PHYTOCHEMICAL RESEARCH AND DRUG DEVELOPMENT: RANDOM THOUGHTS

By Alfredo C. Santos, Dr. phil., Academician

A Basic Research and Tie-up with Developmental/Industrial Research

A close tie-up between basic research and developmental research either preceding industrial application, or in close cooperation with industry is necessary for the development of plant/natural products into medicaments. Basic research is carried out mainly in the universities, the main function of which is to advance the frontiers of knowledge [1]. Thus, when a university researcher/professor has elucidated the chemical structure of a natural product, or has determined its biological/pharmacological action and the work culminated in a publication in a journal of recognized/international standing, he is inclined to leave the problem there and move on to another basic problem. But at this stage, the compound is not ready for introduction in therapeutics/general use in medicine. A lot of developmental work is needed, and this is not a problem for the university, but it is rather the function of the research organization of pharmaceutical industries. This kind of research is very expensive, and to be able to maintain it, there is need to grant them exclusive rights in the form of patents.

In the Federal Republic of Germany, the AFG [2], a Federation of National Research Council carries out a considerable amount of pure and applied basic research in selected areas of interest. Their facilities, financial and personal requirements exceed that of the normal scope of the university. As soon as commercial application becomes feasible the projects are turned over to industry. In Australia, the CSIRO (Council of Scientific and Industrial Research Organization) has similar functions.

In this connection and in the inadequacy of such organizations in the Philippines,* the report of Dr. Paul Byerly, Jr. — the writing of which was stimulated by a request from the NSDB to the Director of Mission, FOA, for a research advisor concerning industrial research, stated in part: . . .

"A society's problems are largely capable of solution only by the results of competent research . . . .

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"The Survey Group recommends that in the public service the primary responsibility for basic research and that part of applied research in agriculture (industry) requiring well-trained scientists be placed with the University of the Philippines, and that testing, demonstration, control and regulation, be left to the responsibility of the appropriate bureaus of the Ministry of Agriculture and Ministry of Natural Resources . . . ."

It may be mentioned here, that when Dr. Juan Salcedo, Jr., Academician and National Scientist, was the Chairman of both the NRCP and the NSDB, a delineation was marked, whereby the National Research Council of the Philippines is to take care of basic and fundamental researches and the NSDB of the applied and industrial researches.

Drugs from plants (?)

Improved technology in chemistry and pharmacology during the last few decades permits now a faster and more systematic research on medicinal plants. What before took years of painstaking experimental research work in the laboratory using classical chemical methods to isolate and determine the chemical structure of a natural product, can now be done, using physical tools, in a very much shorter time. In this connection, we would like to recall our own experience in the case of the alkaloids of *Phaeanthus ebracteolatus* (Presl) Merr [3].

In spite of these advances, drug development – although of great importance remains expensive. It is estimated that the chances for a new compound to become a drug are at least 3,000 to 1. A drug company is known to have spent more than $20 million without obtaining a marketable product. Among the criteria to be assessed are: intensity and specificity of action, side effects, acute and chronic toxicity, and disposition within the body. [4].

The need for *continuous research* may be seen further in the case of tetrandrine, the optical antipode of phaeanthine.

Although isolated long ago (in 1928) and its structure subsequently determined, it is only recently that its potentialities are being discovered as: (a) an effective antitubercular agent,[5] active vs. 16 strains of *Myobacterium tuberculosis in vitro*, at 8-33 ug/ml; and as (b) an anti inflammatory agent[6] it is at least as effective as cortisone.

It would be very interesting to test phaeanthrine if it would exhibit biological activities similar to those of tetrandine. In the case of phaeantharine, the findings of Leticia Angeles, are summarized in a paper presented in part in a Poster paper presented at the 6th FDA Science Symposium on Aquaculture

held in New Orleans, La. on February 12 to 14, 1980. Major advantages are:

(1) larvicidal, hence a more discrete and direct method of pest control

(2) less wasteful

(3) will not contribute to environmental pollution

(4) risks to non-target species are minimal

(5) development of resistance is practically nil

(6) will not accumulate in body fat

(7) it is not only non-carcinogenic but even exhibits some anti-tumor activity in experimental animals

(8) the chemical nature of the active principle suggests susceptibility to biodegradation and

(9) negligible cost.

