SERIES
XLVII-XLVIII

THE HARVEY LECTURES

delivered under the auspices of
THE HARVEY SOCIETY OF NEW YORK
1951-1953

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THE HARVEY LECTURES

DELIVERED UNDER THE AUSPICES OF
The HARVEY SOCIETY of NEW YORK

1952–1953

UNDER THE PATRONAGE OF THE NEW YORK
ACADEMY OF MEDICINE

BY

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SERIES XLVIII



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THE HARVEY SOCIETY

A SOCIETY FOR THE DIFFUSION OF KNOWLEDGE OF THE MEDICAL SCIENCES

CONSTITUTION

I

This Society shall be named the Harvey Society.

II

The object of this Society shall be the diffusion of scientific knowledge in selected chapters in anatomy, physiology, pathology, bacteriology, pharmacology, and physiological and pathological chemistry, through the medium of public lectures by men who are workers in the subjects presented.

III

The members of the Society shall constitute three classes: Active, Associate, and Honorary members. Active members shall be laboratory workers in the medical or biological sciences, residing in the City of New York, who have personally contributed to the advancement of these sciences. Associate members shall be meritorious physicians who are in sympathy with the objects of the Society, residing in the City of New York. Members who leave New York to reside elsewhere may retain their membership. Honorary members shall be those who have delivered lectures before the Society and who are neither Active nor Associate members. Associate and Honorary members shall not be eligible to office, nor shall they be entitled to a vote.

Members shall be elected by ballot. They shall be nominated to the Executive Committee and the names of the nominees shall accompany the notice of the meeting at which the vote for their election will be taken.

IV

The management of the Society shall be vested in an Executive Committee to consist of a President, a Vice-President, a Secretary, a Treasurer, and three other members, these officers to be elected by ballot at each annual meeting of the Society to serve one year.

V

The Annual Meeting of the Society shall be held at a stated date in January of each year at a time and place to be determined by the Executive Committee. Special meetings may be held at such times and places as the Executive Committee may determine. At all meetings ten members shall constitute a quorum.

VI

Changes in the Constitution may be made at any meeting of the Society by a majority vote of those present after previous notification to the members in writing.

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CONTENTS

CONSTITUTION OF THE HARVEY SOCIETY vii

OFFICERS OF THE HARVEY SOCIETY ix

HARVEY LECTURES 1952–1953

THE HORMONAL CONTROL OF PLANT GROWTH . . . 1
James Bonner, Professor of Biology, Kerckhoff Laboratories of Biology, California Institute of Technology, Pasadena, California.

EXPERIMENTS ON CHEMICAL ALTERATION OF VIRUS INFECTIONS 35
Frank L. Horsfall, Jr., Member, The Rockefeller Institute for Medical Research, New York, New York.

BIOLOGICAL SYNTHESIS OF CHOLESTEROL 68
Konrad Bloch, Professor of Biochemistry, University of Chicago, Chicago, Illinois.

CONGENITAL MALFORMATIONS INDUCED BY MATERNAL DIETARY DEFICIENCY 89
Josef Warkany, Associate Professor of Pediatrics, University of Cincinnati, College of Medicine and Fellow, Children's Hospital Research Foundation, Cincinnati, Ohio.

THE FUNCTIONS OF THE LUNG 110
Julius H. Comroe, Jr., Professor of Physiology and Pharmacology, University of Pennsylvania Graduate School of Medicine, Philadelphia, Pennsylvania.

GLYCOGEN STRUCTURE AND ENZYME DEFICIENCIES IN GLYCOGEN STORAGE DISEASE 145
Gerty T. Cori, Department of Biological Chemistry, Washington University School of Medicine, St. Louis, Missouri.

MECHANISMS FOR STABILIZING THE ALKALINE RESERVES OF THE BODY 172
Robert F. Pitts, Professor of Physiology and Biophysics, Cornell University Medical College, New York, New York.

ACETYL COENZYME A AND THE "FATTY ACID CYCLE" . 210
Feodor Lynen, Professor of Biochemistry, University of Munich, Munich, Germany.

