but it lengthens, too. Thus, we have protected our crops. Thus, we have killed the microbial pathogens during the inoculation stage. The contribution of all of these to the science and the art of plant pathology will be treated in Volumes II and III.

During all this time, we have neglected internal therapy. Chemotherapy now gives us hope in the attack on diseases where chemical protection has failed or is impractical. Most of the modern research is
aimed at vascular fungus diseases, at virus diseases, or at bacterial diseases. Few of these have receded before the onslaught of protectants. Perhaps, they will yield to chemotherapy!

Several general and specific discussions on the chemotherapy of plant disease have appeared during the past decade. The potentialities have been covered by Stoddard and Dimond (1949), Crowdy (1952), and Brian (1952a, b).

A compound that initiates a curative or mitigating effect, either directly or indirectly, is termed a “chemotherapeutant.” Perhaps an ion or an atom may as well be the active agent as a compound. The pathogen may injure only surface cells or a localized area of tissue. On the other hand, it may systemically injure the entire plant or any major part thereof. Treatment of the former is topical chemotherapy. Treatment of the latter is systemic chemotherapy.

Therapy will advance as we learn how “toxins” act, whether by destroying tissues or by inhibiting or stimulating essential metabolic functions. A key point is the initial reaction that takes place between the invading organism and the host tissue. Such knowledge would permit defining more accurately the specific cellular functions disturbed during the infection period, and would perhaps suggest a therapeutic measure; how to selectively neutralize the pathogen or its metabolic products within the tissues of the host.

Chemotherapy has contributed its part to the subtle realization that only minute concentrations of some chemicals are required to kill fungi and stop disease in plants. Painstaking laboratory techniques and the use of the log-probability curve as a device for estimating the microbial and plant toxicity of compounds have also contributed their part in changing our ideas of biological activity from pounds per hundred gallons of water to parts per million.

A. Therapeutic Index

Ehrlich of salvarsan fame was surely the founder of chemotherapy as a direct killing action. He emphasized very strongly, indeed, the principle of the chemotherapeutic index; namely, that the dose of the drug needed to kill the pathogen must be below that to kill the patient. The wider the ratio, the bigger the index, and the safer the treatment. In the plant pathologists’ jargon, the chemical must not be seriously phytoxic. This principle dictates the screening techniques to be used and phytotoxicity tests must come early in the procedure.

The literature on the inner therapy of plants has been summarized by Müller (1926). In addition to his own experimentation, there is assembled an orderly, comprehensive account of other investigations on
internal plant therapy before 1926. He repeats the idea that "therapy" is direct control, particularly useful for living endopathogenic and inanimate causal agents. He evaluates chemotherapeutants according to a "Therapeutic Index," which represents the curative dose divided by the tolerated dose \( (I = c/t) \). Factors affecting the curative dose are pointed out as: (a) kind and condition of the therapeutant, (b) duration of absorption period, (c) desired degree of saturation, and (d) local conditions, i.e., time of year, temperature, air movement, relative humidity, and cloudiness. Factors affecting the tolerated dose by the pathogen (i.e., kind, state of development) and by the plant (i.e., family, morphology, volume, stage of development) are thought of in relation to the strength of the outbreak, the kind of infestation, and the site of the disease.

The topical application of medicaments to surface lesions in order to reduce infection has been practiced for centuries; even though they have been only dung, urea, lime, sulfur, or charcoal. The caustic action of lime sulfur was found to "burn out" the scab fungus \( (Venturia inaequalis) \) on apple leaves, but often it injured the plant tissue also. Perhaps the largest commercial success of such therapy is the cure of apple scab with water-soluble organic mercurials, introduced as phenyl mercury triethanol ammonium lactate ("Puratize") by Howard and Sorrell (1943).

Another commercial success is the curing of cereal seed invaded by the smut fungus (Tisdale and Cannon, 1929). Success has been reported for the cure of cedar rust by Strong and Cation (1940) with sodium dinitrocresylate. Ark (1941) successfully treated bacterial crown gall with the same chemical. Therapy by the surface treatment of tree branches with chemicals that permeate the bark has been practiced for many years. A zinc chloride-glycerine-alcohol preparation has been used in California for the control of bacterial blight of pear. Coal tar oils are applied in Poland to check brown rot \( (Sclerotinia \text{ spp.}) \) cankers on stone fruit trees.

Vegetative parts of plants used for propagation are commonly dipped or soaked in solutions of antimicrobial agents to rid them of established pathogens. An example once widely used is the treatment of seed potato tubers by immersion in solutions of formalin or mercuric chloride. While fairly effective as a curative measure, the phytotoxicity is high and the general presence of \( Rhizoctonia \) sp. and/or \( Streptomyces scabies \) in fertile soils militates against its use.

The seeds of many plants (Chen, 1920) are infected internally with bacteria or fungi and the practice of destroying the pathogen \textit{in situ} has generally been referred to as disinfection or disinfestation. Mer-
curials, particularly organic compounds, are most widely used because of their vapor phase activity. Dithiocarbamates, aryl quinones, phenols, and formaldehyde are also used as slurries, dips, or dusts.

Plain water alone is credited with curing disease. Tyner (1957) reported that loose smut, caused by *Ustilago nuda*, can be eliminated from barley by water soaking. He suggests that the effect is not due to microorganisms or their chemical products accumulating in the soak water, but rather to quinones formed in the germ of wheat or barley during the soaking.

Accelerating the healing of wounds by stimulating callus formation through surface application of chemicals has been attempted for many years. Lanolin was found to improve the initial stimulation of healing by Shear (1936) and was further enhanced by addition of such growth-regulating compounds as 4-chloro-3,5-dimethylphenoxyacetic acid and 2,4-dichlorophenoxyacetic acid (Crowdy, 1953). Crowdy found little evidence that the duration of the healing period can be extended markedly by chemical treatment or that out-of-season healing can be stimulated in this way. The improved healing may be due either to an earlier start of the healing process, or to an accelerated rate. Timing of chemical treatment with normal growth activity of the plant seems very important.

IV. SYSTEMIC CHEMOTHERAPY

A. General Concept

Internal systemic medication is the real frontier of therapy. This challenges us so much because it offers hope of chasing a pathogen into the farthest leaflet of the plant and killing it. The entomologists are ahead of us here. They can kill a leaf miner in the highest leaf of a birch tree by spreading an ounce or so of an organic thiophosphate over the soil in the spring. We must some day be able to repeat this astonishing performance for the Dutch elm disease. Perhaps we can console ourselves in our slowness by saying that the thiophosphate acts as a nerve poison on the insect larva and that trees have no nerves. Our fungus, *Graphium ulmi*, has no nerves either and, hence, is not damaged.

We must not forget the ancient and hoary principle in human medicine that every disease has its specific remedy. We researchers in chemotherapy are aiming at that objective. This subject has been neglected hitherto; because individual plants have been considered expendable, because the problem is intensely complex, and because we did not have access to the formidable array of chemicals and antibiotics now available to us.

In this chapter we shall not be describing, however, very many
practically useful chemotherapeutants. We shall concern ourselves with the nature of the problem, with some of its pitfalls that we have noted, and with some of the challenges. Other facets of the subject have been considered recently by Dimond (1959) and by Dimond and Horsfall (1959). We hope to suggest that “the water is fine” and to encourage others to try a swim. We hope to shed some light on the problem posed by the old hymn: “Watchman, tell us of the night, what its signs of promise are.”

B. Nutritional Imbalance

Between therapy by physical measures and what is generally thought of as chemotherapy, is the well-established principle of correcting nutritional disorders of the plant cell. Most commonly, plant disease is thought of as being caused by animate pathogens. However, therapy can and has been, consciously or unconsciously, applied to correction of inanimate causes of disease—those nonliving factors that affect adversely the natural or normal functioning of plant cells, namely, imbalance of water, oxygen, and nutrient elements.