Field trials on the crude preparations are suggested. Significant implications in agriculture (pest control) and medicine (disease vector control) cannot be over emphasized.

Synthetics or Medicinal Plant Preparations (?)
S.E.E.S. (Side effects eliminating substances)

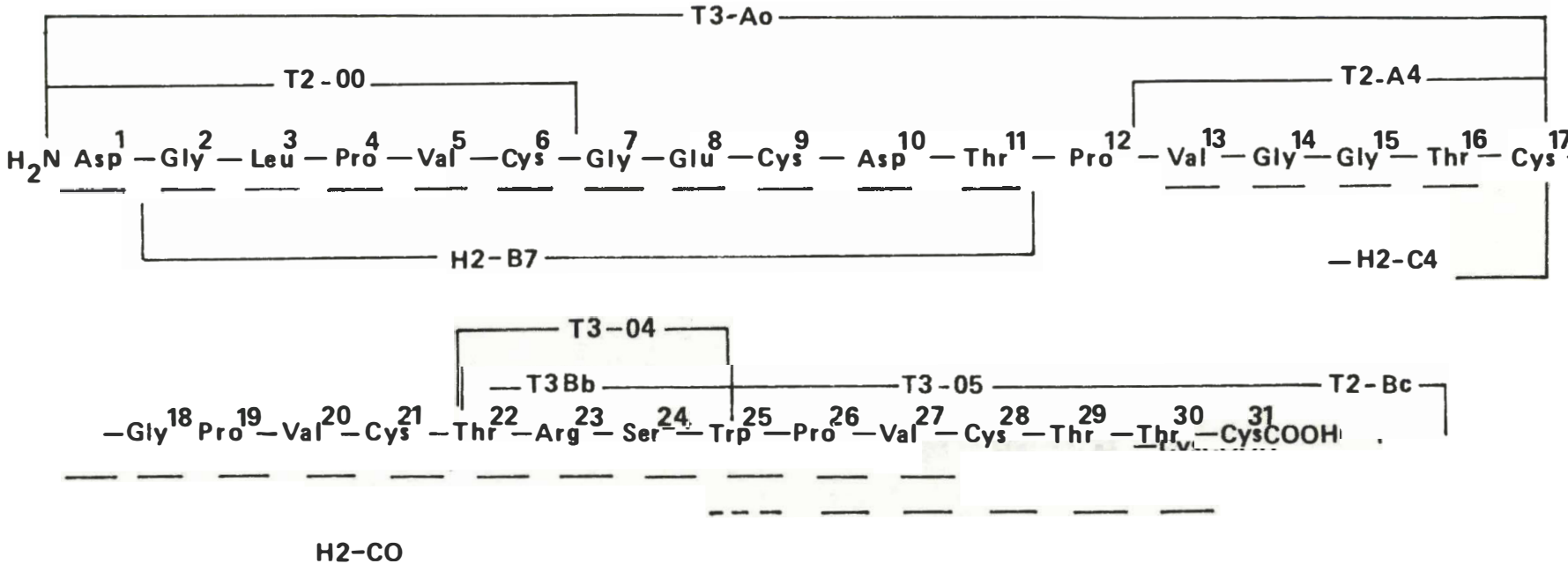
The experience in Zaire. Missionaries have found out that the natives have been using successfully a medicinal plant, which was found to be *Oldenlandia affinis*[7] (Fam. Rubiaceae) — to hasten parturition. Phytochemical investigations in Oslo, Norway, showed that the oxytocic effect is due to a number of polypeptides, among which one (cf. formula) was extremely active.[8] Unfortunately it produced very irregular heart beats, so the tests had to be abandoned. It would be very difficult to find the right/correct combination that would produce the desired effect of hastening parturition, without the side effects. Certainly for the people of Zaire, it would be much easier to use an aqueous extract of the plant.

