WHAT HAS THE CHEMIST GOT TO DO WITH HEALTHCARE DELIVERY?

BY

HERBERT A. B. COKER

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WHAT HAS THE CHEMIST GOT TO DO WITH HEALTHCARE DELIVERY?

An Inaugural Lecture Delivered at University of Lagos Main Auditorium on Wednesday, June 22, 2005.

by

PROFESSOR HERBERT A. B. COKER
B.Sc. (ABU), Ph.D. (Strathclyde)

Professor of Pharmacy and Pharmaceutical Chemistry
Faculty of Pharmacy
University of Lagos

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1. INTRODUCTION

Mr. Vice Chancellor sir, It is indeed my pleasure to let this august gathering know how pleased I am for the opportunity afforded me by the University of Lagos in rendering this assignment.

Firstly, let me congratulate you Mr. Vice Chancellor and the Principal Officers of this great University for the tremendous strides made to date and for keeping the ideals and dreams of the University of Lagos aloft, inspite of the hard times we all have to contend with.

The Lord is your strength, please keep the flag flying. May I also note with some nostalgia and admiration the motherliness, sisterliness, simplicity and the administrative candour of our unassuming and wonderful Registrar, Mrs. Olumide. The likes of her lieutenants, Mrs. Abegunde, Mr. Adeeyo, Mrs. Ajose-Adeogun, Mr. Kalu (and recently retired Mr. Momodu) are not easy to come by.

May the good Lord continue to provide you all the **strength** and **succour** with which to shoulder the massive administrative machinery of this great University.

I give many thanks to God Almighty for His inestimable love, guidance and protection throughout life and for making it possible to be employed in a gratifying vocation. I am a happy and successful teacher, and also a productive research scientist, or so I think.

My **vocation** has provided me with the veritable means of touching many lives, the fundamental essence of my creation and existence.

Mr. Vice Chancellor sir, part of my happiness derives from the concurrent news of the tremendous feats and achievements attained by products of this great institution in the overseas countries and at home, Nigeria. These products of the Faculty of Pharmacy, University of Lagos are now chieftains of many Pharmaceutical establishments and industries in Nigeria and in the overseas countries.

I consider myself a successful teacher having learned how our **graduates** make use of undergraduate lecture notes and knowledge gannered from this University as templates for assailing professional exams and postgraduate programmes in countries such as Great Britain, the USA and Canada. In other words sir, this "academic culture of ours" attests to the fact that the Faculty of Pharmacy of the University of Lagos in its own unique way has been imparting standard academic and professional knowledge to our younger colleagues for the past 20 years.

Mr. Vice Chancellor sir, this may very well explain why one of our postgraduate (M.Sc.) students in Pharmaceutical Chemistry, Mrs. Ijeoma Florence Uchegbu, departed Nigeria for the University of London many years ago. She completed her Ph. D. programme under Professor Sandy Florence and got a job as a Lecturer at the University of Strathclyde, Glasgow. About 5 years ago she became the first African female to become a Professor of Pharmacogenomics and Drug Delivery within the British academic Establishment, at a tender age.

It is my pleasure to acknowledge (as far as my own investigation shows) that of the many hundreds of our products working abroad and at home, no one has ever been implicated in any one dismeanour or the other.

In other words, Mr Vice Chancellor, at the Faculty of Pharmacy, University of Lagos, we impart knowledge as well as inculcate in our students **Education** (i.e. the development of the mind and character), and the elements of **professionalism**.

We sincerely thank the good Lord for all the opportunities and privileges lacing our trajectory to this point in time.

My Inaugural reminds me of the saying of the English poet, Thomas Gray, who in the mid 19th century wrote: "for writing maketh a man".

The Honourable V.C. sir, Principal Officers and distinguished guests, I have put pen to paper in the bid to convince the entire house that at the end of this mandatory exercise H. A. B. Coker deserves to be acquitted and discharged, and duly certified to proceed to his *Exaugural*.

There is the English adage which posits that "Health is Wealth".

It is quite doubtful if all Nigerians appreciate this dictum. The average Nigerian believes that money alone maketh a man. He subjects himself to so much stress in the bid to generate money, and often at the expense of his health. It just could be easily argued that the average Nigerian needs money to secure good health and food.

There is no doubting the fact that good health is *sine qua non* to human vitality and productivity, and associated national economic development. These factors in themselves invariably govern the well-being and vibrancy of a country.

The overall health status of a nation and the quality of life of its citizenry are highly dependent on the quality of the healthcare apparatus and services and the efficiency of the delivery system. The quality of health enjoyed by the citizen can be an extant index of the level and adequacy of the healthcare delivery, education, economic empowerment and to some extent political stability in a nation.

Nigeria is a massive country with a population of about 120 million people. More than 60% of Nigerians live in poverty and poor health conditions. In my 54 years of existence I am not aware that Nigeria has suffered any visible natural disasters – akin to volcanic eruptions, landslides, hurricanes or the Tsunamis.

With careful planning and good national policies on health, it is the belief of **health experts** that health for all Nigerians is an achievable venture, inspite of Nigeria's and Nigerian peculiarities.

Given the ongoing restructuring and repositioning of health programmes in the country, I am full of admiration for the Honourable Minister of Health, Professor Eyitayo Lambo, for the tremendous progress he and his able lieutenants have impacted on the health sector. By the year 2004 alone, the National Health Policy which was last visited in 1988, had been revised in line with current health needs. The ministry has lent its weight in favour of the ongoing Health Reforms which commenced in 2004. The Professor's deft managerial skills in getting all stakeholders on board of the various immunization programmes as conducted by the NPI is commendable.

His innate penchant towards eradicating Nigeria and some neighbouring countries of the Polio virus and

poliomyelitis is quite commendable. The Chief Executive and National Coordinator of the National Programme on Immunization [NPI], Deaconess (Dr) Dere Awosika, whose unflinching love for the Nigerian child doggedness and highly disciplined mien and efficiency have continued to provide the fulcrum for galvanizing all the successes achieved this day on the immunization of Nigerian children and Nigerians in general. Her yeoman efforts deserve a place in the historical annals of this great country.

The ministry's endeavours at containing the HIV/AIDS spread in Nigeria, through the point man at NACA, Professor Babatunde Osotimein have yielded worthy dividends.

The supposedly problematic National Health Insurance Scheme (NHIS) has finally taken off.

Mention must be made of the tremendous successes recorded by NAFDAC, championed by Dr (Mrs) Dora Akunyili, its chieftain.

