PHARMACY AND DRUGS IN THE CONQUEST OF DISEASE

INAUGURAL LECTURE 1984

AJIBOLA A. OLANIYI

UNIVERSITY OF IBADAN

PHARMACY AND DRUGS IN THE CONQUEST OF DISEASE

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by

AJIBOLA A. OLANIYI
Professor of Pharmaceutical Chemistry
Faculty of Pharmacy

UNIVERSITY OF IBADAN

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INTRODUCTION

It gives me distinct pleasure and honour to be accorded the opportunity to inaugurate the Chair of Pharmaceutical Chemistry before this distinguished audience. I am aware that this is the first inaugural lecture in Pharmaceutical Chemistry to be given in this pre-eminent Nigerian University and indeed in any university in black Africa. It is particularly gratifying to mention that this lecture is being delivered from the new Faculty of Pharmacy which was accorded professional recognition by the Pharmacists Board of Nigeria about a year ago and will be graduating its first set of students tomorrow. I consider it a privilege to be the first person to give an inaugural lecture emanating from it.

It is my belief that the audience and the public are entitled to demand of whoever is giving the university's first inaugural lecture in pharmaceutical chemistry and indeed in pharmacy an explanation of the relevance of the subject pharmaceutical chemistry and of the pharmacy profession. He should also discuss the discipline's inestimable contributions towards improving the quality of life through better health and conquest of disease, with consequent greater human happiness.

Pharmacy and its Sciences

The system of knowledge that embodies pharmacy does not grow in isolation but in close alliance with developments in other scientific disciplines. Pharmacy has always been closely related to chemistry which, in the beginning was responsible

for the birth of pharmacy as a science. A typical student of pharmacy acquires his knowledge of the physical characteristics of naturally occurring substances of plant or animal origin, their identification, cultivation, preservation, evaluation and isolation from the study of pharmacognosy. He develops his expertise in the development of drugs, their physicochemical properties, quality control and analysis in pharmaceutical chemistry. The technique of formulating, preparing and presenting the developed drug into appropriate dosage forms is gained in pharmaceutics and pharmaceutical technology. Lastly, information on the therapeutic or toxic effects of the drugs on the living system is acquired in the area of pharmacology.

Pharmaceutical chemistry, which deals with the chemistry of substances used in medicine, is an interdisciplinary area requiring a sound knowledge of several contributing sciences. The student of pharmacy is prepared for professional practice by being conducted from basic chemistry over a bridge of medicinal chemistry, pharmaceutical analysis and natural products chemistry, to other pharmaceutical sciences and related disciplines. The chemistry of a drug embraces its development from natural or synthetic source, its structural, physical and chemical properties, its chemical reactivity, stereochemistry, identification, mode of action, qualitative and quantitative analysis, the identification and synthesis of its metabolic products, and the relationship between its molecular structure and biological action. A drug is any substance or mixture of substances that is manufactured, sold, offered for sale, or represented for use in:

(1) the treatment, mitigation, preventation, or diagnosis of disease, an abnormal physical state, or the symptoms thereof in man or animal or

(2) restorating, correcting, or modifying organic functions in man or animal.

The term 'drug product', as will be used in this lecture, refers to a dosage form containing one or more active therapeutic ingredients, added along with other substances during the manufacturing process.

Pharmacy has been described as a gateway profession. The dynamic development of new curative agents against diseases and ills of mankind and animals has made the profession one of the most rapidly growing fields of our time. A vital need exists for research to discover remedies for diseases against which no adequate drug is known, for the preparation and efficient distribution of drugs in ever increasing amounts and for wider dissemination of health services. The needs will remain boundless so long as human beings are susceptible to disease. It is important that the pharmacist who holds a key position in the area of drug production, control and distribution, should be recognized as a key person in the provision of health services to the Nigerian people. He is both a scientist and a practitioner, for he must provide quality drug products and all necessary information about them to his clients and patients and to his colleagues in the health care area.

The primary function of the pharmacist is to prepare, select and distribute medicines, to serve as an information source to members of the medical and other health professions and advise patients in the proper use of prescribed or self-selected drugs. His professional activities and opportunities are without limits because the study of the agents used in the treatment or prevention of disease in man or other animals is a continuing process. The expert knowledge and the effective products provided by modern pharmacy have contributed in a large measure to the prolongation of man's life expectancy. The services rendered by the pharmacist in various areas (community, public health, hospital, wholesale distribution, manufacturing, quality control, academics, government position and pharmaceutical journalism) are so important and some of the substances he compounds are so

dangerous that his activities must always be governed by accuracy, honesty, cleanliness and professional skill.

In pharmaceutical chemistry, teaching and research encompass medicinal chemistry, which may be synthetic, theoretical or analytical; physical chemistry; pharmaceutical analysis, and natural products chemistry. Medicinal chemistry has been aptly defined as a field which applies the principle of chemistry and biology to the creation of knowledge, leading to the introduction of new therapeutic agents. Synthetic medicinal chemistry has as its goal the preparation of more effective and less toxic compounds to be used for the cure or treatment of disease. The development of new drugs via synthesis and structural modifications has made noteworthy contributions to medicine and to society as will be illustrated later. Theoretical medicinal chemistry is a relatively new interdisciplinary field combining chemistry, mathematics and applications of the computer to determine the solutions to various biological and medicinal problems.

It is noteworthy that a great scientist like Paul Ehrlich, who at the beginning of the century foresaw with such insight some future trends in the development of the synthesis of drugs and their correlation with living systems, was unable to arrive at a successful preparation of salvarsan for the fight against syphilis until his 602nd experiment. Today, however, the picture is different, as a result of our knowledge of processes, the laws of structure and the relevance of structure in living systems, and by means of mathematical models and modern methods of physics, chemistry and biology. Drugs can be designed and tailored to have specific properties because of established theories on the relationships between structure, function and therapeutic effects. The interplay of biological activity and chemical structure is a highly intriguing problem to all those who are involved in the study of bioactive compounds.

Research activities in the area of drug design and the applications of Quantitative Structure Activity Relationship (QSAR) models to the skeleton of biologically interesting molecules have grown exponentially in recent years.[1] QSAR studies help to accelerate the development of drugs by reducing variables and also help to reduce the work and overall research expense. In our research efforts, we have been able to establish a quantitative relationship between the antisickling activity and the physico-chemical properties of substituted benzoic acids, using the Hansch approach with a view to determining the optimum structural modifications for antisickling activity.[2]

In analytical medicinal chemistry, attention is focused on problems dealing with detection of trace impurities and decomposition products of medicinal agents in pharmaceutical preparations and with *in-vivo* and *in-vitro* study of absorption, distribution, metabolism and excretion of drugs. The recognition of the limited duration of therapeutic activity of drugs, largely because they are deactivated by metabolism, and of the importance of drug metabolism and disposition as a major factor influencing the pharmacological and toxicological effects of a drug, has contributed to the rapid development of research interest in the field of drug metabolism. The results of biotransformation research have been profitably used for the development of new drugs through formation of active metabolites from inactive preliminary ones (prodrugs). The results have also provided useful information, such as the complex influence of food intake on metabolism and bioavailability of drugs; the influence of age, disease and genetic differences, and the influence of drugs and environmental chemicals on drug metabolism in man.