A System of Phytochemical Research

The international journal "Phytochemistry" classifies research works published in the following areas: Biochemistry, Biosynthesis, Chemotaxonomy and Phytochemistry (proper).

For the utilization in therapeutics of medicinal plants products/preparations-phytochemical and biological, microbiological, pharmacological and clinical are necessary.

A selection at random, and mass biological screening of large number of plants is expensive and not advisable. In this connection, Norman R. Farnsworth,[9] of the University of Illinois, utilizing a computerized natural-product-data-bank was able to select 17 plants from a list of 575 plants suspected to possess sedative activity, with 9 out of the 17 yielding extracts with equal



Formula Kalata-peptide

or greater sedative activity than the selected model of pentobarbital sodium.

Search for New Drugs. A System of Phytochemical Research

In the search for new drugs there is a need for a combined chemical and biological/pharmacological cooperation. One usually begins by making an extract of the plant and subjecting this to a preliminary biological/pharmacological screening. For the purpose, ethanol would be a suitable solvent. A method for the preparation of plant extracts is described in "Phytochemical, Microbiological and Pharmacological Screening of Medicinal Plants.[10] Methanol has been used also, but in this case, the plant extract should be completely deprived of methanol, which itself is poisonous.

A method of Dr. Y. C. Kong, is based on the separation of constituents into non-polar, semi-polar and polar by sequential extraction with hexane or petroleum ether for non-polar constituents, such as oils, terpenes, followed by subsequent extraction with alcohol, and partition between chloroform and water, whereby the semi-polar constituents, like glycosides, go into chloroform, while the polar constituents, like glycosides, go into the aqueous phase. All crude extracts — ethanolic, or hexane, chloroform and aqueous extracts are subjected to biological screening. The individual extracts are subjected to biological-screening. The individual extracts possessing biological activities are then subjected to chromatographic separations, similar fractions, i.e., with the same Rf values are collected together and subjected again to biological testing. In the isolation process, the mother liquors should always be tested for biological activity, for the biologically active constituent may not be the nice crystals, but in the mother liquors. Fractions without biological activity may be discarded.

UNESCO, IFS Sponsored Programs in the Philippines

International agencies/foundations have been helping developing countries in the utilization of medicinal plants.

Unesco sponsored programs in the Philippines:
Phytochemical screening programs

(1) On phytochemical, biological, microbiological and pharmacological screening of Philippine medicinal plants. In cooperation with the UST Graduate School and Research Center, held in March 1978;

(2) On isolation and chemical studies and structure elucidation of natural products. In cooperation with the UP College of Pharmacy and UPLB, held in October 1979.

(3) A sub-regional workshop — a sequel to (1) above, was held recently in April 1980 in the Visayas, at the University of San Agustin, in Iloilo, and like the two above, with participants from Indonesia, Thailand, Hongkong, Singapore and Malaysia.

Problems confronting the utilization of Philippine medicinal plants and their products.

Why are UNESCO, IFS, WHO sponsoring/encouraging research on herbal medicine?

— Could it be because many synthetic drugs are petroleum based?

or — Could it be that rising prices make these drugs inaccessible to many in developing countries who need them, but can ill-afford their high prices?

What is the cause of rising prices?

In this connection, the views of Renato Constantino, Michael L. Tan and the report of the WHO that 50,000 brands of medicine here could be listed under 2,000 generic names only (Times Journal, May 9, 1980) offer interesting food for thought.

Diazepan, B. P., (generic name) costs only ₱0.21/5mg tablet whereas under the brand name Valium its price rises to ₱0.915/4 mg. tablet; Ampicillin B. P., costs only ₱2.331/500mg whereas when sold under the brand names of Pentrexyl, Ambicin, Penbritine — its price rises to almost six times for the same 500 mg tablets.[11]

In a developing country like ours, the main effort of health delivery should be concentrated on prevention rather than cure.