Cognizance is taken of the tremendous strides made so far on the Roll Back Malaria Initiative and activities. The Director of Public Health, Dr (Mrs) Edugie Abebe and the Coordinator of the RBM initiative, Dr (Mrs) O.T. Sofola deserve our adroit support and encouragement.

We salute these **fine mortals** for their foresight and courage.

Healthcare delivery is a complex phenomenon embracing practical concepts and professional inputs which, ultimately impact on the well-being of the nation and the health status of the nation's citizens.

Pharmaceutical Care, Clinical Pharmacy, Public Health Pharmacy, Biopharmacy, Pharmaceutical Technology, Pharmacognosy and **Complementary traditional medicine, Pharmaceutical** and **Medicinal Chemistry, Pharmaceutical analysis, Pharmaceutical Microbiology, Clinical Pharmacology** and **Biochemical Pharmacology, Pharmacotherapeutics, Pharmacogenomics, Health Management Systems** and **Administration** as disciplines in their own right are very essential components of any efficient and successful healthcare delivery system of a nation. They form the pivotal fulcrum on which any successful National Drug Policy must hinge on.

Enshrined in Public Health Pharmacy is the advocacy on prevention as a better option to curative measures. Public health pharmacy and preventive medicine emphasize the avoidance of illness. These are not only predicated on preventive measures, the concept also covers early diagnosis of ailments and treatment of sick persons thereby circumventing degeneration to advanced disease state. The concept also aims at inhibiting the spread of communicable diseases within and outside the community.[1]

Public Health Pharmacy posits the following:

- Every citizen of Nigeria is **entitled** to good health.
- Our leaders must realize that many illnesses suffered by Nigerians are mostly as a result of poverty and adverse environmental conditions.
- Health is domestically intertwined with good home upbringing where emphasis is on healthy behavioural habits and life styles.
- Education and enlightenment promote good and healthy living standards.

- Provision of needed medical facilities, and the associated enabling environment are the responsibility of the state.
- Government must ensure poverty alleviation, vitality, productivity and economic development.

Illness is an abhorred calamity. Poor health is not only detrimental to the well-being of a person, it invariably leads to death if not attended to properly. It carries with it psychological and emotional factors as well as a national burden in terms of declining productivity and economic loss.

2. PHARMACEUTICAL CARE AND PHARMACOTHERAPEUTICS

Illness is invariably the product of a disease condition. Diseases affecting man can be categorized basically into communicable diseases and non-communicable diseases. [1]

Communicable diseases include:

❒ **Infections of the Gastrointestinal tract, comprising**

- **Bacterial infections** such as

a. enteric fevers (e.g. i. Typhoid fever; ii. diarrhoea resulting from *Eschericia coli* — of different forms — enteropathogenic, enterotoxigenic, verocytotoxin-producing, and diffusely adherent *E. coli*, iii. Campylobacter).
b. Bacillary dysenteries (Shigellosis).
c. Cholera — Vibrio cholerae.
d. Bacterial food poisoning — as a result of infections by *Salmonella spp*, enterotoxin-producing Staphylococci, *Clostridium perfrigens*, Vibrio para-haemolyticus.

- **Protozoal Infections** such as Amoebiasis, Trichomoniasis, Gardiasis, Toxoplasmosis, Cryptosporidiosis, Malaria, Balantidiasis

- **Helminthic Infections**
  Nematode (Roundworm) Infections, **Cestode** (Tapeworm) Infections, **Trematode** (Fluke) Infections.

❒ **Human Contact Mediated Infections include**:

a. **Viral Infections** such as Chicken pox (varicella-zoster virus), Viral haemorrhagic fevers (Lassa fever virus, Marburg virus, Ebola virus). Acquired immune deficiency syndrome (Human immunodeficiency viruses)*

Certain sexually transmitted infections — Chlamydia *trachomatis*, serotypes; Soft chancre (*Haemophilus ducrei*); Granuloma inguinale (*Calymmatobacterium granulomatis*); Gonorrhoea (*Neisseria gonorrhoeae*); Sexually transmitted syphilis (*Treponema pallidum*); Yaws (*Treponema pertenue*); Pinta (*Treponema carateum*); Endemic syphilis (*Treponema pallidum*); Trachoma (*Chlamydia trachomatis*, serotypes A-C); Inclusion conjunctivitis (*Chalmydia trachomatis*, serotypes D-K); Leprosy (*Mycobacterium leprae*).

b. **Fungal Infections:** Superficial fungal infections (*Epidermophyton spp., Trichophyton spp., Microsporon spp., Mallassezia furfur*), Candidiasis (*Candida albicans*).

c. **Arthropod Infections:** Scabies (*Sarcoptes scabei*).

Non-Communicable Diseases

These include diseases and organic ailments associated with

- **Cardiovascular disorders** - such as hypertension, Ischaemic heart disease, congestive heart failure, cardiac arrhythmias, thrombosis hyperlipidaemia.
- **Gastrointestinal disorders** - such as peptic ulcer diseases, inflammatory bowel disease, constipation and diarrhoea.
- **Respiratory disorders** - such as asthma, drug-induced lung disease, chronic obstructive airways disease.
- **Hepatic disorders** - such as drug-induced on the liver, liver necrosis of diverse types.
- **Renal disorders** - such as acute renal failure, chronic renal failure.
- **Neurological** and **psychological disorders** - such as Insomnia and anxiety, affective disorders, schizophrenia, epilepsy, Alzheimers disease, Parkinson's disease, and Pain.
- **Endocrine disorders** - such as diabetes mellitus, thyroid and parathyroid disorders.
- **Obstetric and Gynaecological disorders** - such as menstrual cycle disorders, menopause and hormone replacement therapy.
- **Urological disorders** - such as prostrate problems.
- **Haematopoietic disorders** - such as anaemia, drug-induced blood disorders.
- **Rheumatic disorders** - such as rheumatoid arthritis and osteoarthritis.
- **Ophthalmological disorders** - such as glaucoma.
- **Malignant disorders** – such as cancers, leukaemia, Lymphomas, solid tumors.
- **Occupational** health hazards, nutritional disorders, genetic and in-born metabolic disorders.

- Other causes of illness include the **strains** and **stresses** of daily living in metropolitan city like Lagos; **traumatic injuries** due to auto accidents.

Mr Vice Chancellor sir, the aforementioned are amongst the sources of illnesses that can afflict mankind.

But then Mr V.C. I share wholeheartedly in the sentiments that **enlightenment, personal care** and **healthy life styles** may help in circumventing many of these afflictions.

A sick person is a patient needing help and healthcare.