Balancing certain elements in the soil environment or in the plant cells can be used as a therapeutic measure. Tomato fruits low in calcium but high in total nitrogen, iron, and copper are more liable to blossom-end rot according to Taylor and Smith (1957). Conversely, supplying the plants with more calcium and decreasing nitrogen levels has reduced the disease. Similarly, the use of sulfate fertilizers rather than chlorides can reduce succulence of tomatoes and hence mitigate damage. This is therapy of nutritional imbalance.

The major nutrient elements necessary for metabolic equilibrium, viz., nitrogen, phosphorus, potassium, calcium, and magnesium, are taken care of by adjustment of fertilizer practices. The minor elements that may induce the so-called “deficiency diseases”—zinc, boron, copper, manganese, sulfur, and iron—are identifiable from a diagnostic key to symptoms prepared by McMurtrey (1948). One has the option of considering as chemotherapeutants the metabolites or nutrients named above, when used to maintain or to improve the normal cellular activities.

After observing the therapeutic effect of zinc on mottle-leaf of Citrus, Reed and Dufrenoy (1935) explained the action on the basis that the salts of certain metals catalyze the partial oxidation of sulfhydryl compounds. Certain of these compounds are present in all living cells and control the life processes through maintaining the energy at a given level by oxidation. This level is defined as the oxidation-reduction potential; which when low, may result in pathological symptoms cor-
related with an accumulation of suboxidized metabolic substances as in mottle-leaf of *Citrus*.

Profound changes in the cytological conditions are associated with the recovery of mottled trees after the entry of zinc, applied either to the soil or to the foliage in the form of a spray. Zinc accumulates in the meristematic cells of buds and in the palisade cells of green leaves. After zinc sulfate has been applied, the symptomatic trees resume normal leaf cellular activity as judged by normal nuclei, fibrillar cytoplasm, and normal chloroplasts, and as exhibited by accelerated growth of new shoots. These effects suggest that some reaction has been initiated by which the proteins and carbohydrates of the cells have been utilized to supply energy to the cells. Steroids accumulate in cells of mottled citrus leaves, but are scarce in leaves to which zinc is applied. Seemingly, the stabilizing of the sulfhydryl compounds by zinc promotes the oxidation of cell metabolites and thereby liberates energy for vital processes.

Undoubtedly, zinc is linked with sulfur compounds in maintaining normal green plant cellular functions. Yet, in solution, zinc at concentrations of 5 to 25 p.p.m. has been reported to stop the growth and kill corn and citrus seedlings. How the zinc requirements of plants can be met without toxicity has been explained by Masé (1914). Presumably, in the presence of calcium carbonate, zinc is precipitated as an insoluble salt. Necessary quantities are dissolved out by root excretions and absorbed as required by the plant without toxic accumulation. Thus, zinc carbonate or a similar basic salt would serve as a “safe” or sublethal reservoir of the essential toxic metabolite. This same principle can and has been used with other metal ions in other “deficiency” diseases of plants.

Molybdenum in very small amounts has been reported as needed for the physiological reduction of nitrates in plants (Turner and McCall, 1957). Nitrates accumulate in the tissues of molybdenum-deficient plants, and the protein content of the plant is reduced. This upset metabolism results chiefly in characteristic hypoplastic symptoms, as for example “whiptail” of crucifers. Treatment with a few parts per million of available molybdenum suffices to cure this growth condition.

In contrast, an excess of a single nutrient or a combination of nutrients may directly or indirectly result in injury. Here we get into the area of chemical antagonism and physical changes in the state of the plant protoplasm. Of major importance is the accumulation of sodium salts and resultant “alkali” or “salt” injury. Nevertheless, the removal of an excess injurious salt or element, even modification of soil reaction to within the range for normal plant growth, is a chemotherapeutic practice in the broadest sense.
Healthy living cells are believed to have an approximate balance of hydrogen and hydroxyl ions. They are able to maintain an internal neutrality because of their slight permeability to these ions. The internal pH can be upset by the greater penetration of undissociated molecules of acidic and basic substances than of their corresponding ions. Hence, when the plant cells are exposed to low pH values, weak nonionized acids enter the cells and damage them. Similarly, weak poorly dissociated bases are toxic at pH values above 7.0 because they can permeate the cell at that pH. Hence, correcting the chemical environment will cure the harmful effects.

Feldman et al. (1950) observed that the Dutch elm disease organism (Graphium ulmi) forms its most toxic metabolite when the pH is 4.2 and successively less as the pH of the medium is raised to 7.0 or above. Therefore, an alkaline formulation containing lime was developed for the impregnation of soil around elm trees, to suppress or avoid the development of symptoms. A check in vivo of the pH of the tree sap indicated a rapid rise in alkalinity for a few days following soil application and then a dropping back to normal. The experimental results suggest that some curative effect was attained; either from the pH modification, or the high calcium hydrated lime and other ingredients used.

C. Biochemical Specificity

The idea of finding a chemical that may be used as a systemic medicine is based on the principle of biochemical specificity as instanced above for the birch leaf miner. The idea of biochemical specificity, perhaps, goes back a century to the recognition by Louis Pasteur that microorganisms are so specific in their biochemical reactions that they can separate optical isomers. Ehrlich (1913), 50 years later, seems to have had in mind selectively active substances when he established the term "chemotherapeutics." Dubos (1958) has stated recently that "under natural conditions, each one of the microbial species concerned in the economy of organic matter, is more or less specifically adapted to the performance of a limited, defined biochemical task."

The concept of chemotherapeutic specificity has been sharpened over the years. Formerly it was considered on the basis of the whole cell, later on the basis of the enzymes, and more recently on the basis of the molecular structure of the substrate.

Dubos (1945) has pointed out that effective therapeutants do not behave as gross protoplasmic poisons which affect indiscriminately the structure and function of all living cells. They interfere selectively with some specific steps concerned in the nutrition, synthesis, or cell division of the pathogen. Other therapeutic agents may react selectively with
well-defined structural components essential to the pathogenic behavior of the cell. This attitude is hopeful for the inhibition of pathogens within the tissues of the host plant.

Yarwood (1955) has presented evidence of "selective accumulation." Although the lethal dose of fungicide per unit of tissue be the same for host and fungus, the fungus may accumulate the toxic agent in larger amounts than the host, and is, therefore, killed at a lower applied dosage than the host. Autoradiographs indicate that this is true for sulfur therapy of rusts. Also there may be "selective toxicity." The amount of fungicide accumulated per unit of tissue may be the same for host and fungus, but the fungus is killed at much lower accumulated dosages than the host. This seems to apply to the sulfur therapy of powdery mildews.

The possibility of finding chemotherapeutants exerting a specific action is strengthened by what has been learned from penicillin. Penicillin presumably blocks the synthesis of a particular wall component of the bacterial cell, but not that of the host. Thus, its action is specific. If growing bacterial thalli are unable to form cell membranes, they undergo osmotic lysis. Undoubtedly, compounds with similar action are waiting to be found for plant chemotherapeutants.

Enzymes capable of specific lysis of fungous structures are sometimes to be found among fungi. As yet, knowledge of these enzymes has not been developed for use in plant therapy. The plasmodia of some Myxomycetes have been observed to destroy the hyphae of fungi with the same apparent speed that a hot iron may cause nylon or acetate fibers to melt. The inky cap mushrooms demonstrate the property for all to see.

Perhaps a better suggestion of possibilities for future specific agents is offered by the diplont or dicaryon stage of certain Ascomycetes. In the so-called sexual phase, a changed metabolic pattern follows differentiation of "fertile hyphae," an ascogonium, and ascogenous hyphae from the somatic tissues of the thallus. This diplont exerts a cannibalistic action on the haplont matrix of the surrounding stroma. This action has been used as an ordinal taxonomic character. It seems possible that the lytic enzymes, produced by the diplont to make room for itself in the body of the haplont, could be isolated and provide the key information required to discover a specific chemotherapeutant useful in plant therapy.