THE HORMONAL CONTROL OF PLANT GROWTH*

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Professor of Biology
Kerckhoff Laboratories of Biology
California Institute of Technology
Pasadena, California

THIS discussion concerns the internal chemical factors by which the plant controls and integrates its growth. That the plant does indeed make use of specific chemical substances, or hormones, for the purpose of assuring a well-regulated development of its varied parts, is a fact that has been known to us for exactly 25 years.[1] In the course of these 25 years our growing insight into the developmental chemistry of the plant has found an appreciable number of unexpected but entirely acceptable applications in the agricultural aspects of biology. So great indeed has the practical import of plant endocrinology become that we sometimes tend to lose sight of the significance which this study has for our understanding of the plant. Through basic work on the plant growth hormones, the concept has become available to us that particular substances may be applied to the plant to accomplish particular useful purposes: to make the leaves drop off, to make the fruit stay on, to induce flowering, to inhibit flowering, and even to kill undesired plants.[2] The different chemicals which are used for the supervision of these varied aspects of plant development are almost without exception substances whose biological effectiveness is based upon structural similarity to one or another of the native plant growth hormones. Since a great many substances have been investigated or screened as to ability to evoke this or that plant growth response, we have today what is almost a pharmacology of plants. We will concern ourselves primarily with the knowledge of plants which has accrued to us in the development of this pharmacology.

* Lecture delivered October 23, 1952.

CONCEPT OF HORMONAL REGULATION

It is of course well known that the growth of the plant depends upon the process of photosynthesis by which the CO_2 of the air is transformed into the manifold materials of which a plant is made. The growth of the plant is dependent too on the water and on the varied mineral constituents of the soil which are ordinarily taken up by the root and incorporated into plant materials. As photosynthesis, mineral uptake, and the chemical transformations of metabolism proceed, the plant increases in size and in mass and, in due course, proceeds from the vegetative state to a reproductive one. The total increment of plant which occurs as a result of synthetic reactions must be apportioned among the several organs: the roots, leaves, stems, and, ultimately, the flowers and fruits. It is the harmonious integration of the development of the several plant organs and tissues in space and in time which appears to be the primary function of the plant hormones. Each of these materials is produced in a particular organ in minute amounts, and is then transported to other organs where it then brings about a specific effect on growth. It is through the growth hormones that the individual parts of the plant interact with one another and mutually regulate one another's growth. Let us first consider some aspects of the multiplicity of the plant hormones and discuss the experimental basis of this knowledge.

MULTIPLICITY OF THE PLANT HORMONES

That growth of the root is dependent upon specific chemical substances which are normally supplied by the aerial organs can be shown simply and elegantly by the cultivation of the excised tips of roots. If we remove a tip a few millimeters long from a growing root and place this in an appropriate nutrient solution, the tip will grow into a whole root. This fact was first demonstrated by W. J. Robbins in 1922.[3] If the nutrient solution has been correctly selected, the excised root will in fact grow in length as rapidly as it would have had it remained attached to the intact plant. It is further possible to remove the tip of the cultured root, place it in fresh nutrient, and again allow it to grow into a normal root. Such transfer by repeated subculture may be continued in-

definitely, a demonstration first made by White in 1934.[4] We may now ask ourselves what chemical substances must be added to the nutrient solution used for the culture of excised roots in order to bring about continued root growth. One knows *a priori* that an appropriate nutrient solution must contain a carbohydrate, which may be used by the root tissue as a respiratory substrate and which may serve as a source of building blocks for the synthesis by the root of the many substances of which roots are made. The nutrient solution must necessarily contain also the inorganic nutrients which plants require for their growth. A nutrient solution containing only mineral salts and sucrose is, however, inadequate for the cultivation of excised roots. An excised root tip of flax, for example, cultivated in such a nutrient ceases its growth in a few days or a few transfers. In order to cause excised flax roots to grow at the rate which they would have attained had they remained attached to the plant, it is necessary to add a small amount of the substance thiamine to the nutrient solution.[5] Thiamine, a member of the vitamin B complex, must be present in a concentration of the order of 0.1 part per million of nutrient solution in order to permit a continued, vigorous growth of excised flax roots. Thiamine is, then, a root growth factor, an organic substance which must be added to the nutrient solution in order to permit continued root growth. All of the roots which have thus far been studied in culture as excised roots require the presence of thiamine for continued normal growth. Many species require other growth substances in addition to thiamine. Thus, in the case of the excised tomato root, the addition of thiamine alone does not permit of continued growth. The vitamins pyridoxine and niacin must also be added to the nutrient solution. In the presence, then, of these three vitamins of the B complex, excised tomato roots grow as fast and luxuriantly as they would have had they remained attached to the plant. All of the species of excised roots which have been studied up to the present time require thiamine and in general one or both of the vitamins pyridoxine and niacin, in order to continue growth as isolated roots.[6]