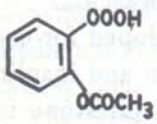
Contributions of Medicinal Chemistry to Medicine

By the isolation or synthesis of therapeutic agents, medicinal chemists have made possible some of the noblest achieve-

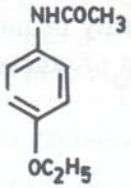
ments of human history. The medicinal chemist, employing the art of synthesis, has been responsible for the vast majority of drugs used in modern medical practice. In the last thirty years, untold suffering and deaths have been alleviated or prevented through the use of these drugs.

A variety of criteria could be used as measures of contributions of medicinal chemistry to medicine. These include estimates of lives saved; reduction in man-days of disability; changed incidence of disease; incidence of uses of specific drugs; monetary values of drugs used; changes in medical practices; or prolonging the span of life. One cannot but pay tribute to hundreds of scientists working in diverse laboratories who have now synthetically produced insulin, some antibiotics, cortisone and other newer drugs for the successful fight against such diseases as tuberculosis, diabetes, heart disease, mental disease, and even cancer.

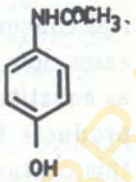
It was relatively easier and cheaper to discover new medicines in the first three decades of this century:[3] for example, the synthesis of acetylsalicylic acid (aspirin) (**1**), the most widely used, most easily obtained and least expensive analgesic; phenacetin (**2**) and paracetamol (**3**) as antipyretic analgesic; the sympathomimetic amines like adrenaline (**4**), amphetamine (**5**), ephedrine (**6**), and the acridine dyes as surface antibacterial agents whose further development led to the antimalarials such as mepacrine (**7**).



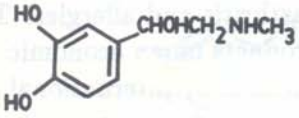
1 Acetylsalicylic acid (aspirin)



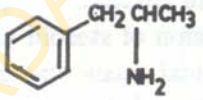
2 Phenacetin



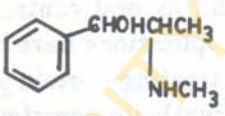
3 Paracetamol



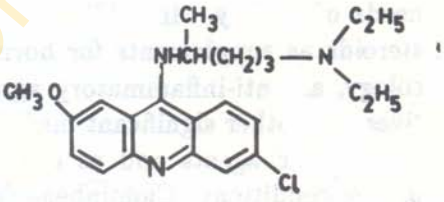
4 Adrenaline



5 Amphetamine



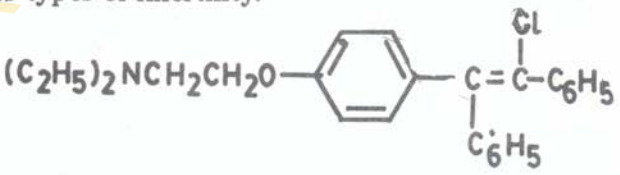
6 Ephedrine



7 Mepacrine

Major contributions to nutritional requirements have been made by rather quickly elucidating the structures and developing feasible methods of synthesis of the vitamins. In some societies, where overnutrition or overeating has created medical concern with obesity or incidence of cardiovascular diseases, low calorie food products have been developed for use as substitute meals. The development of insulin and insulin products for use in diabetes remains a major milestone in this century.

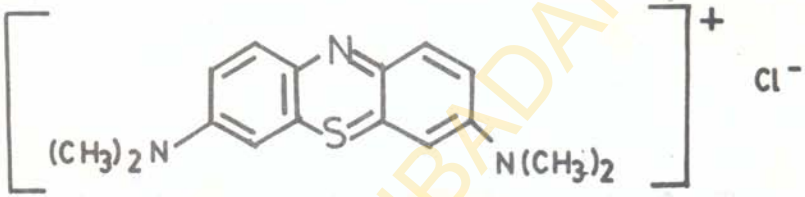
In the hormone field, the outstanding medical contributions from medicinal chemistry have been related to adrenocorticosteroids and their derivatives and cogeners which have provided the basis for the treatment of steroid hormone deficiencies and have also led to major contributions of products for the treatment of rheumatoid arthritis and allergies. The provision of steroid antifertility products on an economically practical basis was an accomplishment of international research and development efforts. The oestrogen-progestagen oral contraceptive agents introduced in 1957 appear to be a development in which medicinal chemistry has to date made its greatest favourable impact on some of the social needs of society. In addition to the major application of steroids as supplements for hormone deficiencies in gynaecology, as anti-inflammatory agents and as oral contraceptives, two other significant medicinal applications have been as anabolic agents and as drugs for treating certain neoplastic conditions. Clomiphene (8), a synthetic non-steroid, anti-oestrogen, induces ovulation and facilitates conception in some types of infertility.



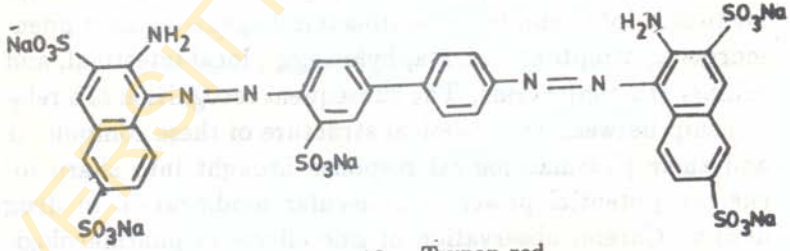
8 Clomiphene

Second to cardiovascular disease, cancer is the greatest killer in most of the developed countries. In few disease fields have as many human and financial resources been applied to research as in efforts to discover chemicals useful in the treatment of cancer. In proportion to the effort expended, medicinal chemistry has made only a modest contribution to cancer chemotherapy.

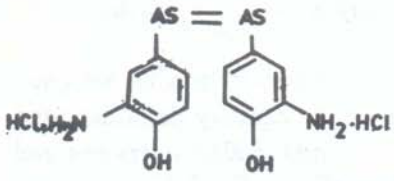
The fatherhood of modern chemotherapy can be assigned to Paul Ehrlich who at the turn of the century demonstrated activity of methylene blue (**9**) against malaria; trypan red (**10**) as a trypanosomicide; and synthesized and demonstrated the utility of asphenamine (**11**) and neoarsphenamine (**12**) for syphilis.[4]



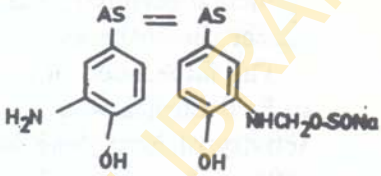
9 Methylene blue



10 Trypan red



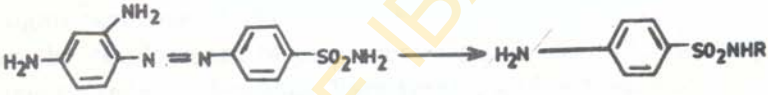
11 **Asphenamine**



12 **Neoarsphenamine**

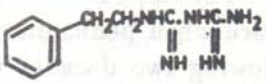
The fuse to an explosive growth period for chemotherapy was lit by the work of Mietzsch, Klarer and Domagk in 1932, who demonstrated the *in-vivo* anti-streptococcal activity of prontosil (**13**). One of the most fascinating and informative chapters in medicinal chemistry, highlighting the roles of skilful planning and serendipity in drug research is the development of sulphonamides as antibacterial agents against pneumococcal, streptococcal, staphylococcal, local intestinal, and urinary tract infections. The subsequent recognition of a relationship between the chemical structure of these compounds and their pharmacological response brought into sharp focus the potential power of molecular modification in drug design. Careful observation of side effects in pharmacological and clinical studies on the early sulphonamides revealed new and unanticipated activities; the successful exploitation of these 'leads' opened up such new areas in therapy as oral

antidiabetics, for example, chlorpropamide (**14**) phenformin (**15**); carbonic anhydrase inhibitors as diuretics, for example, acetazolamide (**16**), hydrochlorothiazide (**17**); antithyroid agents, for example, methyl thiouracil (**18**); and antigout and antileprotic diaryl sulphones. It also emphasized the importance of side-effects of drugs as a source of new 'leads' in drug design.