D. Microbial Disease Therapeutants

1. Intake or Entry

Clearly we must start with the problem of intake or entry of chemotherapeutants. Our medical colleagues call this "route of admin-
istration.” Through what routes can systemic therapeutants enter the plant? There are really only three practicable routes of administration for plants—root, stem, foliage. Mechanical injection is possible through each. Roach (1939) has published a basic treatise on the injection of materials and their subsequent distribution in the plant. Each portal of entry has its advantages, each its drawbacks.

Roots grow in soil. A compound aimed at roots must go first through the soil and be subjected to its severe subtractive influences: distance, adsorption, direct chemical alteration, and biological degradation.

The significance of distance is obvious. The farther the compound must go before it can reach the roots, the less will reach the roots. This follows from the simple laws of diffusion and dilution and is not of necessity related to any loss along the way due to hazards of the route.

Adsoption is a much more serious source of trouble. If a substance bears a strong charge, it will be adsorbed onto soil particles, presumably by van der Waals forces, and it may never arrive alongside the root to take it. Streptomycin bears such a charge according to Siminoff and Gottlieb (1951) and, thus, it is not an effective chemotherapeutant when applied to the soil. The same is true of thiolutin according to Gopal-krishnan and Jump (1952) and of numerous other antibiotics according to Martin and Gottlieb (1955). Ark and Alcorn (1956) showed some specificity in adsorption. Streptomycin is adsorbed more tightly by bentonite than by pyrophyllite. When Ark and Alcorn changed the charge on the clays with K₂HPO₄ the streptomycin was released.

Since soil is a reasonably reactive medium, it decomposes many candidate chemotherapeutants and reduces them to impotence. Our knowledge of this is pretty limited, but what we have is clear. Antibiotics seem to have provided more information to date than other types of therapeutants. According to Jeffreys (1952), many antibiotics such as albiddin, gliotoxin, and viridin come apart in soils where the pH is unfavorable. Even if the pH is not unfavorable, some antibiotics such as penicillin and streptomycin break down.

The soil is so full of microbes that it is not surprising that they, too, degrade chemotherapeutants very rapidly. Very few molecules have demonstrated radical resistance to microbial decomposition. DDT is an example, but, of course, it is not antimicrobial. Very probably the two are related. If DDT reacts with microbes to damage them, then the microbes will react with DDT and damage it. Thus, we fight an uphill battle when we introduce antimicrobial substances into a milieu loaded with microbes.

Jeffreys (1952) has shown that antibiotics such as griseofulvin, patulin, and mycolic acid will survive longer in organism-free soil than in a natural soil full of microbes.
Walker and Smith (1952) show that *Myrothecium verrucaria*, a very widespread cellulose decomposer, can actively destroy cycloheximide (Actidione). Salicylic acid analogues have been shown to contain some systemic chemotherapeutic properties on bacterial blight of bean (Diamond et al., 1952), but Riere (1940) has shown that *Aspergillus*, a common soil organism, can utilize salicylic acid as a source of carbon.

Wright and Grove (1957) have recovered a *Pseudomonas* species from soil that can degrade griseofulvin. This bacterium increases steadily in the soil as griseofulvin is successively added to the soil.

Gottlieb (1957) has published an excellent review of the microbial decomposition of toxicants. We can only conclude that chemotherapeutants destined for entry into the plant through the roots must run a very hazardous gauntlet. This inevitably suggests that screening methods for chemotherapeutants should include a "soil burial" test analogous to that used by our colleagues in wood and fabric degradation.

Even assuming that the candidate therapeutant survives the hazards of the soil and arrives alongside the root, it must pass through the epidermis of the root, migrate through the cortex, if necessary through the endodermis, and finally, into the free-flowing stream in the xylem. This formidable collection of barriers further separates the "sheep from the goats, the men from the mice." The number that survive falls fast. Here also adsorption plays its accustomed role.

Of course, investigations on root entry are best done when the roots are placed in sand or in solutions or suspensions of the test substance, not in soil.

Chapman (1951) has reported on the comparative performance of 8-quinolinol and *n*-octadecyltrimethylammonium pentachlorophenate. The former is almost without charge. It does pass the root barrier and go up the stem of an elm (Zentmyer et al., 1946). The latter compound is highly charged, is substantive to cellulose according to Chapman (1951), and it does not move out of the roots.

The relative performance of these two therapeutants is striking. The former gets into and up the stem of elms to the point where invasion by the Dutch elm disease fungus occurs high in the tree. The latter compound is utterly ineffective on Dutch elm disease, but is reasonably active on *Fusarium* wilt of tomato where invasion occurs through the roots. This compound stops in the roots and is effective there. The other apparently does not stop there and is ineffective there.

In 1947, Anderson and Nienow demonstrated that streptomycin enters roots of soybeans. It also enters the roots of peach (Dye, 1956), cucumber (Pramer, 1953), broad bean (*Vicia faba*) and tomato (Pramer, 1954).

Chloramphenicol can also enter roots, whereas chlorotetracycline,
oxytetracycline, and neomycin can not (Pramer, 1954). The evidence is clear that the following other compounds can enter the plant through the roots: cycloheximide (Wallen and Millar, 1957), griseofulvin (Crowdy, 1957), thiolutin (Gopalkrishnan and Jump, 1952), sulfonamide analogues (Dimond et al., 1952; Crowdy and Rudd Jones, 1956), 4-chloro-3,5-dimethylphenoxyethanol (Davis and Dimond, 1953), benzo-thiazolyl-2-thioglycolate (Dimond et al., 1952) and many others.

The charge on streptomycin affects its adsorption into root tissue just as it affects adsorption onto the soil particles (Pramer, 1954). Streptomycin tends to remain in broad bean roots just as n-octadecyltrimethylammonium pentachlorophenate does, but to a lesser degree. Pramer's work also suggests that chloroamphenicol and griseofulvin are not retained in the roots; presumably, they are not heavily adsorbed there.

Cycloheximide does not seem to be heavily adsorbed onto root tissues (Wallen and Millar, 1957).

Crowdy and Rudd Jones (1956), like Chapman (1951), have related the adsorption of sulfonamides by root tissues to their adsorption on cellulose. Their techniques were somewhat more sophisticated, however. They have shown that the rate of entry of sulfonamides into broad bean roots is related to their $R_F$ values (the ratio of the distance traveled by the material to the distance traveled by the solvent) on cellulose chromatograms. This looks like a smart approach to the problem.

The ratio of entry to the $R_F$ value on cellulose is a constant for the neutral compounds that are fat soluble, but the more water soluble the compound, the higher the proportion of aqueous phase in the chromatograph system needed to maintain the same ratio. Apparently, neutral compounds and those with high pKa values (pH where ionization is least) enter the plant as undissociated molecules, but those with low pKa values enter as ions. Of course, when the pKa value is near 7, pH is very important in dissociation and, hence, is closely associated with entry of the compound.

Bearing in mind that systemic chemotherapeutants must move through living cells of the root before entering the xylem, one is not surprised to note from the literature that the process requires energy as many permeative processes do (Brian et al., 1951, and Stokes, 1954). Griseofulvin shows an initial rapid entry into wheat roots and this is inhibited by such respiration inhibitors as nitrophenol, phenylurethane, and sodium azide. At the concentrations used, these inhibitors do not inhibit the entry of water, however, according to Crowdy et al. (1956). If the inhibitors were applied for a prolonged period, some griseofulvin did enter the root presumably with the uninhibited water of the transpiration stream.

Crowdy and Rudd Jones (1956) pursued this line of research also
with the entry of sulfonamides into the broad bean plant. Some of the sulfonamides enter readily, some do not. Those that do, act similarly to griseofulvin. The initial spurt in the entry is sensitive to respiration poisons, but the long time slow entry is not. The latter is related to the rate of entry of water.

Presumably, one could force candidate therapeutants through the roots, but we have no information on such trials.

Much research has been done on entry through wounds in the stem. Stoddard (1947) forced his test compounds into the severed upper ends of the stems of peach seedlings. He seems to have had no followers, but his methods would seem to warrant further exploration.