From the foregoing consideration, it would be desirable to consider the possibility of using dosage forms (tinctures, extracts, infusion, decoction) from Philippine medicinal plants for simpler ailment.

On the integration on the use of medicinal plants into the health care system, the opinion of the participants in the seminar held in Tokyo [12] in September 1977, were summarized in the WHO Report as follows:

> "In certain countries, integration of the use of medicinal plants into health care system has been successfully accomplished with both economic and therapeutic advantages.
>
> "In other countries, no such efforts have been made and the importance of choosing suitable approaches in attempting integration was stressed by many participants.
>
> "The participants noted that an alternative approach to an integrated approach, is the use of medicinal plants in

health care complementary to Western medicines. In certain cases due to consumer approval and/or economic necessity, medicinal plants are more acceptable than certain synthetic drugs and therefore a parallel and complementary system would appear to be a possibility that does not present great difficulty in implementation.

"In general, no opposing views on the potential usefulness of potential medicinal plants in health care were expressed. However, medicinal plants in any country's health care system would remain a national policy decision. Furthermore, WHO should stimulate greater awareness and understanding among national authorities, health personnel and people of the potential value of the use of medicinal plants."

In a paper presented by Dr. Quintin Kintanar before the Economic and Social Commission for Asia and the Pacific (ESCAP) Meeting last May 13, 1980 on the development and transfer of technology for the utilization of medicinal and aromatic plants in the Philippines, he enumerated the following requisites:

1) scientific studies to put its use on a rational basis
2) educational and promotion activities to legitimize the proper use of medicinal plants *vis-a-vis* modern drugs
3) public health programs utilizing medicinal plants in primary health care
4) agricultural and industrial production of selected plants at the community and national or regional level to meet the needs of the country for medicinal plants
5) technical assistance and cooperation among developing and developed countries in the further advancement and transfer of technology in this field.

A thorough study on the utilization of medicinal plants will involve a multidisciplinary approach.

1) the plant must be properly identified by a taxonomist, and a herbarium specimen be deposited in the institution. The pharmacognosist can determine the localization of the active constituents in the plant tissues/organs that will serve as a guide to the phytochemist in the selection of the proper plant part to be collected.
2) in the phytochemical studies where knowledge of chemical methods and physical tools is used in the isolation and structure elucidation, a thorough acquaintance in such specialized fields as the alkaloid, steroid, etc. is necessary.

3) on the biological studies, the cooperation with the microbiologist, biochemist, pharmacologist and clinician is indispensable.
4) the cultivation and propagation of medicinal plants will involve the agriculturist.
5) the pharmacist will take care of the preparation of the proper dosage forms.

The need for fundamental research to insure continuing scientific and technological process can not be overemphasised. Let us not utilize the well-trained researchers to do routinary/administrative work least we kill the goose that lays the golden egg.

Realizing the importance of basic research, the RTC-NAST has proposed the creation of the positions of career scientists, Senior and Junior Research Fellows of the Academy, for fulltime researchers.

The NAST-RTC in Chemistry

A Ph.D. program (studies leading to the Ph.D. degree) was presented before the RTC in Mathematics, Physics and Chemistry for endorsement/recommendation by the NAST to the NSDB for funding. In the field of chemistry, the proposed areas for research (thesis/dissertation) are: natural products' chemistry, and analytical chemistry.

One of the pressing need/problem is the lack of qualified thesis advisers who could assign an original problem: for only faculty researchers who are actually engaged in research and have been publishing contributions regularly in the journals of recognized standing (not newsletters, bulletins which are not abstracted in the Chemical Abstracts, Biological Abstracts, etc.) and are thus acquainted with the current literature, are in a position to act as thesis advisers. A tie-up with researchers/professors abroad who have the necessary physical tools may be necessary.

The next and even more important problem is — how to keep the now well-trained professor/researcher:

He should not be promoted to an administrative position, and be a loss to science.

He should not be lured to industry where, although his salary may be multiplied many times — his research contributions will only be available to serve the interests of the company he is working for/employer.