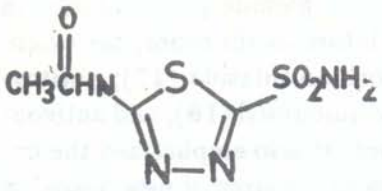


13 Prontosil

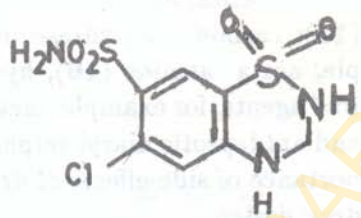
14 Chlorpropamide



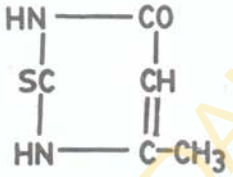
15 Phenformin



16 Acetazolamide

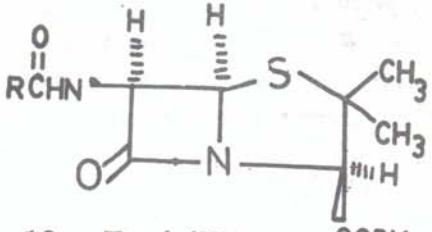


17 Hydrochlorothiazide



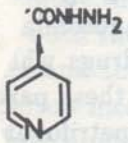
18 Methyl thiouracil

The sulphonamides were barely launched into medical practice when penicillin appeared on the scene (1945). The following two decades witnessed the discovery, determination of chemical structures and evaluation of a host of new antibiotics. The penicillins (19) after more than forty years of use, remain drug of first choice for most Gram positive bacilli infections.

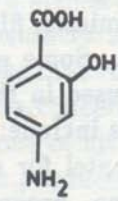


19 Penicillin

Studies on these penicillins and other antibiotics have indicated their growth promoting property, hence they are being used as food additives which have made a significant contribution to the economics of meat production. Tuberculosis, a serious disease in many countries, has virtually been eliminated with isoniazid (**20**) and p-aminosalicylic acid (**21**), together with streptomycin. Dramatic reduction in death rates in influenza and pneumonia has been made possible by a novel type of anti-infective agent, amantadine (**22**).



20 Isoniazid



21 p-Aminosalicylic acid

22 Amantadine

Significant contributions to medicine have also been made in the development of pain relieving and anti-inflammatory agents; sedative-hypnotic barbiturates and anti-convulsants, which have made nearly normal the lives of a significant number of individuals. However, their propensities for abuse are well recognized and legally restricted. The tragedy associated with the use of the otherwise safe but teratogenic sedative, thalidomide, has served to alert us against hidden perils that may have been undetected or undetectable by the current procedures for evaluation of new drugs prior to their extensive use in man.

Psychotherapeutic drugs, "remedies for the soul", such as meprobamate, chlorpromazine, reserpine, chlordiazepoxide, diazepam, etc. — have gained a leading place among modern medicaments. Antispasmodics and antihistaminics have been useful in reducing distress from motion sickness and nausea associated with pregnancy. Notable contributions can also

be mentioned in the development of other medicinal agents, namely: the cardiotonics like digitalis and quinidine; the hypotensives like guanethidine and methyldopa; anticoagulants such as dicoumarol and phenindione; bronchodilators like aminophylline; dermatologicals such as antihistamines and corticosteroids; and neuromuscular blockers like tubocurarine and decamethonium.

Tropical parasitic infections remain major public health problems in many developing countries. Progress has been made in the development of better drugs for the control of six major tropical diseases peculiar to the developing countries — malaria, schistosomiasis, filariasis, trypanosomiasis, leishmaniasis, and leprosy. Some examples of drugs which have been developed and used in the control of these parasitic or protozoal infections include: niridazole, metrifonate, oxamniquine and praziquantel for schistosomiasis; quinine, chloroquine, pyrimethamine, proguanil, trimethoprim and mefloquine for malaria; pentamidine and stilbamidine for trypanosomiasis and leishmaniasis; diethylcarbamazine for filariasis; diloxanide and paramomycin for leprosy; and piperazine, tetramisole and mebendazole for intestinal helminths. Existing drugs are being re-examined and the search for new and improved drugs for the control of parasitic and infectious diseases is being intensified.

Although major contributions have been made here, the problem is still of concern. We should not complacently accept the past accomplishments in the chemotherapy of these parasitic and protozoal diseases as having provided permanent solutions to medical problems.

Drug Product Quality

The profession of pharmacy is a very old one, having common roots with medicine and dating from ca 1500 B.C. In fact, the separation of pharmaceutical from the medical profession did not begin to occur until the late middle ages at which time

responsibilities crystallized into accepted practice for each profession. Pharmacy evolved toward the responsibility for medication, and medicine evolved toward the responsibility for diagnosis and treatment. Although this generalization is perhaps oversimplified, it serves to place in perspective the concern of everyone involved in health care, as regards drug product quality and selection. More efforts are being devoted to this concern today in the light of the technological advances that have made possible high quality products and therapy.

Since the pharmacist's primary role is to serve as a source of both therapeutic substances and information about their use and actions, it follows that the pharmacist should be the person most immediately concerned with the quality of the drug product. Indeed, one of his major responsibilities is to ensure that the drug he produces, compounds, dispenses or sells is of a suitably high quality and effectiveness by assessing the product on the basis of its quality characteristics.

Quality control in relation to drugs has been defined as, "all measures designed to ensure the output of uniform batches of drugs that conform to established specifications of identity, strength, purity and other characteristics." The concept of drug quality has evolved in the course of time. From simple checks of the final product it has expanded into complex quality assurance systems which permeate the whole manufacturing process. Much progress has been achieved in the development of new and more specific physicochemical, biological and biopharmaceutical methods for evaluation of drugs and pharmaceuticals, detection of 'drug-delivery' systems and prediction of storage time. The quality control of drugs in international commerce has been a pre-occupation of the WHO, which has recommended that member states apply "good practices in the manufacture and quality control of drugs" and participate in the Certification Schemes on the quality of pharmaceutical products moving in international

commerce.

In Nigeria, the agencies charged with the regulation and supervision of the quality of drug products and the enforcement of drugs legislation are the Food and Drugs Administration (FDA), created in 1974 by the Food and Drugs Act,[5] and the Directorate of Pharmaceutical Services in the Federal Ministry of Health. It is a matter for regret that we do not yet feel the impact of the FDA and the Directorate in ensuring the quality and safety of drugs in the Nigerian market, and in setting up the necessary machinery for effective quality assessment and registration of drugs before they go into circulation.

For a drug product to be effective, it must not only be pharmaceutically suitable; it must also release its active ingredient in such a way as to make it available to the body for transport to the site of therapeutic need. This is the concept of bioavailability. The realization of bioavailability problems, arising from differences in the formulation and in methods of manufacture of a product containing the same drug, particularly those drugs which have low therapeutic indices, highly potent therapeutic value, or unfavourable physical properties, has led to the inclusion of bioavailability as an essential aspect of quality control of drugs in the current British Pharmacopoeia and the United States Pharmacopoeia (1980). As a consequence of these developments, we are making efforts to establish bioavailability regulations aimed at ensuring that the generics and brands of any drug being marketed in the country are bioequivalent.