The uptake of chemicals by stems through bore holes has been very popular. This technique has been resorted to largely because it permits estimation of the dosage within the plant. Howard (1941) used the method for his work on diaminoazobenzene for bleeding canker of maples, and so did Zentmyer et al. (1946) in their earlier researches on Dutch elm disease.

Radial bore holes were used at first and the compounds used were water soluble. Later, Howard and co-workers (Anonymous, 1955) developed a method of injection that depends upon tangential bore holes arranged in an ascending spiral around the tree. The holes are filled with the compound in paste or powder form and sealed. The tangential boring assures that the chemical is accessible to the maximum number of xylem vessels and the “dry” packing assures a longer lasting supply of chemical. The method, when properly timed, seems to be successful with 4,5-dimethylthiazolyl-2-thioglycolate for Dutch elm disease, but not for 8-quinolinol benzoate.

Is a tree “cured” of disease when the development of symptoms is stopped? For example, a 25-year-old elm tree about 8 to 10 inches in diameter at breast height became naturally infected with Graphium ulmi as proved by tissue culture from wilted terminal branches. Immediate chemical treatment upon sighting the symptoms checked further wilt. Subsequently, the dead branches were removed and the tree appeared healthy (symptomless) for 2 years until another attack developed. This was confirmed as due to Graphium ulmi by laboratory diagnosis. Again prompt treatment by the bore-hole method resulted in checking the disease and it has remained “healthy” for 3 years.

In another case, an elm was proved to be infected with Graphium ulmi by isolation of the fungus from branches bearing wilted leaves. It was promptly treated by soil impregnation of the rhizosphere and a further development of symptoms was stopped. The next two seasons, normal foliage appeared on undamaged branches and the killed ones
were cut off. However, discolored streaks in the xylem, formed during the year of active disease, were separated from the cambium by annual layers of new wood. This discolored wood yielded pure cultures of the pathogen. Thus, it would appear that a sometime pathogenic fungus can continue to exist in a quiescent state in a host plant without causing injury. There may be a "walling-off" effect brought about by the interposition of cells having thicker walls or unfavorable chemical composition, or the metabolic environment is not favorable for pathogenesis.

To test this, ax cuts were made through the bark and into the discolored area harboring the "quiescent" pathogen, with the result that in some cases symptoms again developed. Beckman (1958) now believes that arresting Dutch elm disease by 4,5-dimethylthiazolyl-2-thioglycolate treatment creates an unfavorable physiological environment, rather than a mechanical barrier for walling-off the fungus.

Sometimes severed stems are used in exploratory work on chemotherapeutants especially in studies on host tolerance. Robison et al. (1954) have shown that antibiotics enter more readily through cut stems than through roots, but this, of course, is not unexpected.

Some work has been done on entry through intact stems. This is a technique first used by growth hormone investigators. Mitchell et al. (1952) applied streptomycin to bean stems by mixing it with lanolin and a nonionic detergent. Streptomycin will also enter the intact stems of tobacco (Hidaka and Murano, 1956) Polychlorobenzoic acid (Beckman, 1959) will readily enter when painted on the bark of young elms and affect the development of the Dutch elm disease.

If we could find or tailor-make chemotherapeutants that enter readily through intact foliage, we would be a long way toward a practical solution to the entry problem. If the compound enters the foliage, it is very near to the site of action of all above-ground diseases. It need not be translocated very far, and it can be easily and cheaply applied as a spray or, perhaps, as a dust.

Many compounds do enter through intact foliage; some directly through the cuticle and others through natural openings. This problem also has been pioneered by the growth-hormone investigators. The problems are similar to those encountered in root entry. The compound must pass through the epidermis, through the parenchyma tissue, and into the xylem or the phloem. The problem is further complicated by the presence of the waxy cuticle which is pretty inert. It is eased by the absence of soil and its complications and it is eased by the presence of stomata and hydathodes. Curtis (1943) has shown that compounds can enter through the hydathodes where guttation drops form.

Crafts (1948) has contrasted the types of compounds that might
enter through foliage or through roots. He feels that compounds that enter the leaf should be somewhat less polar and more lipid-soluble than those that enter roots.

A mixture of aluminum sulfate, kaolin, and calcium carbonate, (Cuneo Mixture) administered either to the foliage or in proximity to the roots of trees or herbaceous plants, is claimed (Mosca, 1958) to act as a systemic fungicide for several diseases. Mosca believes that all polar (+ charged) compounds of metal derivatives conductive of electricity have fungicidal properties. Their fungitoxicity is proportional to the degree of dissociation. When a polar substance is dissolved in water, it decomposes into atoms furnished with electric charges (free ions)—the ionization of polar substances is spontaneous. According to Mosca (1952), Al+++ in the ion state acts as a "systemic fungicide with a universal action," because the aluminum ions are conveyed by the protein substances throughout the plant.

Of course, it is now common knowledge that phenoxyacetic acid analogues penetrate foliage very easily.

It is interesting to note that sodium benzothiazolyl-2-thioglycolate penetrates elm foliage and has definite therapeutic effects on Dutch elm disease (Dimond et al., 1952). This compound has an —S—CH₂COOH, which is the sulfur analogue of the —O—CH₂COOH side group of 2,4-D (Fig. 1). Similarly, van der Kerk's (1956) new systemic fungicide has precisely the same group attached to it. This compound is disodium ethylene bisdithiocarbamyl-dithioglycolate. It is also interesting that captan has a similar tail (—S—C Cl₃) attached to the imide grouping. The —S—C Cl₃ has the important similarity of —S—CH₂COOH in that the electronegative groups C=O and Cl₃ are separated by one carbon from the sulfur.

Captan does not enter intact foliage as easily as sodium benzothiazolyl-2-thioglycolate or 2,4-D, but it does seem to possess local chemotherapeutic properties as Stoddard (1954), and Rich (1956) have shown for cucumber scab. It would appear that —S—CH₂COOH is a better "shaped charge" (Horsfall, 1956) than —S—C Cl₃.

These results suggest that, perhaps, permeation and, perhaps, translocation are encouraged by R—S—R' or its oxygen analogue.

When one surveys some of the known synthetic chemotherapeutants, several structures of this type appear as shown in Fig. 1. The R seems to vary but apparently the R' should contain an electronegative group.

From these structures, one can see others that perhaps should be tried. Nirit, the protective fungicide, is 2,4-dinitrophenylthiocyanate. Here the cyanate group provides the electronegativity. Perhaps, it would be therapeutic. Perhaps, substitution of chlorines for the nitro groups
Sodium benzothiazolyl-2-thioglycolate

Sodium 4,5-dimethylthiazolyl-2-thioglycolate

Sodium 2,4-dichlorophenoxyacetate

Disodium ethylene bis-dithiocarbamyl-dithioglycolate

4,5-Cyclohexene-1,2-dicarboximide (captan)

Sulfanilamide

Calcium sulfamate

Benzene sulfonic acid

N-(4-nitrophenyl)-3,4-dichlorobenzene sulfonamide

Fig. 1. Permeating structures.
would make it a close analogue of 2,4-D and, perhaps, improve its activity.

Antibiotics also enter uninjured plant leaves. Davis and Rothrock (1956) demonstrated that griseofulvin applied to one surface of tomato leaves controlled *Alternaria solani* applied to the other. Similarly, Dye (1956) applied streptomycin to the lower surface of peach leaves and protected them against *Pseudomonas syringae* applied to the upper surface.

A few data are available on the weather factors that influence entry through intact foliage. The longer the applied material remains damp the longer the time available for entry. Thus, high humidity delays the drying and promotes entry as Dye (1956) has shown for streptomycin. This principle has been exploited by Gray (1955) to improve the entry of streptomycin. He used glycerine in the water drops of streptomycin to delay drying. It improved the entry.

Goodman (1954) has used Cellosolve and Carbowax 4000 for the purpose of increasing the entry of streptomycin and oxytetracycline for fire blight control on apple and pear.