A researcher is usually wedded to his/her work and provided he/she is given a reasonable salary to maintain a decent — not necessarily luxurious living, and given some fringe benefits that would provide education for his children, housing and transportation facilities/allowances, he will stick to his research.

One of the main difficulties encountered in the experimental researches on the chemical and biological studies of Philippine medicinal plants is the difficulty of surveying the literature.

In a conference with the Technology Resource Center Staff, Dr. Paulo Campos, President of the National Academy of Science and Technology (NAST) indicated the need of a Computerized Data Bank to help researcher in the survey of the literature and keep them abreast of the more recent developments. In this connection, we have surveyed the world literature on the chemistry and biological/pharmacological studies of Philippine medicinal plants, up to 1980 under an NRCP Research Project I.D.-22 entitled "Philippine Medicinal Plants and Their Contained Natural Products: (Phase III) Biological and Pharmacological Survey."

We have been repeatedly asked by several researchers as to when will our survey be published. Even the Technology Resource Center (TRC) wanted to get our material to be fed on their computerized bank. Of course the data bank will only give the original title, author and journal reference and one has still to go to the various scattered libraries to read the article. In our survey, the main results are tabulated, and provided the material, usually needed in the abstract of the original article.

Career scientists, Research Professors, Fellows of the Academy:

The NAST, under the sponsorship of its President, Academician, Dr. Paulo C. Campos, has presented a program where selected scientists/researchers would be given a reasonable emolument, to enable them to concentrate mainly in research work. It is said that a university is only as good as its faculty. It is hoped that time will come when scholars from other countries would come to undertake research work in our universities/ institutions.

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Modesto T. Chua, Ph.D., Discussant

In this paper, Dr. Santos touches on many of the issues tied up with phytochemical research and with development of drugs from plants in the Philippine context.

Phytochemical Research in the Philippines Today

There is a lot of interest in natural products research on the part of chemists and pharmacists in the Philippines. This is in keeping with the present world-wide intense research activity on medicinal plants as a source of new drugs to replace or supplement synthetic drugs.

Fundamental research on medicinal plants, as Dr. Santos states, is best done in the universities. There are many examples of university-based productive research groups in many countries: Tchesche in Germany, Bacton in England, Kochethov in Moscow, Woodward in the United States, to name some highly visible ones.

Each of these research groups represents a dynamic scientific hierarchy. In Bonn, Germany, Tschesche is at the apex of his hierarchy. Below him are 3 or 4 assistants, who are themselves senior scientists working toward their professorships. Working with each assistant is a group of postdoctoral, doctoral and magisterial students, each working full-time on related researches. At the bottom of the hierarchy are the undergraduate students, who at some point in their training are asked to work on projects connected to the on-going graduate and postgraduate researches.

The research group "system" in the universities represents a very efficient way to conduct research, as can be gauged from the output in both scientific papers, as well as scientific workers. Research on natural products remains at it has been in the past, an excellent, demanding training ground for chemists, pharmacists and other scientists.

In the research group, scientific attitudes, techniques, feel for molecules, and information gathered over the years are efficiently transmitted. This constitutes the "living tradition" of the group.

If we are to aim for more effective progress in natural products research, where ability to carry out the isolation, testing and structural elucidation of *new* active principles is enhanced, then we need substantially increased investment in the advanced training of chemists and biologists in our universities.

The proposed Ph.D consortium among the University of the Philippines, La Salle University and Ateneo de Manila University is a step in the right direction. Through a pooling of scarce scientific manpower, the three institutions hope to reach a "critical mass", whereby self-sustaining growth may lead eventually to stable research groups in natural products.

Multi-Disciplinary Research on Medicinal Plants

For efficiency, this is the approach to take, a type of task-force method involving the phytochemist, biologist, biochemist, pharmacologist, clinician, the agriculturists.

There are many models for this: the one which springs quickly to mind is the Materia Medica Institute of the Chinese Academy of Sciences, Peking. This Institute has six departments:

Phytochemistry
Pharmacognosy/Botanical
Pharmacology
Synthetic Organic Chemistry
Experimental Plantations

These departments work together on plants of interest. The extensive data covered are fed to computers for easy retrieval.