Pharmaceutical Care is that branch of pharmacy practice and pharmaceutical sciences which places great importance on the **patient** as the primary beneficiary of healthcare. The Clinical Pharmacist brings to bear on the patient the totality of his professional skills, knowledge, attitude, concerns, commitment, moral and ethical responsibilities in the provision of the appropriate and efficacious medicinal therapy and care in **any given disease condition**.

Pharmacotherapeutics is that aspect of pharmaceutical care where appropriate medication, therapeutic drug monitoring, adjustable and responsive pharmacokinetics and pharmacodynamics combinedly ensure satisfactory **treatment** outcome.

The ultimate goal of **Pharmacotherapy** is geared towards achieving definite therapeutic outcomes ensuring the **patient's restoration** to **good health, better quality** of **life, vitality** and **continued contribution to the country's progress and development**.

The **Pharmacist** is an inalienable member of the healthcare delivery team whose primary function is skewed in favour of the patient first, and every other attendant circumstance. He ensures that the patient receives efficacious and safe medicines, and also supports measures aimed at affordability. He is involved in productive health planning, meaningful and effective health management systems and productive governmental health policies.

Medicines, the finished form of drug dosage preparations, are pharmacotherapeutic agents that have been subjected to controlled clinical trials during drug development and are registered by NAFDAC for use in Nigeria. Pharmacotherapy ensures that efficacious medication is predicated on well-defined clinical end points, such as fever clearance and pain abatement. Surrogate markers such as reduction in blood pressure or blood cholesterol which can be correlated with patients' response or clinical outcome can also serve as end points.[2]

Pharmacotherapy recognizes factors that may influence patients response to medicines which include the patients age, physiological status of elimination organs, kidney and the liver; drug-drug and drug-food interactions, genetic factors that may affect therapy outcome and a variety of idiosyncratic factors militating against optimum benefits from therapy. This underscores the importance of therapeutic drug monitoring (TDM) in patients, and drug pharmacokinetic and pharmacotherapeutic profiles in order to preempt and avert hazardous drug toxicities.

Adverse events may be minor and reversible, or major and irreversible. For healthcare providers, caution and vigilance are of the essence during patient medication.

3. PHARMACEUTICAL RESEARCH AND DRUG DEVELOPMENT

Medicines are medically recommended remedies intended for ameliorating disease conditions, and restoring good health and vitality to man. However drugs or pharmacologically active substances have to be developed into suitable forms for human use.

The final (or finished) product reaching the clinics and certified suitable and safe for medication purposes is usually the end-product of the combined efforts of numerous research scientists and professionals in the **research** and **development** (R & D) of new medicines.

The team of expert researchers, ideally, may consist of the following:

- the pharmaceutical and medicinal chemist
- the pharmacognosist, the botanist and biologist
- the tissue pharmacologist
- the experimental and human physiologist
- the clinical pharmacologist and toxicologist
- the pharmaceutical microbiologist
- the pharmaceutical technologist or drug formulation expert
- the clinical pharmacist, biopharmaceuticist and pharmacokineticist
- the pharmaceutical physician and drug clinical trials expert
- drug registration and regulatory agencies e.g. NAFDAC.

Medicinal Chemistry is a science with strong antecedents in Chemistry and the Biological Sciences. It is traditionally a branch of organic chemistry (and some inorganic chemistry). Medicinal chemistry has presently assumed

enormous level of complexity. It employs some of the most advanced and sophisticated technological instrumentation such as the Ultraviolet/Visible (UV/Vis) spectroscopy, Infrared (IR) spectroscopy, Nuclear Magnetic Resonance spectroscopy (NMR), Mass Spectroscopy (MS), High Performance Liquid Chromatography (HPLC), Gas Chromatography (GC) and hyphenated systems such as GC-MS and HPLC-MS, including powerful molecular graphics with 'drug-design' software systems and the use of robotic system.[3]

Drugs must act on living tissues to produce pharmacologic and therapeutic effect. Cognizance must also be taken of the very complex chemical nature of living matter and receptor conformation. Drug action can only be explained in terms of the chemical and physico-chemical attributes and reactions of the drug with the chemical constituents of living tissue.

The medicinal chemist must have a profound knowledge in pharmacology, toxicology, biochemistry, biopharmaceutics to be able to adequately rationalize the chemical and physico-chemical properties of drugs in terms of understanding drug-tissue receptor interactions.

Medicinal chemistry therefore must of necessity be conceived to explain the symptomatic and curative properties of drugs in man and domestic animals. The complex structural and tissue organization of higher animals requires consideration of the chemical, biochemical and physico-chemical properties of drugs in line with each of the following gross factors which can influence response to the drug:

- absorption and transport across biological membranes
- selectivity of location and target organs or tissues

- selectivity of action on precise receptors
- bio-transformation reactions and the nature of such metabolites.

4. PERSPECTIVES IN DRUG DISCOVERY

The use of natural remedies by man as means of ameliorating uncomfortable health conditions dates back to almost 5000 years before this time of reporting, that is year 2005. It therefore makes sense that if we really must understand and appreciate the usefulness of the over 1000 medicinal preparations or drugs in current use, a perusal of the historical antecedents to the discovery of these chemical entities becomes rather essential.

The plant kingdom served as the main source of active metabolites. Other natural sources included minerals, animal parts and the microbial world.

It has been argued that plants were endowed with a good number of these secondary metabolites to serve as poisons and repellants which helped repel would-be adventurous predators. The metabolites were protective measures to save such species from extinction.

Mankind, intuitively and by trial and error, was able to identify those plant species that suited his purpose. History has no record of the human casualty rate arising from poisoning due to plant ingestion by man.

The post renaissance era heralded attempts to elucidate the identities of these plant metabolites and the evaluation of their biological properties, and the acclaimed therapeutic properties of these remedies.

The Ancient World and Traditional Remedies (5)

One of the earliest documentary record of drug therapy could be found on a **Sumerian** clay tablet from around 2100 BC, which records several recipes without indicating what they are used for. The Egyptian medical papyri, especially the **Ebers papyrus** dated around 1550 BC remained the major source of information on ancient world traditional remedies. The Ebers papyrus contains more than 800 prescriptions many of which are accompanied by ritual incantations requesting divine intervention to alter the course of the disease.

The strong tradition and cultural links between Egypt and Greece might have aided the transfer of medical knowledge from the Egyptians to Greeks. The first century physician **Dioscoride's** five-volume treatise **'De Materia Medica'** was by far the largest and most authoritative treatise on natural remedies. In discussing over **600 plants**, **35 animal products** and **90 minerals**, it added considerably to the knowledge of drugs in the ancient world. This was to be handed over to generations of practitioners thus transmitting a major influence on the Arabian physicians and, ultimately, on Europe during the Renaissance. **Dioscoride's** writings and renditions had a great bearing on plant nomenclature by the 16th century medical botanists and even bonatists of the present age.