Glycerine sometimes does not improve entry as Shaw *et al.* (1957) have shown for tobacco foliage and Rich (1956) for cucumber foliage.

2. Translocation

If we are to attain systemic chemotherapy, we must attain excellent translocation from the point of entry to the point of need. If we are concerned with leaf spots, we must obtain long distance translocation upward if we use root application. If we are concerned with root rots, we must obtain long distance translocation downward if we use foliage application. Conversely, foliage application is more likely to succeed for foliage diseases and root application for root diseases. Vascular diseases and systemic viruses are hard to reach from either end.

We in plant pathology are more hampered than our medical colleagues by translocation problems. An antibiotic injected into an artery or into a vein will appear in all parts of an animal in a fraction of a minute. The plant, unfortunately, has no such circulation system. And what circulation system it has occurs in microscopic units. We have no tubes as big as the arm vein, for example. We cannot inject very well the whole body from a single point.

The upward system is different from the downward. By and large upward translocation seems relatively simple. Many compounds applied to the roots will appear pretty well all over the tops, but compounds applied to the tops often do not travel downward at all. One day this problem will have to be solved. Delay in its solution will delay the success of chemotherapy of plant diseases.
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The assay of translocation is seldom simple. A few antibiotics produce characteristic biological effects. For example, griseofulvin produces a characteristic curious curling of the germ tubes of *Botrytis allii*. Its presence can, thus, be detected and has been so used by Brian (1952a) and his associates.

The bacteriologists have developed strains of *Escherichia coli* that must have streptomycin or they die. If streptomycin-treated plant tissue supports their growth one can be reasonably sure that streptomycin is there. Mitchell *et al.* (1953) have studied streptomycin uptake and translocation with this dodge.

Van Raalte (1952) has devised a partial answer to translocation. He applies the test compound to a cut end of a short piece of potato stem standing on an agar plate seeded with bacteria or other organisms sensitive to the test compound. A zone of inhibition indicates translocation.

Phelps *et al.* (1957) have shown that cycloheximide, cycloheximide acetate, and oligomycin travel in the xylem if injected into the stems of oak trees. Robison *et al.* (1954) have found that antibiotics vary greatly in xylem movement even if they enter unhindered through cut stems. Presumably, this is the ancient old bugaboo of adsorption to the cellulose. The tetracyclines move upward much more rapidly than streptomycin and neomycin. We have already learned, however, that the streptomycin molecule is charged and that it is readily adsorbed. We have seen that \( K_2HPO_4 \) will elute streptomycin from clays. The same authors (Ark and Alcorn, 1956) also have shown that \( K_2HPO_4 \) will keep streptomycin moving in the xylem elements of *Pyracantha* cuttings.

Streptomycin appears to move in the xylem more rapidly in the peach (Dye, 1956) than in some plants because the concentration in the leaves rises above that in the roots. In the broad bean (Pramer, 1954) streptomycin concentrates more in the roots than in the leaves. Griseofulvin and chloramphenicol move steadily out of the treated broad bean roots and accumulate in the foliage. Griseofulvin acts in tomato, according to data of Crowdy (1957), like streptomycin does in the broad bean. There is a gradation from the roots right out to the highest leaves. It must be bound by the first sites and moves further only as the lower sites become saturated.

There seems no doubt that many of these compounds tend to move in the xylem because some of them show up in the guttation drops that exude from the hydathodes, i.e., cycloheximide (Wallen and Millar, 1957), and griseofulvin (Brian, 1952a). Other evidence is that entry of some antibiotics over the long pull or in the presence of respiration inhibitors is proportional to the amount of water lost in transpiration (Crowdy *et al.*, 1956).

On the other hand, Hidako and Murano (1956) concluded that if
streptomycin is applied to tomato stems it moves in the pith and phloem, not in the xylem.

Napier et al. (1956) applied streptomycin to the simple primary leaves of bean plants and observed an effect on halo blight as far away as the fourth trifoliate leaf.

Crowdy and Pramer (1955a, b) summarized data on translocation. They concluded that neutral or acidic compounds such as griseofulvin move readily in the plant, that basic compounds such as streptomycin and amphoteric compounds such as the tetracyclines give different results with different plants.

Our ignorance of the field is profound.

3. Host Action on the Therapeutant

No host will sit idly by when it is treated with a therapeutant. It may detoxicate a therapeutant, enhance its effect, or possibly even excrete it through the leaves or roots. Hilborn (1953) has presented a tantalizing abstract showing how different hosts affect chemotherapeutants. We regret that he has not elaborated it. He shows, for example, that chloramphenicol reduces verticillial wilt of potato, but not of tomato.

a. Detoxication in the Host. We have already seen how soil microbes may destroy a chemotherapeutant. Likewise, the living host also may degrade a chemotherapeutant and render it impotent. This is a very well known phenomenon in human medicine and much is known of the mechanisms of degradation.

In plant chemotherapy, however, about all we know is that some compounds must be degraded because their effect is lost. 8-Quinolinol derivatives are evanescent in the plant. The sulfate lasts a few days, the benzoate a few days longer. We do not know what happens to them, but perhaps they are degraded.

The term “half-life” is common these days to quantify the rate of loss. One may, thus, rate chemotherapeutants in terms of half-life. Some of the systemic phosphate insecticides have a half-life that can be expressed in weeks, but most microbial chemotherapeutants have half-lives measured in days, perhaps even in hours.

Brian (1952a), for example, showed that griseofulvin has a half-life of only a few days. Crowdy (1957) has determined this number to be about 4 days. Prescott et al. (1956) have shown that cycloheximide has a half-life of about 24 hours in the cherry fruit but much longer in cherry foliage. According to data of Wallen and Millar (1957), cycloheximide may have a half-life in wheat foliage of 2 or 3 weeks. Data of Hidaka and Murano (1956) suggest that the half-life of streptomycin in tobacco foliage also may be as much as 2 or 3 weeks.
In the human body, acetylation is a very common device for detoxicating drugs. Esterases are common among most living organisms. One would expect that higher plants would be able to make esters out of poisonous substances. Unfortunately, only a few have searched for such reactions. Rudd Jones and Wignall (1955) have shown, however, that the broad bean can acetylate sulfanilamide. Undoubtedly, many more cases of such reactions await discovery. We shall return to this reaction below in discussing possible means of producing effective chemotherapeutants.

Other devices are undoubtedly available to host plants in their fight against a foreign chemical, the introduced therapeutant. Gottlieb (1957) has discussed how microbes can detoxicate toxicants. Some, perhaps all, of these mechanisms are available to the host. He mentions hydrolyses, esterification, chelation, direct reaction with metabolites, oxidation and reduction, and displacement effects. We need much more research in this field. Sanwal (1956) has shown that fusaric acid is decarboxylated by the tomato plant and transformed into a nontoxic substance.

b. Activation by the Host. The host can react with a compound to enhance its effect, just as it can react with a compound and reduce its toxic effects.

Martin (1950) showed fairly early that the systemic insecticide bis-(bisdimethylaminophosphonous)-anhydride is more toxic after it has been acted on by the host than before. Similarly, the effectiveness of 4-chloro-3,5-dimethylphenoxyethanol to reduce fusarial wilt of tomato improves with time (Davis and Dimond, 1952).

This type of evidence is not conclusive proof that the compound actually changes. The improved effectiveness with time could be due to production of a more effective compound or to an increase in the resistance of the host. The phenoxyethanol probably is oxidized in the plant to phenoxyacetic acid. Since, however, the effects of phenoxyacetic acid also increase with time, one is more inclined to suggest as did Davis and Dimond (1953) that the resistance of the host is increased as well.

Gray (1958) has evidence that tobacco tissue converts streptomycin amine and streptomycin oxime to a more toxic compound, probably into streptomycin itself or dihydrostreptomycin. Similarly, Lemin and Magee (1957) have found that cycloheximide acetate is deesterified by the host to cycloheximide itself. Rombouts and Sijpesteijn (1958) suggest that the cucumber and broad bean may convert the nonfungitoxic carboxymethyl derivative of pyridine-2-thiol-N-oxide back to the fungitoxic thiol compound.