The importance of a rational approach to drug therapy and the various problems in the developing countries, such as dumping; inadequate control of money spent on drugs; insufficient government supervision of the importation and distribution of drugs; and the lack of investment in the development of new and effective drugs for tropical diseases, prompted the WHO to set up an expert committee in 1977

to draw up a model list of essential drugs which would provide adequate primary health care in the Third World countries.

The criteria used for the selection of essential drugs include: the most favourable relationship between benefit and risk; long experience with the drug; the possibility of local production from simple materials; stability in a tropical climate, and low price.[6] An essential drugs list, which is recommended to the developing countries as a guideline, is expected to make a significant contribution to a rational, effective and economic medical care and drug therapy in developing countries.[7]

It is necessary to develop quality control and analysis courses at undergraduate level of pharmacy degree programmes so that young pharmacy graduates, by their training, will be reasonably equipped to work in quality control laboratories as drug analysts. In view of this, our Department of Pharmaceutical Chemistry is focusing its attention on the teaching of drug quality control and pharmaceutical analysis courses at undergraduate level and hopes to introduce in the very near future postgraduate courses aimed at specialization on analytical and quality control methods. This, I believe, is one of the surest ways of producing the requisite manpower for drug quality control departments in the pharmaceutical industry, private and government establishments. The constraints of trained pharmaceutical manpower for the inspectorate and analytical arms of the profession would have been overcome, thus leading to more effective functioning of our drug regulatory bodies.

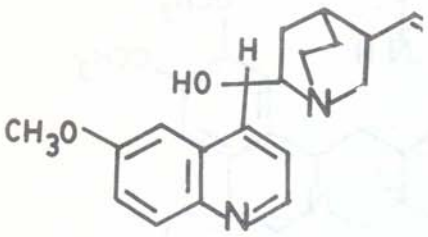
Natural Products Chemistry

The study of natural products of established or of potentially therapeutic value has always been of great interest, not only because of the medicinal applications of their active principles, but equally because they offer an intellectual exercise in understanding nature's process and purpose. It is

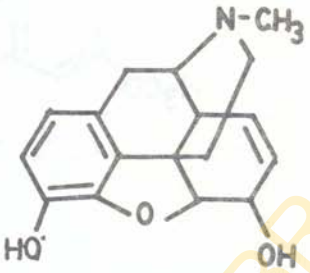
ne of man's oldest and most cherished dreams to be able to comprehend nature, to imitate and perhaps to improve on it. What is the nature of the organic compounds one finds in the higher and lower forms of plant and animal life? Why are they there and how did they get there and for what purpose? These are questions to which answers can best be provided by natural products chemists.

Records abound of the preparation in the most ancient civilizations of medicines from herbs and plant extracts obtained from the bush. Thus, the Chinese drug Ma Huang has been in use in the orient for centuries. In the biblical days, the prophet Isaiah prescribed a hot poultice of figs to heal King Hezekiah's boil (2 Kings 20:7). Today, we find such practices widespread in various parts of the world, Nigeria being an intimate example. Over the last four decades, scientific research into the constituents of natural products, which include plants, animal organs and microbes, have yielded noteworthy results which have saved the lives of millions of people. Thus, the plant kingdom has long served as a prolific source of useful drugs. Classic examples such as quinine (**23**) from Cinchona bark; morphine (**24**) from *Papaver somniferum* (opium); cocaine (**25**) from *Erythroxylum coca*; reserpine (**26**) from *Rauwolfia serpentina* or *R. vomitoria*; emetine (**27**) from *Cephaelis ipecacuanha*; vinblastine (**28**) and vincristine (**29**) from *Catharanthus roseus* (Vinca roseus); and digitalis (**30**) from *Digitalis purpurea*, to mention a few, serve to remind us of the debt that medicine owes to plant-derived compounds.[8] Each of these drugs has an interesting history of discovery and development, culminating in their use in medical practice.

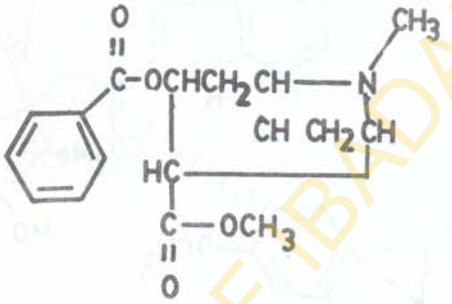
Drug development encompasses those activities that are involved from the point of selection of the drug as a possible candidate for evaluation in man or other treatment target species, to the release of the product for commercialization.