Many of the products cited in Dioscoride's works are still with us today – and these include almond oil, aloes, belladonna, calamine, cherry syrup, cinnamon, coriander, galbanum, galls, ginger, juniper, lavender, lead acetate, marjoram, mastic, mercury, olive oil, opium, pepper, pine bark, storax, sulfur, terebinth, thyme and wormwood.

Galen (129-199 AD) was another remarkable **Greek physician**, whose enthusiasm for humoral medicine ensured its perpetuation through the reproduction of his extensive writing over the next 1600 years. The thrust of Galens work and medical treatise was "On the Art of Healing" and his writings formed the basis of the curricula of medical schools of the middle ages. Galens works also had a great influence on the development of therapeutics during latter 16th century and 17th century since the emphasis was in correcting an imagined humoral imbalance in the patient rather than seeking an external cause of disease. Galen was recorded as the most probable influential physician of all times.

By the 9th century greater part of the Roman Empire was under siege from the **Muslim world**. The **Arabic conquerors** demonstrated elemental decency and good judgement by preserving and nourishing Greco-Roman science and medicine, ensuring that the writings of Dioscorides, Galen and others did not disappear given **the structural attitude of the church then which construed the practice of the healing art to be an attempt to thwart divine providence.**

The Apothecary and Medicine in Post-Renaissance Europe (6)

The reintroduction of medical lore into the European countries had its antecedents in the arrival of the Jewish physicians in the European courts and this was accentuated by the invention of the printing press in the 15th century which made the works of Dioscorides, Galen and others readily available throughout Europe.

The influence of Dioscorides and Galen was brought to bear on the first printed formularies and pharmacopoeias. The 16th and 17th century European

practitioners were to reawaken intense interest in herbal remedies, because of the wide circulation of old medical texts containing various description, properties and benefits of these herbal remedies.

However the dawn of scientific enlightenment was beginning to show that some of these herbal remedies were not as therapeutically beneficial as once thought.

The world of pharmaceutical drugs and herbal therapies was changing rapidly during the scientific revolution. Apothecaries (Renaissance Pharmacists), physicians, and surgeons, the three organized branches of medicine, were at the center of these changes. In addition to dispensing drugs, apothecaries in many areas provided primary medical care, which often led them into conflict with the better organized and more powerful physicians who wanted apothecaries to simply dispense the remedies physicians prescribed. **There were legendary quarrels between the powerful Society of Apothecaries of London, chartered in 1617, and the London College of Physicians over the right of apothecaries to practice medicine and the right of physicians to sell drugs.** Apothecaries gained the right to practice in England in 1703 by a decision of the House of Lords. On their other flank, apothecaries had to defend their monopoly over specifically medical substances from grocers and the wandering vendors of unlicensed medicines.

Apothecaries were government regulated and often treated with suspicion, as it was believed that some dealt in poisons. Other herbal practitioners included housewives, who engaged in making up simple herbal recipes for their families, and cunning village men and women. Their practice was much less affected by scientific change than was that of the commercial apothecary, however.

Paracelsianism and the movement to **chemical medicine** encouraged the use of drugs that were the result of chemical preparations such as distillation rather than "simple" parts of plants used in their more natural form.

The course of chemical medicine was championed by alchemists and apothecaries such as Johan Glauber. The interactions between the Europeans, Chinese and South Americans were to usher in important plant medicaments such as the Cinchona bark, the (only source of Quinine) whose decoctions were used to treat feverish conditions. Modern quinine is still derived from this source.

Like other medical professionals, apothecaries contributed to the volume of medical literature by writing on their own profession. Great museums of pharmaceutical material were located in many parts of Europe.

The advent of modern chemistry ultimately resulted in the demonstration of the merits or demerits of ancient herbs as their long-hidden constituents were finally isolated and subjected to scientific examination.

The first gentleman to champion this course was **Scheele** (1742-1786, AD), the father of plant chemistry, who had isolated tartaric acid in his pharmacy by 1768. Subsequently he was able to isolate gallic acid, oxalic acid, lactic acid, citric acid and malic acid although none of these demonstrated any appreciable physiological activity.

This was followed by a flury of scientific activities bordering on biological activity- guided plant research. Plant extracts and herbal remedies were observed for a

particular biological activity or claims in folklore medicine, attempts were then made to isolate the active biological principles and re-evaluated in refined systems for intrinsic activity. In many instances the desired pharmacological activity was found while therapeutic benefits may be inconclusive because of certain factors such as toxicities of such isolates. Structural modifications of chemical entities may have to be embarked upon resulting in derivatives and variants that are clinically acceptable.

In some cases the isolated principles from plant may demonstrate unexpectedly different pharmacological activity necessitating a new directional research endeavour.

5. Plant Metabolites as Lead Compounds for the Development of Newer and Safer Therapeutic Agents

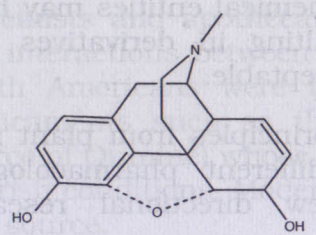
5.1 The Opium Alkaloids (Opiates).

Morphine and **codeine** are the main alkaloids from the dried latex of the opium plant (*Papaver somniforum*). Morphine is a powerful narcotic analgesic employed for the management of pain. It inhibits the opioid receptors in the central nervous system, the μ (min), δ (delta), κ (cappa), α (alpha) and ϵ (epsilon) receptors.

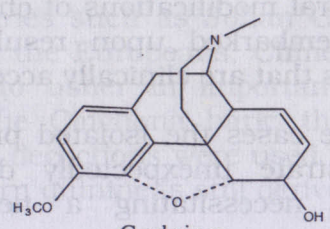
The universal central nervous system (cns) depressant action of morphine and opium is the cause of the undesirable side effects associated with the use of morphine as a therapeutic agent – notably respiratory depression (the cause of death from morphine overdose), constipation and nausea. The **addicting** and **dependence liability** of morphine and its congener

heroin are responsible for the antisocial menace demonstrated by addicts.

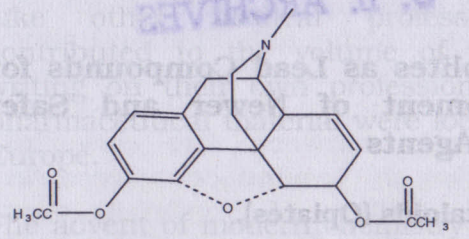
Morphine has been employed by medicinal chemists as template for the development of relatively safer analgesic drugs such as **meperidine**, **pentazocine** **pethidine**, **levophanol**, **methadone**.