These three vitamins of the B complex constitute, then, root growth factors. It is possible by simple plant physiological

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experiments to show that these vitamins of the B complex are produced in mature green leaves, primarily in the light. They are then transported from the leaf, through the stem to the root.[7] Since roots cannot produce these vitamins of the B complex and since these materials are required for root growth, thiamine, pyridoxine, and niacin constitute root growth hormones. They are, as required by the definition of a hormone, produced in one organ, the leaf, in minute amounts and transported to another organ, the root, where they are required for the support of a particular physiological process, namely, root growth.

From an anatomical standpoint, thiamine is required by roots for the support of cell division in the meristematic region.[8] From a biochemical standpoint thiamine is required by excised roots, as by other tissues, as constituents of the carboxylases which are involved in the cleavage of CO_2 from respiratory intermediates.[9] We see, then, that there are various ways of regarding the economy of thiamine in the plant. From an anatomical standpoint, it is a cell-division factor for the root. From a biochemical standpoint, it is a constituent of a particular group of enzymes. From the standpoint of the plant as a whole, however, thiamine and the other members of the B complex are root growth hormones.

The same basic kind of experiment used for the demonstration of the presence in the plant of root growth hormones may be used for the demonstration of the existence of other types of growth hormones as well. Thus an immature leaf of a pea plant when excised and cultivated on nutrient solution fails to grow appreciably unless a principle contained in mature leaves or in seeds is added to the basal nutrient. Mature leaves thus contain some material which is needed for the growth of immature leaves and which the latter are unable to synthesize. The chemical nature of the principle has been elucidated,[10] and in the pea plant at least this type of leaf growth activity is to be attributed to the purines adenine and hypoxanthine.

Still further correlational growth substances have been demonstrated by the excision-*in vitro* cultivation technique. The embryo, for example, has its own pattern of specific growth substance requirements, a pattern which shifts from more complex to less complex as the embryo develops from a fertilized egg toward a

seedling plant.[11] The growth of the fruit too has been studied by the same technique, and we realize that fruits in general require for their development particular growth factors of an as yet unknown chemical nature.[12]

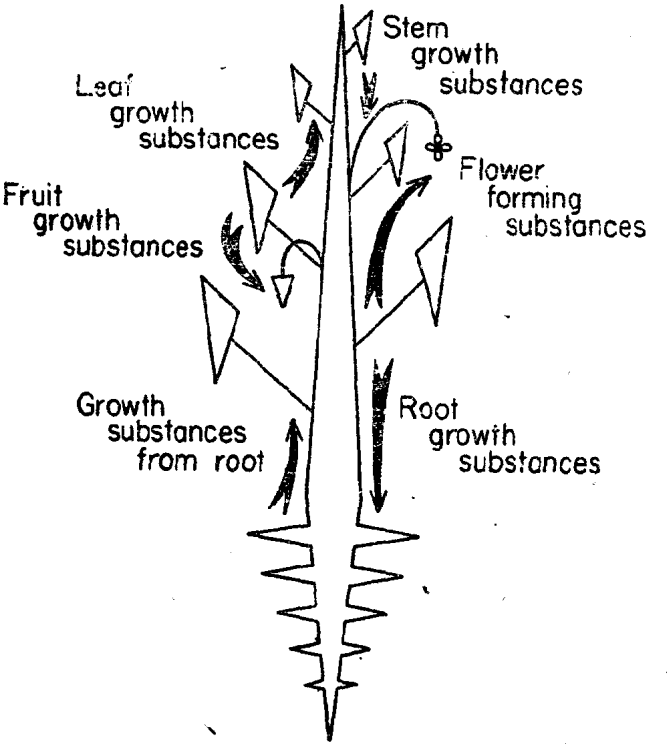


FIG. 1. A few of the principal currents of hormone movement in the growing plant.