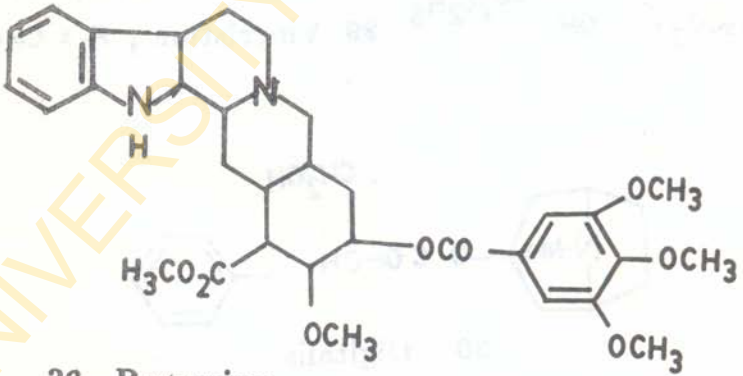
23 Quinine



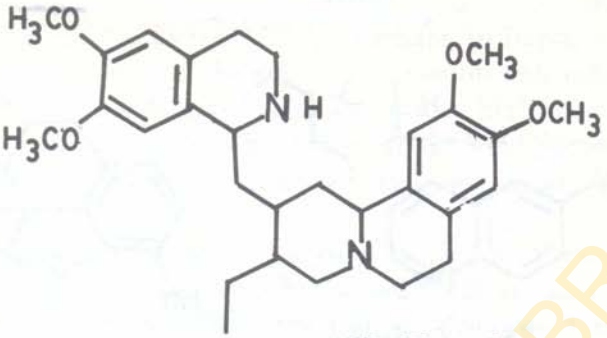
24 Morphine



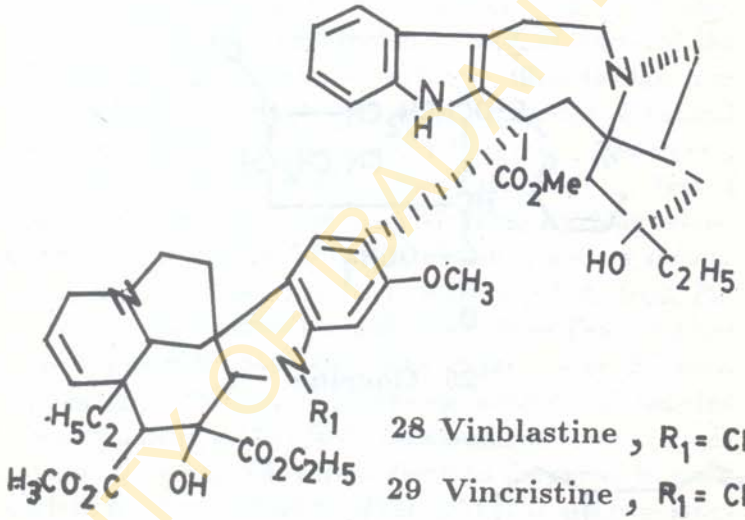
25 Cocaine



26 Reserpine

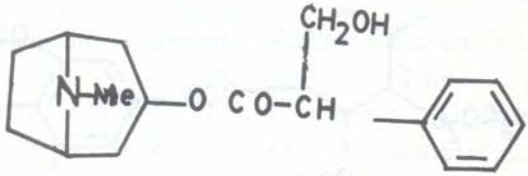


27 Emetine



28 Vinblastine , $R_1 = CH_3$

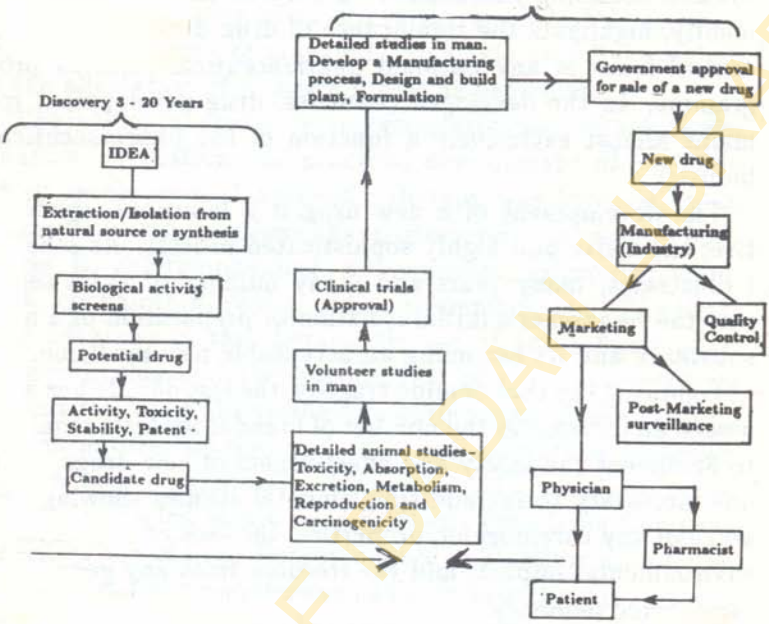
29 Vincristine , $R_1 = CHO$



30 Digitalis

SCHEME]

Safety, Efficacy and Manufacturing 5 - 8 Years



The stipulated objectives of drug development can only be attained by a pharmaceutically industrialized nation or by a country that has a defined focus and has evolved a policy towards attaining pharmaceutical industrialization. This, evidently, highlights the significance of drug development as a central focus in any national pharmaceutical research programme. In the developed countries, drug development remains almost exclusively a function of the pharmaceutical industry.

The development of a new drug is a laborious, speculative, expensive and highly sophisticated process. As scheme I illustrates, many years and many millions of naira separate the researcher's initial isolation or preparation of a new substance and its becoming an acceptable new medicine.

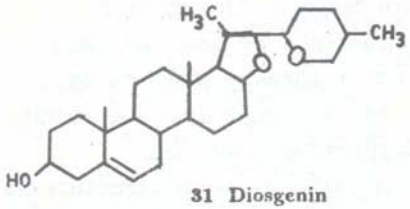
Following the thalidomide tragedy, the last decade has witnessed an increase in the number of mandatory tests required to document the safety and effectiveness of new drugs. It is now necessary to include supplemental studies showing absence of any carcinogenic properties, the lack of any adverse environmental impact, and the freedom from any genetic or teratogenic tendency.

In the development of drugs from natural sources, synthetic modifications of naturally derived molecules and the synthesis of similar compounds, using the natural product molecule as template, have resulted in the formation of some new and effective drugs.

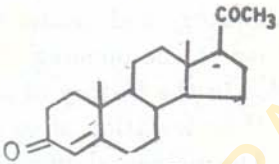
I would like to highlight briefly some of the achievements recorded in the development of drugs from natural sources, and more importantly, on their therapeutic successes, particularly when one recognizes that the isolation and structural elucidation of new compounds from plant materials or animal organs is still just a prologue but the drama only unfolds when these 'children of nature' are taken by man and are returned to participate in the dynamics of life in other systems. The domain of natural substances that has brought the great-

est therapeutic success of the last forty years is, no doubt, that of antibiotics. Fifty-five years ago, a green mould fortuitously landed on a culture plate in Alexander Fleming's laboratory and produced a substance we now call penicillin. It led to the opening of an era in therapy which is unparalleled in the history of mankind. No single drug has resulted in the alleviation of so much illness as penicillin.

The incidental discovery, successful isolation, structure elucidation, evaluation and practical development of penicillin which revolutionized antibiotic therapy was followed by an extensive search for others like streptomycin, bacitracin, polymyxin B, chloramphenicol, tetracyclines, neomycin, ampicillin, cephalothin, cephaloridine rifampicin, etc. The practical advances in the therapeutic use of anti-inflammatory glucocorticoids and the introduction of oral contraceptives rest entirely upon the systematic purification of steroids from various natural sources and their use as starting materials for new organic synthesis. Diosgenin (**31**), which occurs in Dioscorea species, is now used by Boots Pure Drug Company for extraction of pure diosgenin, used as starting material for the synthesis of progesterone (**32**). In recent years, interest has become focused on the steroid sapogenins as cortisone precursors, and also as precursors of sex hormones and on the triterpenoid sapogenins for their desoxycortisone-like and anti-inflammatory effects, exemplified by glycyrrhetic acid (*Glycyrrhiza glabra*). It is significant to note that about 77 percent of the world's supply of streoids is now derived from plant sources. Although much of the research into the development of new oral contraceptives has centred on synthetic modifications of existing steroids, the potential value of plants as sources of new antifertility agents has been recognized.

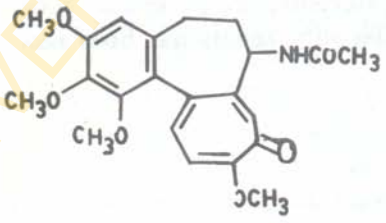


31 Diosgenin

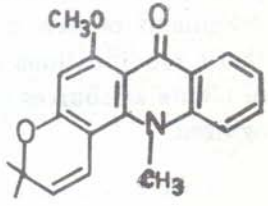


32 Progesterone

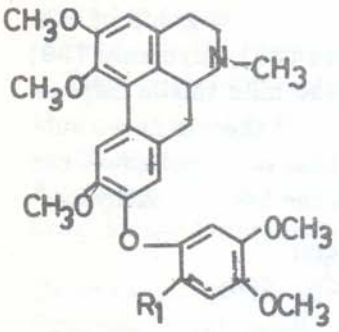
The isolation and identification of active alkaloids (vinblastine and vincristine) in *Cantharanthus roseus* G. Don (Rose Periwinkle) afford an example of the application of modern analytical chemistry to the problem of separation and complete identification of very complex compounds. The clinical application of these two natural products (for treating childhood leukemia as well as certain neoplasms) has been an undoubted stimulus to the natural product research geared towards anticancer activity. Cancer research has led to a re-assessment of many primitive plant cures and a massive search for other natural products that may, perhaps, one day provide effective drugs for this disease. A few structures are selected here to illustrate the diversity of these natural anticancer agents: colchicine (**33**) from *Colchicum automnale*, traditionally used against gout; acromycine (**34**) from various Acromychia species; thalisidine (**35**) from *Thalictrum dosycarpum*, allamandin (**36**) a constituent of an Apocynaceae plant, podophyllotoxin (**37**), lignan from Podophyllum.