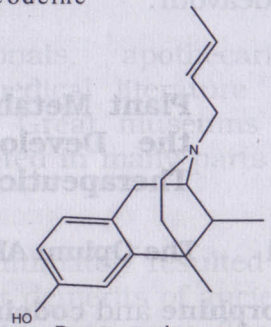
Morphine



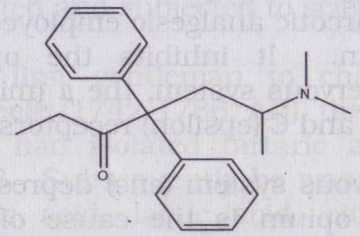
Codeine



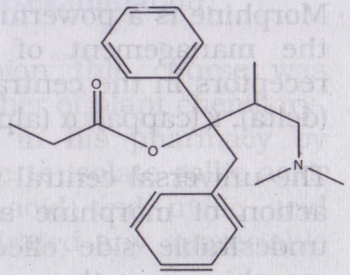
Heroine



Pentazocine

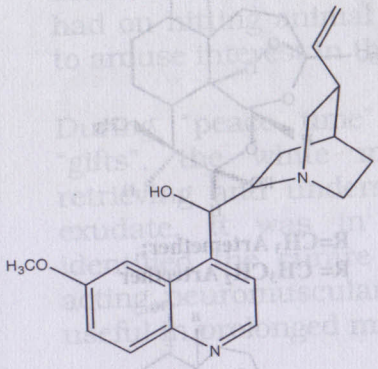


Methadone

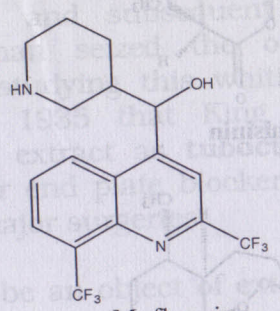


Propoxyphene

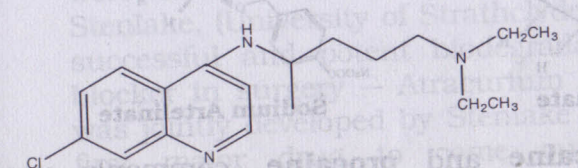
5.2 **Quinine**, a naturally occurring antimalarial drug from **Cinchona** bark served as template for the development of synthetic analogues such as **chloroquine**, **amodiaquine** and **mefloquine** (the **quinolines**).



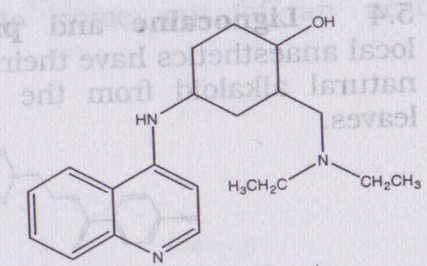
Quinine



Mefloquine

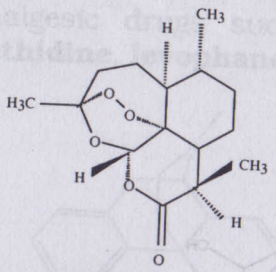


Chloroquine

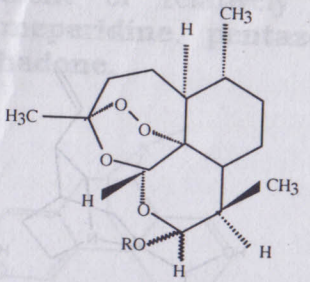


Amodiaquine

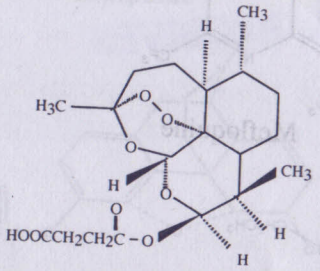
5.3 Another important antimalarial of natural origin is the sesquiterpene, Artemisinin from Aretemisia annua (Quinghaosu). Derivatives of artemisinin include **artemether**, **arteether**, **artesunate** and **artenilate**.



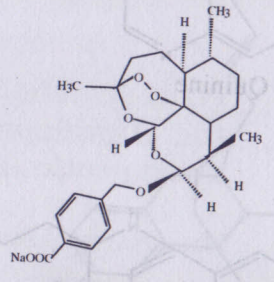
Artemisinin



R=CH_3 Artemether;
R= CH_3CH_2 Arteether

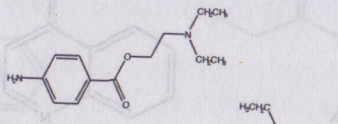


Artesunate

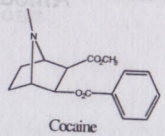


Sodium Artelinate

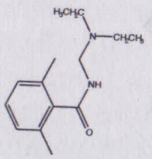
5.4 **Lignocaine** and **procaine**, commonly used local anaesthetics have their antecedents in **Cocaine**, a natural alkaloid from the plant **Erythroxylon coca** leaves.



Procaine



Cocaine



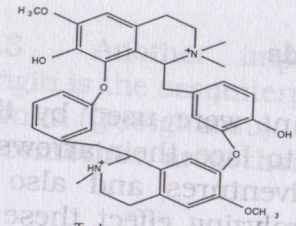
Lignocaine

5.5 The Curare Alkaloids

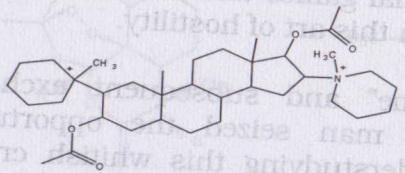
Extracts of the curare plant were used by the Red Indians of South America to lace their arrows before embarking on hunting adventures and also during internecine wars. The paralyzing effect these arrows had on hitting animal games and human enemies was to arouse interest in this art of hostility.

During "peace time" and subsequent exchange of "gifts", the white man seized the opportunity of retrieving and understudying this whitish crystalling exudate. It was in 1935 that King and workers identified the curare extract as **tubocurarin**, a long acting neuromuscular end plate blocker, that became useful in prolonged major surgeries.

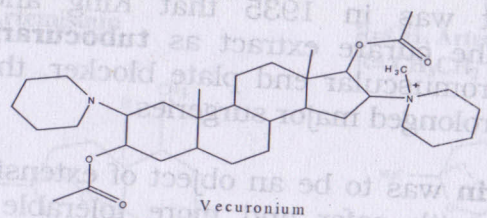
Tubocurarin was to be an object of extensive studies. Analogues with safer and more tolerable properties were later introduced in surgery. Professor J.B. Stenlake, (University of Strathclyde 1982) introduced a successful and potent biodegradable neuromuscular blocker in surgery — Atracurium Besylate. The drug was jointly developed by Stenlake and Wellcome. The first major drug to come out of an academic establishment.