We must then visualize the growing plant as containing many currents of transport of a variety of growth regulating substances. The mature leaves, as shown in Figure 1, produce the vitamins of the B complex which are transported to and used in the regulation of root growth. These same leaves produce the leaf growth factors such as adenine, as well as the hormones which regulate flower initiation and reproductive development, hormones which are possibly protein in nature.[13] Still other factors produced in

the roots are required for the growth of the aerial parts, possibly also for such metabolic functions as maintenance of the protein level of leaves. And to this array of known or suspected correlational carriers we will doubtless add in the future further hormones whose existence is not even suspected today.

THE AUXINS

A major portion of our knowledge of plant growth substances has been derived from the study of one particular group of materials, a group known collectively as the auxins. This term is a physiological one and the auxin concept physiological rather than chemical. An auxin is a substance produced in the apical bud and young leaves of the plant and transported from this point to the growing region of the stem where it is used in the support of stem elongation.[14] That special chemical substances do have to do with the regulation of stem elongation can be simply demonstrated. If we excise sections from the growing region of say a seedling oat plant and place the sections in a nutrient solution containing only sugar and mineral salts, they grow but little. If however we add to the nutrient a small amount of the substance indoleacetic acid (IAA), the rate of growth of the sections is greatly increased and may in fact achieve or surpass the rate normally attained in the plant.[15] Of the many plant parts and plant tissues which have been used in this way for the study of IAA-induced cell growth, the tissues of the seedling oat coleoptile (*Avena coleoptile*) are perhaps the most satisfactory. The excised sections of this organ combine a great sensitivity to applied IAA with a negligible endogenous or residual growth. That IAA is a naturally occurring plant material has been shown by isolation from a variety of plant products.[16] It is produced in the apical bud and young leaves and transported downward through the stem and thus satisfies the requirements of the auxin concept. IAA is in fact the best known and perhaps the most important of the stem growth regulating substances produced in and used by the plant.

Although the relation of IAA and of auxins generally to plant growth was first appreciated in relation to stem elongation, we know today that the functions of this hormone are actually

manifold. IAA appears to act as a master hormone, inciting cells or tissues to activities of the most varied kinds. Among the terminal manifestations of auxin-induced activity[17] are growth in length (stems), suppression of growth in length (roots), induction of cell division in the cambium, in callus, and in tumors, inhibition of leaf and fruit fall, production of adventitious roots, and finally the production or nonproduction of other and more

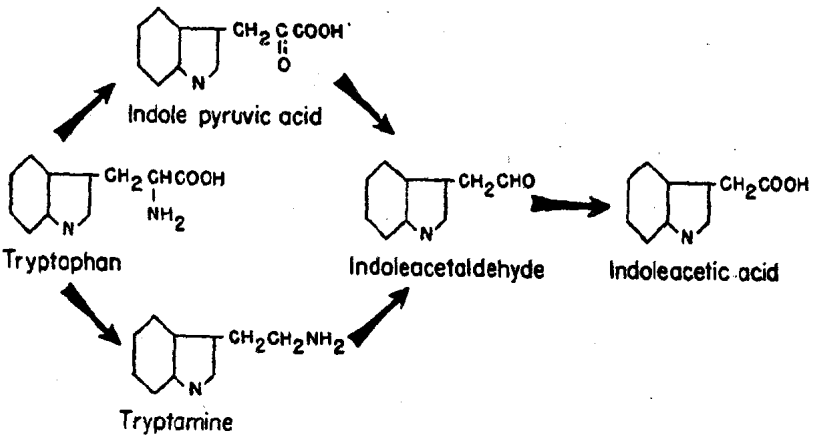


FIG. 2. Alternate pathways for the biogenesis of indoleacetic acid from tryptophan. The upper pathway has been suggested as operative in spinach leaves,[19] the lower in pineapple leaves.[20]

specific hormones which are in turn responsible for further responses such as the initiation of reproductive activity.[18] It is precisely because of the wealth of different responses which can be brought about by appropriate auxin application that plant hormone therapy has assumed such agricultural significance today, and this therapy is in turn largely based on our knowledge of auxin physiology. We shall not here be concerned with the manifold responses of plants to auxin but shall concentrate rather on the basic mechanisms which appear to underlie them all.