The establishment of problem-oriented research institutes, such as this, will work only if the necessary highly-trained manpower and support are available.

Support from UNESCO and other International Organizations

UNESCO has supported the establishment of a Southeast Asian Network for Chemistry of Natural Products. This network has a program of activities directed towards the promotion of research in natural products. Aside from the workshops mentioned in the paper, there were two earlier UNESCO-sponsored ones: (1) a training workshop on Isolation and Structure Elucidation of Natural Products — 18 April — 28 May 1977 — at the Ateneo — 20 participants from various institutions. (2) Seminar/Workshop on the Application of Spectroscopic Techniques to Structure Elucidation of Natural Products. (Subregional activity, 5 participants from other Asian countries) 29 May — 9 June 1978, held at the Ateneo.

Vital Role of Access to Scientific Information in Research

This point is clearly made in this paper. Scientific researchers constitute a community, where links among workers in various forms constitute a vital life line. In certain cases, the links may even be formalized into cooperative researches.

The examples given where work done by others provides stimulus and guide for a researcher's own work illustrate this. The examples may be extended. For instance, (+)-tetrandrine (from *Stephania tetrandra*) has been found to have antihypertensive activity. Similarly, work done elsewhere detect broad-spectrum antibacterial activity in 4 compounds isolated from *Andrographis paniculata*. Most active is neoandrographolide.

In his paper, Dr. Santos highlights the many bright and some dark aspects of work on medicinal plants in the Philippines.

Speaking from the vantage point of many years of active research in this field, he points out the scientific as well as the economic benefits accruing from research and development work directed towards producing drugs and drug raw materials from plants. At the same time, he sees some difficulties and problems besetting the research effort. For some problems there are no easy solutions.

In any endeavor, one of the key ingeredients is the availability of human resources to pursue it. As is common with other research areas, research on medicinal plants suffer from too few trained researchers. In addition, these researchers are, as a whole, looking separately into the pharmacological, phytochemical and biological aspects of the plants. Moreover, there is no indication, with the present system, that the desired increase in number of researchers will come about in the foreseeable future. Earlier this morning, Dr. Campos was speaking of the sigmoidal curves of growth, where a low-level activity reaches a dynamic stage where growth suddenly expands and accelerates. The vital ingredient for this expansive growth of research has to be found in the system which motivates and trains new researchers.

Historically, universities have been the focus of research in natural products. Research is an integral and necessary part of univeristy activity, serving both to express and develop the creativity and skill of the teaching faculty as well as to train and educate young researchers. Skills, knowledge and insight are passed on whereby the new researchers become not clones of the teachers, but hopefully will surpass them.

In our universities today, with a few exceptions, the number of faculty members actively doing research has not increased, but has in fact diminished. Various pressures have led to this. Natural products research is demanding. It requires not only certain expertise in order to be productive, but also the ability to grow in skill and a continuing acquaintance with developments in the field.

This is best accomplished under situations where researchers do not work alone, but rather in tandem with others within the same field and also with related disciplines. This ensures that communication and enthusiasm do not diminish. Coordinated research

on the phytochemical, pharmacological and biological aspects of selected plants, for instance, would be most favorable.

If we wanted to modify our research structures in the universities, it would be useful to consider, as models, the set-ups in other countries, such as in Germany, the United States, Japan and England. The common feature in the productive universities in these countries is the way the "research group" is made up. The research group has a pyramidal structure, with a distinguished professor at the top. Working under him and with him are two or three lower level professors, usually also former students of him. Each of these professors has, in turn, a number of postdoctoral and doctoral students under their guidance. At the bottom of the pyramid are the graduate and undergraduate students.

In systems like this, you have the "infrastructure" where attitudes and skills, scientific traditions are efficiently passed down.