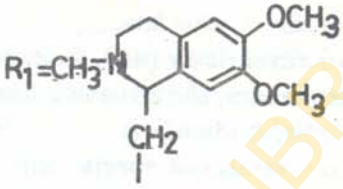
33 Colchicine

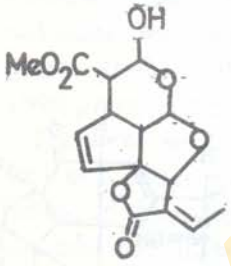


34 Acromycine

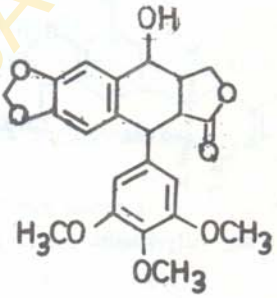


35 Thalisidine



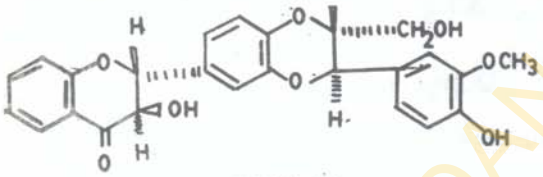


36 Allàmandín

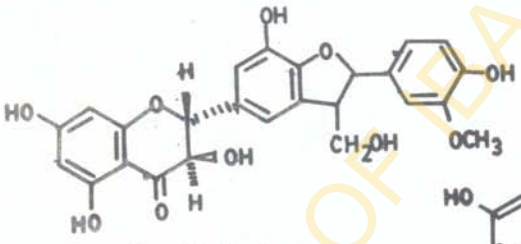


37 Podophyllotoxin

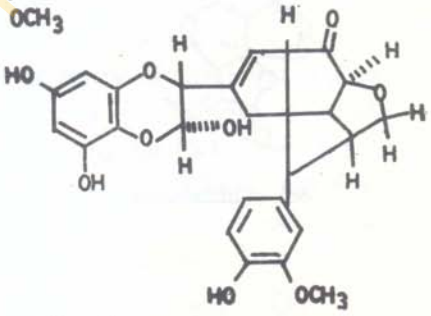
Until recently, it has been accepted almost as a dogma that there was no satisfactory drug treatment for liver diseases. The only drugs used at all were corticosteroids or immunosuppressive agents, sometimes in very high doses. Now, however, as a result of the discovery of a new group of substances — the flavolignans — silybin (**38**), silydianin (**39**) and silychristin (**40**), isolated from the milk thistle ***Silybum metrianum***, the situation has altered and there is now a substantial body of evidence indicating that the flavolignans can exert an almost specific influence on the liver parenchyma.[9]



38 Silybin



39 Silydianin



Recent evidence indicates that orally effective hypoglycaemic and hypotensive agents can be obtained from plant sources while antiviral inhibitory effects have been observed in diverse taxa of the plant kingdom.

The absence of suitable sweeteners as alternatives to cyclamates and saccharin (reported as potential carcinogens) has led to a renewed interest in sweeteners from natural sources.

The structures of naturally occurring compounds possessing a sweet taste range from simple sugars to complex, intensely sweet proteins, like monellin from 'serendipity' berries (*Dioscoreophyllum comminsii*). Some of the natural sweeteners are already being exploited for industrial production, for example, Thaumatin from *Thaumatococcus daniellii*.

Plant-derived chemicals serve many important uses other than as drugs, for example, as sources of such economic materials as industrial oils, gums, suspending agents, colorants, flavouring agents, binders, lubricants and disintegrants in drug dosage formulations.

Orientation to Drug Development from Natural Sources in Nigeria

The untapped vast flora of this country is recognized and the conscious efforts that are being made by pharmaceutical scientists, chemists and related scientists to exploit the constituents from plants growing in Nigeria, which have been proved traditionally to be of medicinal value, have started to yield promising results.[10]

I believe we in Nigeria have the technical know-how to find new drugs which are useful in therapy. In view of the extent of the expense required for drug innovation, one may ask whether, in a developing country such as ours, we need to go through such developmental stages, especially when our traditional medicines would cost much less in purification, standardization and testing processes. Therefore, in view of the complexity, sophistication and expensive nature of pharmaceutical research and drug development, and in full recognition of the considerable potential of drugs from our natural environment, we need to evolve a definite policy towards developing new drugs from our medicinal plants through modern scientific methods, as modern drug research and development are a long-term investment. We need to advance in our task to ensure that we as a nation cease to

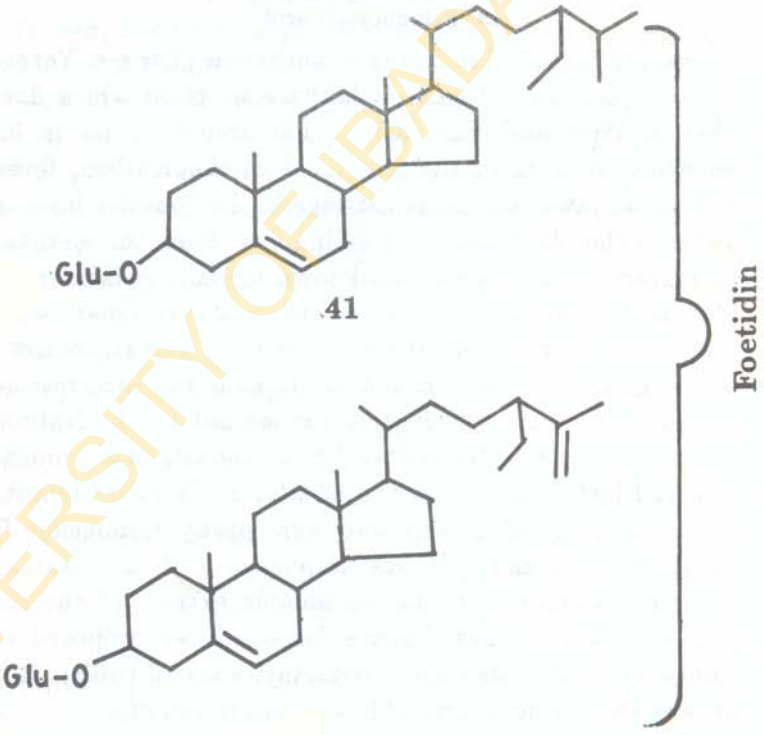
be short-term pragmatists accustomed to dealing with the future only when it becomes the present.

While one would admit that traditional medicine has its assets and limitations, it is very essential that thorough and adequate scientific studies should be made in order to promote and mobilize medicinal plant applications to the benefit of mankind. We need to look into the entire area of traditional medicine and identify the areas which are useful, compatible with modern living and consistent with scientific ways of thinking. In view of the limited number of research capabilities and the ever diminishing financial resources, the challenge can be taken up by carrying out medicinal plant research on a broader and systematic interdisciplinary basis, with comparable scientifically recognized screening methods, better co-ordination and a greater use of modern documentary means. At a time when many Nigerians are crying out for a massive research into and exploitation of medicinal plants growing in Nigeria, the successes of the past should provide the necessary stimulus and encouragement for further work. In the words of Carl P. Swanson, "The details of nature are revealed to him who has eyes to perceive, the patience to observe and the ability to analyze."