Van der Kerk (1956) has synthesized the carboxymethyl ester of nabam. It has the following structure: HOOC—CH₂—S—C(S)—NH—
C₂H₄—NH—C(S)—S—CH₂COOH. In this form it enters the plant readily. Inside the plant, it seems to be reconverted to the fungicidal substance, nabam, by deesterification.

All of these results suggest ways of producing new chemotherapeuticants and some of these will be discussed below.

c. Excretion from the Host. Our medical colleagues have made great strides in learning how chemotherapeuticants are lost from the host by excretion. Indubitably, plants also excrete chemotherapeuticants but our knowledge of the subject is meager indeed.

Presumably, the compounds can be excreted through the leaves or through the roots. In the leaf, the most obvious excretory organ is the hydathode. Some chemotherapeuticants have been recovered from guttation water. Notable among these are griseofulvin (Stokes, 1954) and cycloheximide (Wallen and Millar, 1957). Gopalkrishnan and Jump (1952) were not able to recover thiolutin in the guttation water.

The idea that roots excrete all manner of compounds has only recently been given detailed consideration. Sadasivan and Subramanian consider all aspects of this fascinating subject in Chapter 8 of Volume II of this treatise.

We must have more knowledge about root excretion of compounds if we are to combat root rot diseases by spraying the foliage. Halleck and Cochrane (1950) and Zentmyer (1954) have made a start to search for compounds that could be applied to the foliage, translocated to the roots, and excreted into the soil. This would appear to be a promising lead to follow.

V. Modes of Chemotherapeutic Action

Having found an effective therapeutant; having preserved it from degradation by soil, microbes, and host; having found that it is translocated to the infection court; having saved it from excessive excretion, what do we know about its mechanisms of action?

Research so far suggests three major mechanisms of action: vivotoxins are destroyed; the pathogen is killed by direct action; or the resistance of the host is enhanced. These we shall now discuss.

A. Inactivating Vivotoxins

Plant pathogens excrete sewage products into the medium where they grow. Sometimes these are called "staling products," because they inhibit the very fungus that excretes them.

Plant pathologists, seeing such effects in fungus cultures, have suggested for a half century or more that such products must also be produced by the fungus in the invaded plant and must participate in the pathogenesis of disease. In such cases the substances are called toxins.
This has always been an intriguing hypothesis. It is discussed in all of its implications by Ludwig in Chapter 9 of Volume II of this treatise.

Dimond and Waggoner (1953) insisted that the alleged substances must meet Koch’s rules of proof, if they are to be implicated as causal factors in disease. For one thing, they must be recovered from the diseased host. It is not enough that they be found in laboratory media.

Those that can be recovered from the hosts were labeled vivotoxins. Since vivotoxins probably do occur in the chain of causality, one is intrigued by the possibility that pathogenesis can be reduced by neutralizing such toxins. Howard (1941) first proposed such a possibility to account for his alleviation of the symptoms of bleeding canker of maple with diamino-azobenzene. Zentmyer (1942) and Stoddard (1946) offered a similar explanation for the action of 8-quinolinol in alleviating symptoms of Dutch elm disease. In neither case was a vivotoxin proved.

Perhaps the best example of a vivotoxin is that of the wildfire disease of tobacco as investigated by Braun (1950) and by Woolley et al. (1952). The vivotoxin is a complicated amino acid analogue of methionine and it can be antidoted chemotherapeutically with methionine.

A very new comer as a vivotoxin is fusaric acid which clearly is involved in the pathogenesis of fusarial wilt (Lakshminarayanan and Subramanian, 1955). It is an analogue of pyridine. Subramanian (1956) showed that its effects could be antidoted with 8-quinolinol thus putting props under Horsfall and Zentmyer (1942) who had said that 8-quinolinol seemed to mitigate the symptoms of Dutch elm disease by antidoting a toxin.

However entrancing the vivotoxins may be in the genesis of disease, their treatment by chemotherapy may be a delusion. As long as the pathogen remains in the tissue it will presumably continue to excrete the vivotoxin. That means that any antidoting chemical must be maintained continuously in the system. This will be difficult. One is in the position of Alice in Wonderland. He must run as hard as he can to stay even.

Horsfall (1956) says that he had had hopes that perhaps the destructive action of the toxin could be kept under control long enough to enable the host to throw off the invader by other means. As yet, this still remains only a hope.

The future looks dark for successful chemotherapy by toxin control alone.

B. Direct Action on the Pathogen

If the microbe is a primary causal factor in disease, surely we must kill it out if we are to save the host. Success in so doing is very elusive, however. For many years after the modern reactivation of research on
chemotherapy, the number of cases of direct killing were scarce indeed.

Before proceeding to a discussion of such successes as we have had, we should consider direct killing of the pathogen by substances found in nature. These, perhaps, will be useful to suggest further research on synthetic substances.

1. Natural Therapeutants

Plants display a wide variety of cases where resistance to disease seems chemical in nature. This matter is discussed in considerable detail by Allen in Chapter 12 of this volume and need only be referred to here.

The role of phenols and tannins in natural resistance has been discussed for years. The classic example is protocatechuic acid which has been shown by Walker et al. (1929) to be responsible for the resistance of red onions to smudge. Natural therapeutic agents, such as phenolic compounds, have been found in trees by Rennerfelt (1945), and Erdtman (1949).

Rich and Horsfall (1954) have called attention to the fact that quinones are generally more fungitoxic than phenols. Schaal and Johnson (1955), investigating the role of chlorogenic acid in resistance of potato to scab, suggest that the phenol is oxidized to a quinone before maximum resistance is attained. Presumably, this oxidation occurs when the potato tissue is damaged upon invasion.

The phenol situation is interesting in fusarial wilt of tomato. One of the outstanding characteristics of this disease is the darkening of the vascular bundles. Davis et al. (1953) asked themselves, what is the color and how does it originate?

After studying the problem, they decided from their data that the pigment is melanoid, that it derives from a phenol which is oxidized to a quinone, and polymerized to a pigment. They decided that the phenol comes from a phenolic glycoside in the host, that the hydrolytic enzyme comes from the invading fungus, and that the phenoloxidase comes from the host. In brief, the course of events in blackening of the vascular bundle is that a phenol glucoside of the host is hydrolyzed by a fungus β-glucosidase, that the host enzymes oxidize the phenol to a quinone and convert the quinone to a pigment.

Presumably the same situation occurs in other wilt diseases, such as Dutch elm disease, where the vascular elements are discolored. Here, then, is a parallel situation to the potato scab. In potato scab the chlorogenic acid phenol that is liberated is somewhat fungicidal and its quinoidal analogue more so. Presumably, then, the phenols and the quinones that are precursors of the pigments in vascular diseases are fungitoxic also. The question is, do they discourage invasion?
Perhaps the Dutch elm disease might be considered first. We know that the so-called black strain of the Dutch elm disease fungus is a much more pathogenic strain than the light colored strain. Presumably, this can be explained by the results of Rich and Horsfall (1954). They found that Monilinia fructicola, a hyaline fungus, is poisoned by phenols and quinones while Stemphylium sarcinaeforme, a black fungus, generally is not. The black fungus is able to detoxicate phenols and quinones by converting them to bland black pigments, but the hyaline fungus cannot. Possibly, the hyaline strain of the Dutch elm disease fungus is unable to detoxicate the phenols or quinones formed upon invasion, and is thus poisoned. The black strain can detoxicate them, is not poisoned, and thus produces more damage than the hyaline strain. Similarly, Taylor and Decker (1947) report that the strains of the potato scab fungus that form black pigments are more pathogenic than hyaline strains.