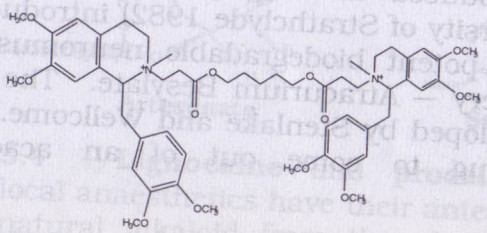
Tubocurarine



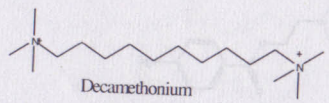
Pancuronium



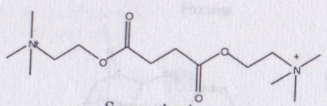
Vecuronium



Atracurium



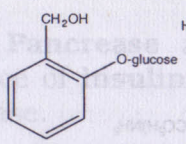
Decamethonium



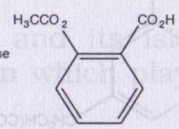
Suxamethonium

5.6 **Salicylic acid**, the precursor to acetylsalicylic acid, **aspirin**, has its antecedent in **salicin** a glycoside from the plant **willow** bark whose decoction had been used by the Chinese for the treatment of fever for over a thousand years.

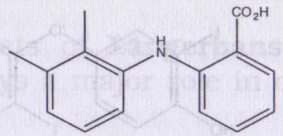
Aspirin, the wonder drug was to serve as template for the development of a host of non-steroidal antiinflammatory drugs (NSAIDS) such as diclofenac, dolobid, orudis, oruvail, naproxen, brufen.



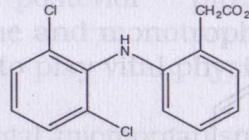
Salicin



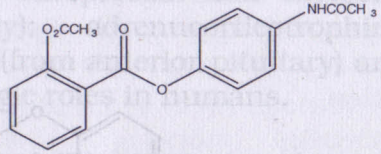
Aspirin



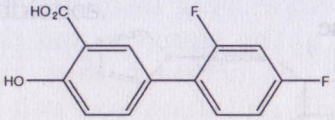
Mefenamic



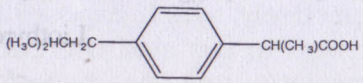
Diclofenac



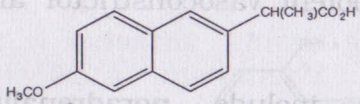
Benorylate



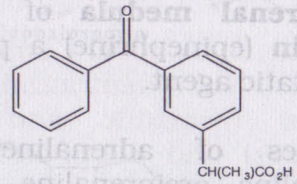
Diflunisal



Ibuprofen



Naproxen

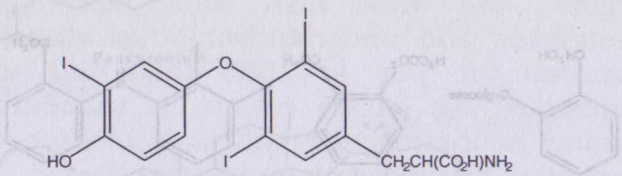


Ketoprofen

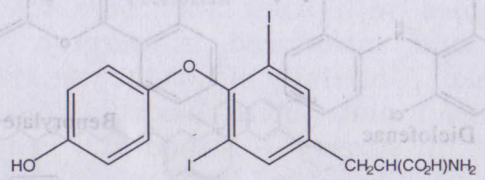
6. Animal Organs as Sources of Leads in Drug Development

Mammalian **hormones** are veritable sources of natural Lead compounds exploited in the development of therapeutic drugs.

Extracts of the **Thyroid gland** paved the way for total synthesis of Thyroxine and the more potent analogue Liothyronine



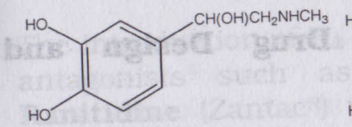
Thyroxine



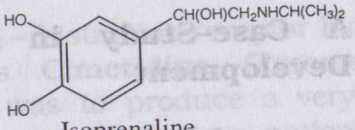
Liothyronine

The **adrenal medula** of sheep is the source of **adrenalin** (epinephrine) a potent vasoconstrictor and haemostatic agent.

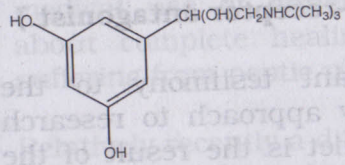
Anologues of adrenaline include noradrenaline isoprenaline, orciprenaline, soteronol and salbutamol which have demonstrated different physiologic activities.



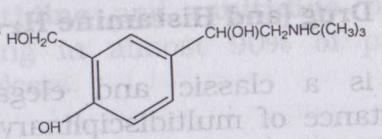
Epinephrine



Isoprenaline



Terbutaline

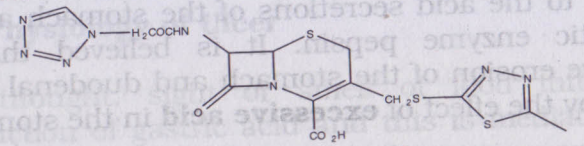


Salbutamol

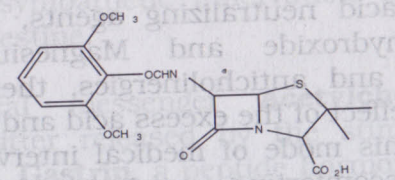
The **Pancrease** and its islets of **Langerhans** is the source of **insulin** which plays a major role in diabetes disease.

The Pituitary hormones – vasopressin and oxytocin (from posterior pituitary); adrenucorticotrophin, cortisone and monotrophin (from anterior pituitary) are known to play vital physiologic roles in humans.

The fungal microorganism **Penicillium notatum** became the natural source of the Penicillins and Cephalosporin antibiotics.



Cephalosporin



Penicillin

7. A Case-Study in Drug Design and Development

Development of Cimetidine (Tagamet^R), an Anti-Ulcer Drug (and Histamine H_2-receptor antagonist.)

This is a classic and elegant testimony to the importance of multidisciplinary approach to research and drug development. Tagamet is the result of the combined efforts of the chemist, experimental pharmacologist, and human physiologist.