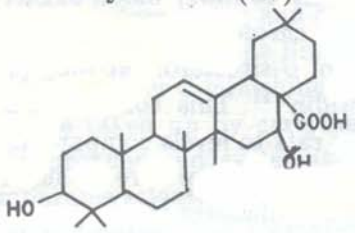
My main research interest, as has now become apparent, is natural products chemistry into which I was initiated by Professor F. El-Said of blessed memory and Dr (now Professor) A. Sofowora of the University of Ife. Our objective was to provide chemical explanation for the claims and potential therapeutic effects of plant drugs, especially when it is recognized that local uses of herbs have in the past provided 'leads' for new drugs and will perhaps continue to do so in the future. As pharmaceutical chemists our approach was to isolate, elucidate the chemical structure of the biologically active principles and to further synthesize or modify the chemical structure in order to obtain more favourable therapeutic agents which could be taken by man to return to participate

in the dynamics of life in other systems. From investigations which spanned over a fifteen-year period noteworthy chemical and biological information has been obtained which, in many of the medicinal plants studied, provide justification for their traditional uses. These will be illustrated by a few examples.

Momordica foetida, family Cucurbitaceae (*Ejinrin*, Yoruba; *Idumuye*, Ibo) used locally to lower blood sugar, was found to contain a crystalline chromatographically homogeneous product of equal parts of β-sitosterolglucoside (**41** and **42**), which we named 'foetidin'.[11] This compound lowered the blood glucose of fasting rats to levels comparable with those produced by insulin, and could therefore be supplemental to insulin in the treatment of diabetes.[12]

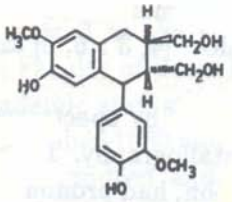


Albizzia adianthifolia (*Ayunre*, Yòruba; *Abu*, Ibo), family Mimosaceae, is widely distributed in tropical Africa and there are many claims of its traditional use in medicine. The demonstration by us of the antibacterial properties of the saponin constituent of the root and bark of the plant clearly supports its use in traditional medicine as in the treatment of scabies and other skin conditions.[13] The genin was found to contain echinocystic acid (**43**).

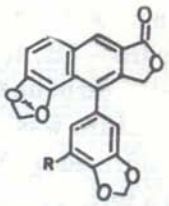


43 Echinocystic acid

Justicia flava, Vahl., family Acanthaceae (*Orosun*, Yoruba; *Damisa* (Quarra), Hausa), a herbaceous plant which flourishes in West and East Africa, has abundant use in folk remedies, such as in the treatment of rheumatism, fevers, diarrhoea, yaws, and as an astringent. The powder from the leaves of the plant is used in killing fish. From the methanolic extract of the leaves, two known lignans, isolariciresinol (**44**) and helioxanthin (**45a**) as well as a new lignan, which we named justicinol (**45b**) were isolated.[14] The structures of these lignans were established by classical and spectroscopic methods. Biological evaluation carried out by the National Cancer Institute in Bethesda, U.S.A., showed that helioxanthin and justicinol were active *in-vitro* in the P-388 lymphocytic leukemia cell culture and were partly responsible for the antitumour and cytotoxic activity of *J. flava* extracts.[15] Chemical studies[16] on the methanolic extract of the root yielded two other new lignans for which we proposed the names orosunol (**46a**) and 8-demethylorosunol (**46b**). Both lignans showed no appreciable anticancer activity.

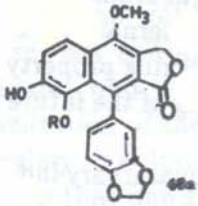


44 Isolariciresinol



45a Helioxanthin, R = H

45b Justicinol , R = OH



46a Oxosunol, R = CH_3

46b 5-Demethyloxosunol , R = H

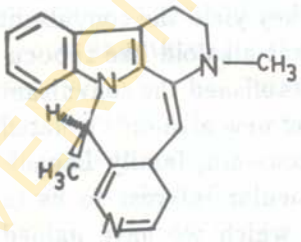
Indeed, the plant kingdom continues to be a prospective and fruitful hunting ground for new tumour inhibitors. Although many of the compounds found to be active may never be used as drugs and hence will not be of direct value to clinical practice, it is difficult to speculate on their overall value. In some instances their toxicity precludes their use, but by studying the way in which they act against experimental cancers it is possible to learn something about the mechanisms involved in cancer formation.

Strychnos is a genus which is widely distributed in the tropical areas. Members of this genus are used as arrow poisons in Africa and South America. They yield the convulsant poison, strychnine and muscle relaxant alkaloid like tubocurarine. In our studies we have now established the convulsant or muscle-relaxant activities of several new alkaloids isolated from the stem bark of *Strychnos decussata*, family Loganiaceae, (Poison arrow).[17–21] Of particular interest to us in these studies are the two alkaloids which we have named 'Decussine' (**47**) and 'Malindine' (**48**) respectively. 'Decussine', according to the IUPAC nomenclature, would give the

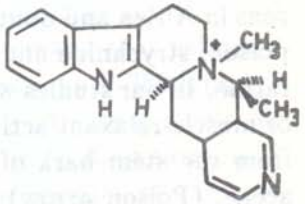
following numbering and generic name: 17, 13 – Dimethyl – 5, 6 – dihydro – 7H, 13H – pyrido – [4, 3 : 6, 5] azepino – [1, 2, 3 – m –] β-carboline.

This structure was determined [19] by spectroscopic methods and confirmed by X-ray crystallography. The compound, which has a tertiary amino function, had pronounced muscle-relaxant effect, both *in-vitro* and *in-vivo* on mice, thus possessing a strong action on neuromuscular junction similar to that of tubocurarine, a quaternary ammonium salt. Its significant neuromuscular blocking property offers a ray of hope for its possible use as a drug of the future as a neuromuscular blocker.[22]

'Malindine', the major quaternary indole alkaloid of a novel structure, obtained from the water soluble fraction of the stem bark of *S. decussata*, showed muscle-relaxant effect when injected intraperitoneally in mice and also produced a 50 percent reduction in amplitude of the concentrations of a diaphragm-muscle preparation at a dose of 0.5mg/ml. It was shown to be mainly responsible for the muscle-relaxant effect of the aqueous extract of the stem bark of *S. decussata*. Its structure was determined by a combination of spectral methods (UV, IR, ^{1}H NMR, ^{13}C NMR, M.S.) and its stereochemistry established by circular dichroism (CD) and Nuclear Overhauser Effect (NOE) experiments.[13]



47 **Decussine**



48 **Malindine**

Pharmacy Education at the University of Ibadan

Pharmacy started at the University of Ibadan as a department in the Faculty of Basic Medical Sciences and Pharmacy with an academic staff strength of eight and twenty-six students in September 1980 and has grown to nineteen academic staff and one hundred and twenty-eight students by 1984, with four academic departments. It attained a faculty status on 1st August, 1983. The teaching objective of the faculty is to produce pharmacists who will have a sound fundamental knowledge of their subject and also be capable, competent and confident graduates who will fit into varied situations and have a clear realization of their responsibilities to their profession and to society in a developing country as Nigeria. It is gratifying to note that our Faculty of Pharmacy is already making some progress toward changing the emphasis of pharmaceutical education through its clinical pharmacy programme which prepares a patient-oriented individual, with a good basic knowledge of drugs, who can work in close association with physicians and others in the health-care team as a resource person for drug information. The goal of our clinical pharmacy programme, which is our focus at Ibadan, is to advance the practice of pharmacy by enabling our products to provide services which promote safe, effective and economic use of drugs as an essential component of patient care. Our other thrust lies in the area of pilot drug manufacture with its attendant complementary units such as drug research and analysis of raw materials and manufactured drugs.