One wonders how the blackening of the tomato xylem fits into the fusarial wilt picture. Apparently the fungus, being colored, can tolerate the phenols or the quinones that are precursors of the pigment. Perhaps the fungus can detoxicate the compounds as Stemphylium sarcinaeforme does. One observation is interesting. Gothoskar et al. (1955) have shown that respiratory inhibitors such as 2,4-dinitrophenol, sodium fluoride, thiourea, and sodium diethyldithiocarbamate break down the resistance of the Jefferson tomato to fusarial wilt. The last two named are active inhibitors of phenoloxidases. Perhaps these two, at least, prevent the formation of a toxic quinone and thus destroy natural resistance.

The case of verticillial wilt of tomato is interesting in this context. Here is a vascular disease in which the vascular system is only weakly discolored, if at all. The quinone or the melanin reaction must be blocked somewhere. This was mysterious until Caroselli (1955) discovered that Verticillium seems to excrete thiourea, at least in culture. If, indeed, it secretes thiourea in the tomato, it could inhibit the polyphenolase system and, thus, prevent the blackening. It probably also prevents the formation of the toxic quinone by the host and thus protects itself from damage. Stated in Gothoskar’s terms, the thiourea secreted by the Verticillium fungus breaks down the host resistance.

The paper of Vörös et al. (1957) fits into an interesting niche here. Streptomycin is not fungitoxic but as a chemotherapeutant, it seems to increase the resistance of the potato to Phytophthora infestans. These authors give evidence that streptomycin activates the phenol oxidase system of the potato so that it produces more of the natural substances (possibly quinones) that are responsible for natural resistance. One wonders if it would not then increase the resistance of the potato to scab.

Certainly much more needs to be learned about the polyphenol
system. Apparently we can increase susceptibility by inhibiting it, decrease susceptibility by stimulating it.

This still leaves hanging the case of the tomato wilt disease. The quinone reaction does not seem to affect the situation in the normal infections. The Bonny Best variety is very susceptible, but the vascular bundles turn very dark. Here is an anomaly. The phenol → quinone → pigment reaction exists, but the fungus is not poisoned. This cannot be a thiourea case, either, because this would prevent coloration.

We can marshal what evidence we have. Davis et al. (1953) showed that *Fusarium oxysporum f. lycopersici* can hydrolyze phenol glycosides and use them as sources of carbon. Presumably, this suggests that the phenol formed in the tomato stem is not toxic to the fungus. The phenol apparently is oxidized by the host to a quinone. We do not know whether it is toxic to *Fusarium* or not. From their colors, we know that *Fusaria* can produce many pigments. Probably, *F. lycopersici* can detoxicate a quinone by forming a pigment, as *Stemphylium sarcinaeforme* does.

The results of Dimond and his colleagues (Davis and Dimond, 1953) on phenoxy and naphthoxy acetic acid analogues seem to find a place somewhere in this area of the reasoning. Essentially, all of these compounds inhibit the blackening reaction in tomato stems that have been inoculated with *Fusarium*. On this basis, the compounds have been rated as chemotherapeutic. They do indeed knock out the commonest symptom of disease.

We are unable to discover any other work on the effect of these compounds to inhibit the polyphenolase blackening reaction of higher plants. Several authors, however, report that 2,4-D inhibits pigmentation in dark-colored fungi, as for example in *Helminthosporium victoriae* (Bever and Slife, 1948).

It seems reasonably safe to assume then that these compounds do inhibit pigment formation. Do they inhibit quinone formation as well? We have no evidence here. The quinone may or may not be important, because the fungus does seem to be able to cope with it in nature.

One wonders what effect the phenoxy compounds would have on the resistant Jefferson variety of tomato. One wonders if the effect would be similar to that of the inhibitors of polyphenolase as reported by Gothoskar et al. (1955). Whether they act on the quinone or not, the fungus is not killed by them because when medication is withdrawn for a few days, the tomato dies from its infection.

These substances are phenol analogues. Possibly they inhibit blackening by acting as phenolic antimetabolites. This brings to mind another interesting result that has occurred in Dimond's tests. 2,4-Dichlorophenoxypropionic acid is not as effective in reducing the blackening reaction
as 2,4-dichlorophenoxyacetic acid. A similar result has been shown on chocolate spot of bean by Crowdy and Wain (1950). This disease also is read in terms of the blackening reaction. The propionic acid derivative does not reduce the blackening. The acetic acid derivative does.

According to Synerholm and Zimmerman (1947), the propionic acid analogue is degraded to a phenol by the host, the acetic acid analogue is not. Thus, the former would add to the blackening, if anything, the latter would not.

What, then, about other symptoms of disease? What about wilting? Generally, the growth substances reduce wilting too. However, Dimond has told us verbally of a compound which prevents the blackening of the vascular bundles but which permits 73% as much wilting as the check. This compound is 2,4-Cl₂C₆H₅—O—(CH₂—CH₂—O)₂—CH₂—CH₂OH. A homologue with four ethoxy groups in the side chain gave similar results. It is obvious that these two compounds can eliminate one symptom of tomato wilt, but not others.

2. Synthetic Therapeutants

Until the modern revival of interest in synthetic therapeutants, most of the cases of successful cure of plant disease were limited to local or topical chemotherapy. Apple scab lesions could be cured with lime sulfur and organic mercurials. Certain cereal smuts could be cured by treating the infected seeds with organic mercurials, but we probably had no translocatable “systemic fungicide.”

By our definition, a systemic fungicide is one that distributes itself systemically through the plant and kills the pathogen by direct toxic action. Crowdy and Wain (1950) spoke of the systemic fungicidal activity of analogues of phenoxyacetic acid. These compounds are only weakly fungitoxic, however. This led Horsfall and Dimond (1951) to suggest that they probably act to make the host resistant rather than to kill out the pathogen. Later researches seem to bear this out (Davis and Dimond, 1952).

Crowdy and Davies (1952) showed that phenyl mercury acetate is translocated from the roots to leaves of bean plants and inhibits the chocolate spot disease.

Antibiotics probably showed the first really good case of a systemic therapeutant that could indeed kill out the invader. Now we know that cycloheximide possesses such properties for wheat rust (Wallen and Millar, 1957) and cherry leaf spot, cycloheximide semicarbazone for Coccomyces hiemalis in sour cherry (Hamilton and Szkolnik, 1958), pyridine-2-thiol-N-oxide for cucumber scab (Sander and Allison, 1956, and Rombouts and Sijpesteijn, 1958), 4-nitrosopyrazole for Alternaria on
tomato (McNew and Sundholm, 1949), and griseofulvin for several diseases.

The antifungal polypeptide, "Phytoactin," has markedly reduced infection with oak wilt when applied in solution through trunk cuts to northern pin oaks (Phelps et al., 1957). In University of Wisconsin experiments on oaks, 3 to 10 inches in diameter and 20 to 40 feet in height, oligomycin yielded an average of 13% healthy trees, Actidione 20%, its acetate derivative 30% for three seasons, and Phytoactin 40% after two seasons. By comparison, 95% of the untreated, inoculated check trees had died. A group of inoculated greenhouse and nursery oaks in Ohio tests were not benefited.

A few reports suggest that viruses can be inactivated in plants. Stoddard (1947) reported curing peach seedlings of X-disease by injecting the outer ends of the stems with calcium chloride and zinc sulfate. The zinc effect has by now been investigated for numerous virus diseases. It seems to be effective for some such as carnation mosaic (Thomas and Baker, 1949) but not for others such as tobacco mosaic virus on Nicotiana glutinosa (Yarwood, 1954).

Respiration inhibitors seem to inhibit virus multiplication (Leben and Fulton, 1951). Similarly, some antimetabolites seem to be effective for viruses, as for instance sulfanilamide (Stoddard, 1947), thiouracil (Commoner and Mercer, 1951), and guanazolo (Matthews, 1951). The inhibition of virus multiplication is treated extensively in this treatise by Matthews in Chapter 12 of Volume II.