The Peptic Ulcer Disease

Duodenal and gastric ulcers (peptic ulcers) affect between 10 and 20% of a population of people who are otherwise relatively fit. The disease causes pain and illness with appreciable discomfort, and often results in a measurable economic loss both to the patient and the nation.

Duodenal and gastric ulcers are localized erosions of the mucous membrane of the duodenum or stomach respectively which expose the underlying layers of the gut wall to the acid secretions of the stomach and the proteolytic enzyme pepsin. It is believed that the ulcerative erosion of the stomach and duodenal wall is caused by the effect of **excessive acid** in the stomach.

The traditional treatment had always being by the use of palliative acid neutralizing agents, **antacids** (e.g. Aluminum hydroxide and Magnesium trisilicate preparations) and anticholinergics, thereby reducing the irritating effect of the excess acid and also the effect of pepsin. This mode of medical intervention merely abated the discomforting experience of ulcer sufferers as only a few proportion of these lesions got completely healed.

The introduction of H_2 – histamine receptor blockers or antagonists such as **Cimetidine** (Tagamet^R) and **Ranitidine** (Zantac^R) was to produce a very marked change in the management of ulcer patients. The medical use of **cimetidine** and **ranitidine** brought about complete healing in almost 90% of patients suffering from peptic ulcers.

Relatively recently a different dimension in the aetiology of peptic ulcer has been introduced into our understanding of peptic ulcers. The stomach residing microorganism, **Helicobacter pylori** has been implicated in the aetiology of peptic ulcers. Contrary to what the medical microbiologist claims, the medicinal chemist finds it difficult to accept or believe that the microorganism H. pylori initiates peptic ulceration.

The medicinal chemist posits that like all wounds, infection by H. pylori tends to make peptic ulcer management more difficult, in most cases necessitating co-administration of a H. pylori susceptible antibacterial such as **amoxycillin** for a successful and unhindered treatment of peptic ulcers.

The Physiology of Ulcer

The thought, sight or smell of food initiates the production of gastric acid and this is mediated by the autonomic nervous system via the **vagus** nerves which provide parasympathetic innervation to the stomach and small intestine.

The chemical messenger **Acetylcholine** is the neurotransmitter released by the stimulation of the vagus nerve. **Gastrin**, a peptide hormone, is produced by special gastrin – producing 'G' cells on stimulation by the vagus whose branches innervate the antral

region of the stomach. Apart from vagus stimulation, gastrin is also released as a result of presence of food in the stomach. Gastrin is released into the bloodstream and is conveyed to the stomach where it causes specialized stomach cells called parietal cells to release **hydrochloric acid** (gastric acid). Hydrochloric acid is physiologically essential for digestive purposes, but in excess it becomes injurious to the stomach wall.

It had been shown earlier, round about 1920, that histamine when injected into dog caused the secretion of gastric acid and that **histamine** exists naturally within the lining of gastric mucosa. The relationship between these three chemical messengers **acetylcholine**, **gastrin** and **histamine** was not too clear to physiologists for a long time.

Surgery has always been employed as an alternative to drug treatment. This involves the excision of the part of the acid secretory and gastrin – producing regions of the stomach (e.g. partial gastrectomy) or selectively removing vagal nerve branches supplying the acid secretory region. The attendant hazards associated with such procedures are only known to gastroentology surgeons.

At the turn of the early 1960s, physiologists had improved tremendously their understanding of the physiology of gastric acid secretion and also with the advances made in the concept of drug receptor interactions two approaches were conceived as the rational direction of research.

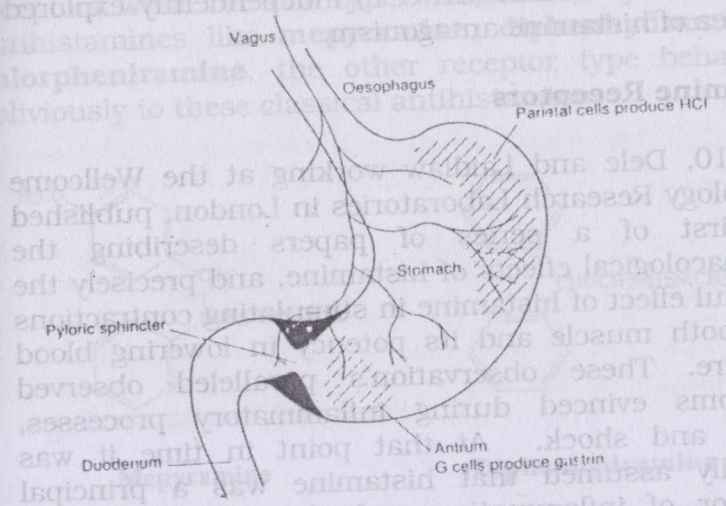


Fig. 2: Diagram of the stomach showing vagus nerve and position of G cells (producing gastrin) and parietal cells (producing HCl).

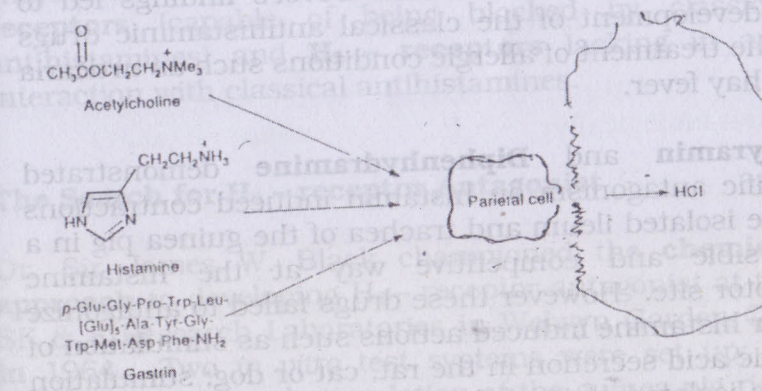


Fig. 3: Three chemical messengers stimulate the production of hydrochloric acid from the gastric parietal cell. The formulae show acetylcholine cation, histamine monocation (the most prevalent species at physiological pH of 7.4), and human gastrin I.

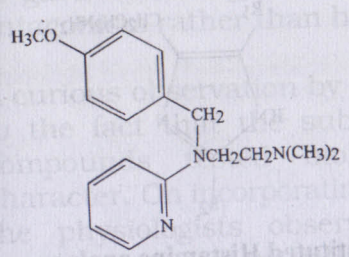
In the United Kingdom, while ICI Pharmaceuticals initiated a search for a gastrin antagonist, Pfizer and SmithKline & French (SK & F) independently explored the idea of histamine antagonism.