A recent move by the UP, Ateneo and De La Salle for a consortium towards a Ph.D. degree in Chemistry may be a start of a promise along this line. The NAST has lent its prestige towards supporting this move. This development may pull together the few professors from these universities towards a group, to do research in selected areas, including the chemistry of natural products.

We hope that this move gains ground as a concrete step promising accelerated research on medicinal plants in the future.

Quintin Kintanar, Ph. D., Discussant

As suggested by the phrase "Random Thoughts" in the title, this paper touches on many issues and subjects, some of which transcend the confines of Phytochemical Research and Drug Development — the main subject of the paper.

For instance, the issue of the role of basic research encompasses all of science and technology. On global scale and on a long time horizon, there is no question that advancement in any field will require basic research. The new knowledge and understanding of nature in the natural sciences and of man and his socio-economic institutions, in the social sciences, are the foundations of technological progress and national development. Any country in this modern age cannot afford to neglect basic research for long without paying the price of being left behind by the more enlightened societies who march with the increasing tempo of scientific and technological development. This is not to say that developmental and applied research is less important, for indeed they are necessary if we are to derive economics and social benefits from the fruits of basic research. Both types of research are necessary and must be supported. This is aptly demonstrated in the field of drug development discussed in this paper.

Some of the plans of NAST for a Ph.D. program in the breeder Sciences of Mathematics, Physics and Chemistry and an endowed career scientist or research positon mentioned by Dr. Santos, are indeed very laudable. This will help insure an adequate supply of highly educated and trained scientists who can devote their full energies and talents to scientific work without having to worry much about where the next meal is coming for him and his family. Most of the time it is the economic factor which induces a scientist to take on an administrative or management position or to go into private industry. Let us hope that these plans will find enough support so that it will not result in a still-birth.

The other aspects of the paper devoted to a discussion of research and development in the field of pharmaceutical and medicinal plants are too brief at times, but covers a lot of grounds.

The full development of a drug from plants as pointed out in the paper, is of course an expensive and time-consuming process which requires the expertise of agriculturists, botanists, pharmacognoscists, phytochemists, pharmacologists, clinicians, engineers, industrialists and managers. If all of these personnel can be put effectively under one roof, or at least under one integrated program, the time requirement per unit of output will of course materially diminish, resulting in greater over-all productivity.

The efforts of NSDB and NRCP in the field of medicinal plants are noteworthy. The NSDB-supported Integrated Medicinal Plants Research and Extension program brings together a multi-disciplinary group of medicinal plants researchers from the College of Pharmacy, College of Medicine and College of Agriculture of the University of the Philippines and from the National Research Council of the Philippines and the National Institute of Science and Technology, who work in cooperation with health planners of the Ministry of Health to promote the scientific application of medicinal plants in health care. The NRCP on the other hand is interested in establishing an Institute of Materia Medica which would serve as a Center under one roof, for the study and development of medicinal products from medicinal plants. Similar Centers exist in the large cities of the Peoples' Republic of China, where medicinal plants are widely used.

Towards the end of his paper, Dr. Santos quotes the statement of a WHO-sponsored seminar regarding the two strategies that can be used in the utilization of medicinal plants namely 1) complete integration into Modern Medicine or 2) mere complementation of modern medicine with medicinal plants for economic reasons or because of end-user's preference. The situation actually varies from one country to the next, calling for different strategies. In some countries there is a long tradition of Oriental herbal medicine which has not been eroded by the onslaught of scientific modern medicine. In these countries there has been a substantial uninterrupted and well-accepted use of medicinal plants, such as China and Sri Lanka.

On the other hand, in other countries like the Philippines, the western scientific influence has largely displaced the traditional modes of treatment at least in the urban areas. In these countries a major effort is needed to legitimize the use of medicinal plants particularly in the eyes of doctors educated in Western-type schools.

As I have pointed out recently, in order to maximize the benefits from medicinal plants in the Philippines, there is a need for:

1. Scientific studies to put its use on a rational basis.
2. Educational and promotional activities to legitimize the proper use of medicinal plants vis-a-vis modern drugs.
3. Public Health Program utilizing medicinal plants in primary health care.
4. Agricultural and industrial production at the community and national level to meet the needs of the country for medicinal plants.
5. Technical assistance and cooperation among developing and developed countries in the further development and transfer of technology in this field.