Therapeutic action of sulfonamide and related sulfa compounds is currently believed to be by interference with enzymes necessary for growth. They disturb the utilization of para-aminobenzoic acid and, hence, inhibit the action of certain coenzymes essential for bacterial and actinomycete growth. A possibility for curing systemic bacterial diseases is the internal application of translocatable sulfones capable of breaking down in vivo into diamino-diphenyl sulfone which exercises antibiotic action similar to the sulfonamides.

3. Possibilities for a Tailor-Made Therapeutant

Perhaps something can be derived from our experience to date to suggest possibilities to make better therapeutants. As we have seen, phenols and quinones seem to be involved in natural host resistance. It seems probable that our knowledge of these compounds will increase.

The evidence is fairly clear from Allen's review (Chapter 12 of this volume) and from the work of Davis et al. (1953) that in the very act of invasion phenols may be freed from natural nontoxic compounds such as phenolic glycosides.
This suggests that we feed such detoxicated phenols to the host. They should not be phytotoxic. They would lie in wait for an invading microbe which would free them from their bound form. Thus, the microbe would poison itself at the point of invasion. In effect, this would be a case of synthetic hypersensitivity which is discussed by Müller in Chapter 13 of this volume.

The work of Byrde and Woodcock (1952) suggests a device that would work on this principle. 2,4-Dichloronaphthoquinone is a powerful fungicide used commercially as a protectant. Byrde and Woodcock reduce it to the dihydroxynaphthalene form and then acetylate the two phenolic groups. This procedure renders the compound nontoxic to apple foliage when applied to the surface.

The apple scab fungus, *Venturia inaequalis*, can deacetylate the compound by means of a fungus esterase. According to Byrde and Woodcock, the dihydroxynaphthalene thus liberated is toxic. Horsfall (1956) suggested that the compound is probably oxidized by the fungus back to the still more toxic naphthoquinone.

If, now, the diacetoxy derivative were used as a chemotherapeutant, it should be the answer to our prayers. The invading fungus should free the phenolic form, the host should convert it to a quinone. It cannot be converted to a pigment because the chlorine blocks the important position. Thus, it should be an ideal chemotherapeutant.

The concept is too simple. Upon trial we find that the host esterases can liberate the phenol and oxidize it as readily as those of the fungus. The host dies by its own hand even before the pathogen arrives. It works on the surface of an apple leaf, but not inside the tissue.

Other acetylated phenols have followed this one down the drain. Esterases for acetic acid derivatives seem to be too common in nature. Perhaps, we need to investigate other acids, such as benzoic. The linkage here is harder to break according to Byrde and Woodcock (1956), but on the other hand the fungus esterases may not break it either.

An interesting ester is the thioglycolic ester of ethylenebisdithiocarbamic acid as proposed by van der Kerk (1956) as a systemic chemotherapeutant. According to van der Kerk the host deesterifies this linkage and recovers the nabam itself.

Perhaps phosphate or borate esters would work better. The phosphates have solved the problem for systemic insecticides.

Perhaps amide linkages are better sources of detoxication. Whether fungus amidases are more common or more specific than host amidases, can only be settled by empirical attack.

In any case, this appears to be a lucrative source of possible chemotherapeutants that might act differentially on host and pathogen.
C. Development of Resistance to Chemotherapeutants

As soon as one speaks of chemically killing a pathogen, one cannot avoid the possible development of resistance by the pathogen. This problem has plagued our medical colleagues almost from the day of the development of the first successful chemotherapeutant.

Fortunately, it has not been a serious problem for the plant pathologist, perhaps because we do not yet have a chemotherapeutant in wide-scale commercial use. The problems of acquired resistance are treated by Buxton in Chapter 10 of Volume II.

Acquired resistance to chemotherapeutants has been reported for bacteria. Mitchell et al. (1952) report that Xanthomonas phaseoli causing bean blight develops resistance to streptomycin. Strangely enough the halo blight bacterium on beans, Pseudomonas phaseolicola, does not develop resistance so readily. Erwinia amylovora on apple and Xanthomonas vesicatoria on pepper also rapidly develop resistance to streptomycin.

Our colleagues in medicine solve the resistance problem in part, at least, by using mixtures of antibiotics. English and van Halsema (1954) have shown that plant bacteria also develop resistance less rapidly if more than one antibiotic is used.

D. Increasing Host Resistance

Increasing natural resistance to development of the pathogen by chemical modification of the host cell is possible. Weintraub et al. (1952) suggest that the antiviral effect of Stoddard’s (1947) zinc sulfate is probably a case of increasing host resistance. Chemotherapy may also be used to induce extreme susceptibility or hypersensitivity. This phenomenon of hypersensitivity occurs naturally between wheats and the rust fungus, potatoes and the late blight fungus, etc.

1. Effect of Auxins

Plant growth regulators give striking effects in the amelioration of some diseases. These effects were discovered independently and reported first by Crowdy and Wain (1950) for the chocolate spot of beans and then by Dimond and Chapman (1951) for fusarial wilt of tomatoes. More recently they have been tested by Beckman (1958) for Dutch elm disease.

These compounds were selected originally for testing because they were known to be translocated.

Dimond and his group continued their researches on the auxins and
auxin-like substances and found that almost any auxin that acts on the tomato reduces the fusarial wilt syndrome (Davis and Dimond, 1953).

The striking feature, however, is that the fungitoxicity of auxins is extremely low, so low in fact that it could not possibly account for the reduction in disease (Davis, 1952).

This discovery led to the conclusion that the auxins somehow make the plant resistant to disease. The nature of this mechanism is still vague, but some progress is being made. The final solution must await information on just what the auxins do and can do to the plant.

2. Relation to Sugars

In the meantime, a few statements can be made. For one thing, auxins exert a strong influence on the sugar levels in plants and Horsfall (1956) hazarded a conjecture that the sugar levels are correlated with disease.

This phase of the matter has been pursued in considerably more detail by Horsfall and Dimond (1957).

The effect of auxins on sugar levels varies with the time that elapses after treatment. Usually the sugar rises at first and then falls. Maleic hydrazide affects the phloem and reduces translocation of sugars from the leaves. Hence, it usually raises the sugar in the leaves, reduces it in stems and roots.

Diseases may be high sugar diseases or low sugar diseases, that is, encouraged by high sugar or discouraged by high sugar. Rusts, powdery mildews, and chocolate spot of broad bean are high sugar diseases. They should be reduced by 2,4-D and increased by maleic hydrazide, and they are.

On the other hand, helminthosporial and alternarial leaf spots and anthracnoses seem to be low sugar diseases. 2,4-D increases them.

Fusarial wilt seems also to be a low sugar disease; 2,4-D decreases it at first when stem sugars are high, but the effect wears off as sugar levels fall. Maleic hydrazide, on the other hand, increases fusarial wilt (Waggoner and Dimond, 1957), presumably because maleic hydrazide reduces stem sugars.

We have difficulty in believing that the sugar effects can stand alone. Possibly the sugar effect is direct on the high sugar diseases. In this case sugar reduction could be directly related to disease reduction. The effect on low sugar diseases is less easy to follow. It seems probable that the sugar is a marker for something else. The pathogens that induce low sugar disease are sugar feeders just like the rusts and powdery mildews. It seems likely that low sugar must be correlated with low something
else, and that the low something else is related to low resistance. We must search for the "something else" that might account for resistance to *Fusarium* and to the leaf spots mentioned.

Growth hormones generally increase the resistance of tomato plants to fusarial wilt. For a series of related growth regulants, Corden and Dimond (1959) studied the types of growth hormone activity with which chemotherapeutic activity is best correlated. They showed that the ability of compounds to inhibit root elongation is well correlated. The relation of this hormone function to the nature of pectin composition of the host plant is suggested by this study.

Various chemicals of therapeutic promise against the Dutch elm disease are antagonistic to indoleacetic acid as judged by the pea epicotyl elongation test (Beckman, 1958). A good correlation was found between the inhibition of springwood development and suppression of symptoms.

And thus we end our story. This is where our ideas of "Plant Disease Therapy" stand today. But, tomorrow—who knows?

### References