There is a lot still to be done to build an enviable Faculty of Pharmacy at Ibadan, especially in the area of research and postgraduate training. At this stage, it might be said in the words of Sir Wiston Churchill, that "this is not the end nor even the beginning of the end, we have yet to reach the end of the beginning." I believe that I can speak on behalf of my colleagues that we are determined and indeed confident in our collective ability to continue to meet the challenges

of the nation by contributing to the continuing development and stability of pharmacy profession in Nigeria.

The Challenge Ahead

The rapid events of the past few years have given us much for reflection in the future of pharmaceutical research and development. The best hope in the costly battle against disease lies in the continued discovery and development of new medicines. The search for and development of new and better drugs and improved formulations of existing ones for the control of tropical parasitic and infectious diseases are being intensified. I believe that the best contribution we pharmaceutical scientists in this country can make to therapeutic innovation would be to study the basic biological and biochemical factors responsible for these tropical diseases and focus our attention on developing and providing effective drug therapy in the control of malaria, sickle-cell anaemia; schistosomiasis, trypanosomiasis, filariasis, leishmaniasis and leprosy. Major gains can be made in these areas if we reorder our priorities.

I would like to emphasize some aspects of this lecture which, I believe, require urgent attention. First, I wish to repeat the call, which had been made a number of times, for the establishment of a National Drug Research Centre which will be responsible for co-ordinating, monitoring and compiling information on the preparation, administration and uses of medicinal plants in order to keep the traditional healers, doctors and pharmacists up-to-date with developments in medicinal plant research. Research programmes in medicinal plants should aim at identifying, purifying and evaluating the bio-active principles. The goals of such work are: the identification of new drugs to combat diseases, particularly those that have defied modern medical science and the identification of new sources of existing drugs and the discovery of new materials which could be used as precursors or templates in drug synthesis. Such discoveries would have a

definite commercial value and could form the basis of Natural Drug Industries in Nigeria.

Second, in order to meet the challenge of better safety of medicines and drug products, we need to develop and maintain effective drug quality assessment system which should form an integral part of a national drug control system, designed to prevent the production, export, import and distribution of ineffective, expired, harmful or poor quality drugs. Such a system must be based on appropriate legislation and be supervised by a suitably qualified and properly empowered authority supported by adequate inspection and analytical laboratory services. It is recognized that drugs, despite their seemingly magical contributions to human health and comfort, have always been a mixed blessing. They have a capacity for great harm as well as great benefit. They must therefore be formulated, manufactured, presented and used carefully and knowledgeably so that they will work at the optimal speed at the proper site in the body without harming the patient in any way. These are the factors that make quality relevant and indeed extremely important. We must begin to make full use of the WHO Basic Test Programme which is not intended to replace the requirements of pharmacopoeial monographs, but to confirm the identity of drug products by simple, rapid, readily applicable and practicable methods, especially, in our environment where fully equipped and functional laboratories are not available. Such tests will ascertain the absence of gross degradation or contamination.

Third, we are cognizant of the need for, and must bring into function, the establishment of a National Drug Policy Committee in Nigeria to formulate and prosecute a strategy which will provide all essential drugs at reasonable cost to society, to focus plans towards our attainment of national self-reliance through the use of appropriate technologies of production and rational utilization of local resources and to investigate the overall position of drug manufacture, procure-

ment, supply and use in the country.

The Pharmaceutical Society of Nigeria, conscious of the need for Nigeria to attain economic independence in the production of her pharmaceuticals and medicines through utilization of our raw materials, feels that most manufactured products now imported into the country should be manufactured locally. One of the major constraints against successful implementation of such a policy is lack of raw materials. It is my belief that the role of petrochemical industry in pharmaceutical manufacturing touches the very heart of the matters that relate to pharmaceutical industrialization and the very foundation of all industries that make use of chemicals. There is no way Nigeria can become pharmaceutically industrialized without embarking fully on primary industrial manufacture of drugs through the conversion of simple chemicals derived mostly from a petrochemical industry into complex molecules with desirable biological activity.

It is disheartening to note that the phase III of the petrochemical project (an aromatic based complex) which products will find use in the pharmaceutical industries, is not planned to take off till about the end of this century. In view of the utmost importance of the petrochemical industry, in our bid to industrialize pharmaceutically and save the nation the foreign exchange expended on importation of raw materials and drugs, the Government would need to re-appraise the phasing of the petrochemical project and ensure that the aromatic based complex falls within the phase II if it cannot be accommodated in phase I. The Government will also need to encourage the setting up of chemical industries to complement the petrochemical industry, particularly to meet the demand of the pharmaceutical manufacturing industry and the need for organic chemicals for teaching and research in our educational and research institutions.

Lastly, in order to become pharmaceutically industrialized, we in Nigeria must be able to develop new drugs or modify ex-

isting ones for better therapeutic efficacy, especially against tropical diseases which are prevalent in our environment. To achieve this goal, industrial firms must be interested in such programmes and be willing to support and participate in them As expressed by Schaumann[23], a strong domestic, research intensive pharmaceutical industry is an important national asset to any country for three obvious reasons.

1. It is a vital part of a country's health care system and helps to determine the quality of life of her people.

2. It is significant source of tax revenue and also of foreign exchange earnings.

3. It contributes to a productive research climate in pharmacy, chemistry, biochemistry and biology and can thus help to determine a country's technological future.

The pharmaceutical industries must be committed to, and must invest in drug research and development within the country. They must also provide facilities that will allow academic departments and research units to conduct research into the frontier areas of pharmaceutical sciences. A new interface relationship between the pharmaceutical industry, government and academic pharmaceutical research institutions must develop.

Conclusion

I presume I have shared with you my reminiscences in the field of pharmaceutical chemistry in this rather wide-ranging survey. I have tried to demonstrate its relevance to pharmacy and establish a relationship between pharmacy and drugs, and the importance of pharmacy in the improvement and sustenance of the quality of life through provision of novel and quality drugs.

Indeed, we are living in an exciting scientific era which is moving so rapidly that it is difficult to discern today's

discoveries or the shape of things to come. But despite the haze, we can be certain that just as the unlocking of the atom has had profound technical and sociological consequences, so too will the impact of drugs on health and quality of life be tremendous as we unravel the frontiers of pharmaceutical sciences, push closer to the secrets of life and find how to use this knowledge in pharmaceutical research. But we have to realise that the benefits of scientific discovery and innovation are not automatic. They will be beneficial so long as we are mindful of our responsibilities to the society. Medicine is for the people the world over since disease and problems of health are global and unite mankind in common purpose. In this we share a special heritage of the ages which calls for the noblest efforts of all of us, to treat the sick and the infirm irrespective of boundaries and ideological differences. This thought was immortalized by Louis Pasteur at the occasion of a tribute to him on his 70th birthday and is as applicable today as it was then. "Science and peace will triumph over ignorance and war. Nations will unite not to destroy but to build and the future will belong to those who have done the most for suffering humanity."

May I close with the words of Lar Lanne, which better than any other express my feelings, "That these endeavours may happily tend to the advantage of the society, the health of the sick and the advancement of pharmaceutical sciences, is my earnest wish."

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