Magdalena C. Cantoria, Ph.D., Academician, Discussant

In connection with the paper of Dr. Santos, there are three "random" ideas which I would like to discuss very briefly:

1. The magnitude and complexity of the process of bridging the gap between phytochemical discovery and drug development,

2. The trend in recent systematic studies of testing biologically every fraction of the extract of each of the different plant parts before isolation of the constituents, and

3. The value of participation in national, regional, and international gatherings to phytochemical research and drug development.

The discovery and development of new drugs is a team process. It represents the cooperative efforts of biologists, pharmacists, phamacologists, clinicians, toxicologists, engineers, and, of course, businessmen. Pharmaceutical research is difficult, time-consuming, and it has become increasingly expensive. Drug development is very vital to modern life but its details are poorly appreciated by the lay public, including the media people, the politicians, and even by the scientific and academic community.

The research involved in bridging the gap between discovery of new compounds from natural products and delivery of useful therapeutic agents may be even of a greater magnitude than that involved in discovery. Academic laboratories play an important role in fundamental discoveries, while industrial laboratories have the task of taking a discovery in the field of medicine and pharmacy and developing it to the stage of therapeutic utility. Success results in a new product with new therapeutic value and represents commercial profit that will allow the continuation of the discovery and development cycle.

Every drug that is made available is the result of an extensive development program following the initial discovery of a natural product. A few examples drawn from the areas of pharmacognosy and physical pharmacy in which I have some experience will illustrate the extent of such a program.

a. For the production of the ergot alkaloids, the cultivation of fields of rye inoculated with the parasitic fungus is not always acceptable to farmers. A procedure now developed is to grow a selected strain of the fungus in artificial culture. Alkaloids are produced, which, although lacking the desired pharmacologic activity, may be converted by semisynthesis to the medicinally useful ergot alkaloids.

b. A steroid hormone that occurs in minute quantities in very tiny glands in cattle, sheep, and swine is very expensive to isolate from natural sources. The development of a practical method of production utilizing plant constituents as starting material has substantially reduced the cost.

c. A drug that has been shown to possess beneficial therapeutic activity is not practical if it is so irritating that it can not be tolerated by the body. By modifying its chemical structure, or by synthesizing a derivative or a related compound, or by manipulation of the pharmaceutic dosage form, the harmful side effects are eliminated.

d. A drug that is effective for only a few minutes in the body is not of much use. The proper designing of a formulation will extend the duration of the activity and a prolonged-action pharmaceutical results.

e. The evaluation of drugs in all test systems is another vital link in the process of drug development. In this area the progress is reflected in the emergence of such new terms as pharmacokinetics, bioavailability, blood-level curves, biophase, indepth stability, LADME (liberation, absorption, distribution, metabolism, excretion) system, and others. The researchers in this field must have a thorough background in mathematics to develop models for predicting drug systems, in physical chemistry to predict means by which drugs are absorbed, and in biology to be able to design suitable dosage forms which are well-absorbed or whose absorption is controlled in certain ways to produce very specific blood level patterns and which possess the expected efficacy and a predictable half-life.

It has been the conventional phytochemical practice to study those compounds which are most readily separated from a plant extract. These principles are usually those present in large quantities and which crystallize readily, or those which represent the researcher's field of interest, like alkaloids, terpenoids, glycosides, and others. After workshops, seminars, symposia, training courses, and the like. Such gatherings provide forums for stimulating discussions and exchange of ideas and excellent opportunities to interact personally with colleagues in the field, not to mention the mutual encouragement and inspiration derived. One gets a deeper insight into the details of researches going on in other laboratories which are not readily gathered by merely reading the scientific publications emanating from these laboratories. The knowledge thus gained helps in the individual's researches and the contacts made may lead to cooperative research, exchanges of materials, sharing of laboratory facilities, and even life-long friendships.