THE GENESIS OF INDOLEACETIC ACID

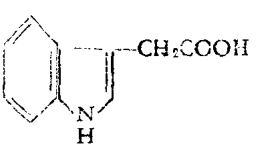
IAA, as shown in Figure 2, consists of an indole nucleus to which an acetate side chain is appended at position 3. It is thus

related in structure to the amino acid tryptophan. IAA is synthesized in the plant from tryptophan by a series of reactions mediated by an enzyme system which is found in apical buds and other centers which possess the ability to generate the hormone.[19] This series of reactions involves the production, by either of two alternative pathways, of indoleacetaldehyde, a material which accumulates in relatively high concentration in many tissues. In the final enzymatic step the indoleacetaldehyde is oxidized to indoleacetic acid itself.

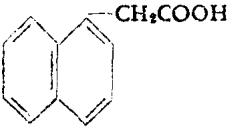
CHEMICAL STRUCTURE AND BIOLOGICAL ACTIVITY IN THE AUXINS

Approximately 15 years ago it became known through the work of Haagen Smit and Went[21] that IAA is not alone in its ability to regulate the stem growth of plants. Certain related chemical substances, not necessarily naturally occurring, were found to be able to duplicate the effects of IAA and to be able, for example, to supplant IAA in causing the elongation of excised sections of stems of oat coleoptiles. Naphthaleneacetic acid is active in this way. Naphthaleneacetic acid is not a naturally occurring plant material and is therefore a chemical substance which is able to simulate the effects of a plant hormone although it is not itself a plant hormone. In the years since 1935 a very great number of compounds have been tested for their ability to replace IAA in the induction of plant growth responses. So much study has been put into this matter that at present our knowledge of the relation of chemical structure to biological activity among the auxins is one of the best documented studies of this nature.[22] Let us therefore see what new insight into auxin physiology these intensive chemical studies have given us.

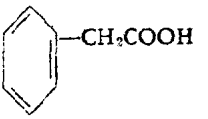
It may first be noted that various cyclic nuclei may be substituted for the indole nucleus and still yield compounds which are active as IAA in supporting stem elongation. Not only is naphthaleneacetic acid active, but so also is phenylacetic acid as well as a variety of phenoxyacetic acids. It is clear then that a variety of ring systems are acceptable in this system. All acyclic compounds which have been tested up to the present time have on the contrary been completely devoid of auxin activity. Not



Indoleacetic acid
Active

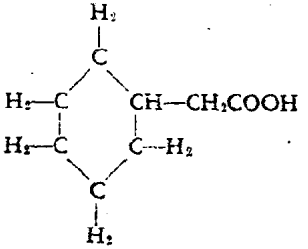


Naphthaleneacetic acid
Active

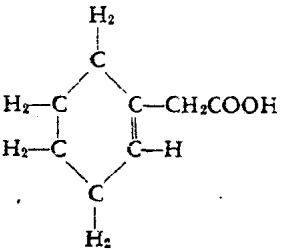


Phenylacetic acid
Active

all cyclic compounds are active, however. Thus, cyclohexaneacetic acid, the structure of which is shown below, is devoid of biological activity. The introduction of one double bond into the ring in the 1,2-position to form $\Delta^{1,2}$-cylohexeneacetic acid, converts the compound to an active one. In general, then, a compound, in order to manifest IAA-like activity, must possess a ring system, and this ring system must contain at least one double bond, this adjacent to the side chain.



Cyclohexaneacetic acid
Inactive



Cyclohexeneacetic acid
Active

The nature of the side chain also exerts an important effect upon biological activity in promoting stem elongation. The side chain must, in the first place, contain a carboxyl group, or a group readily convertible to a carboxyl group. Thus, esters and amides are active in supporting stem elongation, but only in so far as they are converted by the plant into the corresponding free acids. Indolecarboxylic acid, which contains one methylene group less than does IAA, is totally devoid of auxin activity. Indolepropionic acid and indolebutyric acid, on the contrary, are active, although less so than IAA itself. For biological activity of the

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