Histamine Receptors

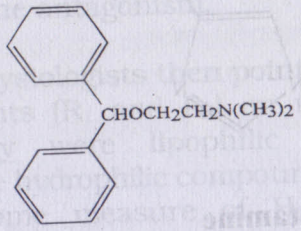
In 1910, Dele and Laidlaw working at the Wellcome Physiology Research Laboratories in London, published the first of a series of papers describing the pharmacological effects of histamine, and precisely the powerful effect of histamine in stimulating contractions of smooth muscle and its potency in lowering blood pressure. These observation's paralleled observed symptoms evinced during inflammatory processes, allergy and shock. At that point in time it was generally assumed that histamine was a principal mediator of inflammation and shock, a suggestion which stimulated a search by Bovet in Paris for substances capable of neutralizing these apparent injurious effects of histamine. Bovet's findings led to the development of the classical antihistaminic drugs for the treatment of allergic conditions such as urticaria and hay fever.

Mepyramin and **Diphenhydramine** demonstrated specific antagonism on histamin induced contractions of the isolated ileum and trachea of the guinea pig in a reversible and competitive way at the histamine receptor site. However these drugs failed to antagonize **other** histamine induced actions such as stimulation of gastric acid secretion in the rat, cat or dog; stimulation of the isolated atria of the guinea pig; inhibition of rat uterus contractions. It was also found that these antihistamines reduced the intensity of, but did not completely abolish, vasodilator actions of large doses of

histamine, and in 1948 it was suggested by Folklow that it would seem there were two types of histamine receptors while the one type was blocked by classical antihistamines like **mepyramine**, **diphenhydramine**, **chlorpheniramine**, the other receptor type behaved obliviously to these classical antihistamines.



Mepyramine



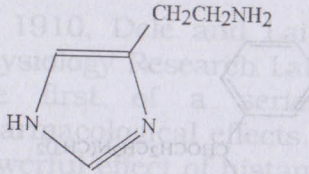
Diphenhydramine

These and other observations were to lead to the characterization of histamine receptors as **H_1 – receptors** (capable of being blocked by classical antihistamines) and **H_2 – receptors** lacking in any interaction with classical antihistamines.

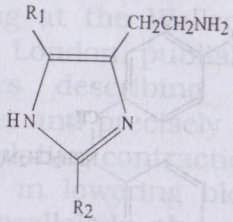
The Search for H_2 – receptor Antagonist

Dr. Sir James W. Black championed the **chemical approach** to developing H_2 – receptor antagonist at the SK & F Research Laboratories in Welwyn Garden City in 1964. Two *in vitro* test systems were set up; (1) histamine – induced stimulation of the guinea pig right atrium (which continues to beat spontaneously *in vitro* because it contains the pacemaker and histamine increases the rate of beating); and (2) inhibition by histamine of evoked contractions of the rat uterus.

The chemical approach to designing a suitable H_2 – receptor antagonist was predicated on the fact that a well-defined biological concept of competitive antagonism was in place. The lead compound was histamine itself.



Histamine



Substituted Histamine analogues

It was now rationalized out that a compound capable of antagonizing histamine must also be recognized structurally by the receptor and that such a compound should have a superior **affinity** for the receptor and also a superior **intrinsic value**.

Many structural derivatives were synthesized and tested biologically.

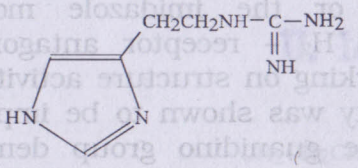
In the first four years about 200 compounds were made and tested. None of these gave the desired result.

Frustration from failures was beginning to set in. With millions of pounds (dollars) down the drain, there was considerable pressure within the company to abandon the research project. Indeed, the American management at the company's headquarters in Philadelphia did eventually order the project to be closed. The British scientists involved in the project were, however, firmly resolved to continue and during

this period the test system was refined and chemical ideas began to crystallize. (The whole idea was British in origin).

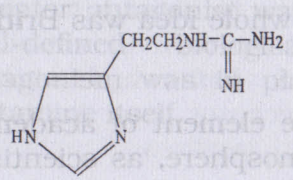
Mention must be made that the element of academic hostility was also rife in the atmosphere, as scientists in gastroenterology were more fascinated with gastrin antagonism rather than histamine antagonism.

A curious observation by the physiologists then pointed to the fact that the substituents (R_1 and R_2) on the compounds tested biologically were lipophilic in character. On incorporating some hydrophilic compounds the physiologists observed some measure of H_2 – receptor antagonism with one compound.

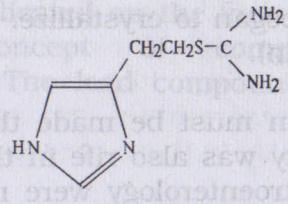


Guanylhistamine

It was missed originally because the compound also acted as a stimulant (agonist); in other words such a compound was referred to as partial agonist. This compound is histamine derivative in which the side chain amine group has been replaced by a guanyl (guanidino) group.



Guanylhistamine

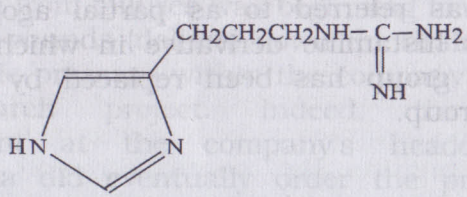


(S) -[2-(imidazol-4-yl) ethyl] isothiourea

Guanyl histamine became the newly found lead compound. The appearance of antagonism, though a weak one, provided a much needed template. Further development involving an isosteric exchange resulted in a more active compound.

The question as to whether the guanyl group, the isothiourea group or the imidazole moiety was responsible for the H_2 – receptor antagonism was addressed by embarking on structure activity studies. The imidazole moiety was shown to be important for activity whereas the guanidino group demonstrated physicochemical properties necessary for 3 dimensional interaction with some protein groups on the receptor.

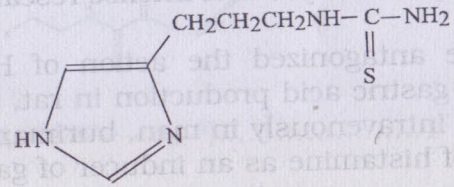
Further development involved the lengthening (3 methylene units) of the side chain in the guanidino compound to give SKF 91235 with an increase in antagonist activity.



SKF 91235

The next stage in development involved chain lengthening to 4 methylene groups. The continued exploration of the amidines and N-substitution was to show that no clear-cut antagonism was achieved. The implication of agonist – antagonist activities (partial agonist) is that although the newly synthesized compounds antagonized the action of histamine, they were not sufficiently inhibitors of gastric acid secretion because of interference from their inherent stimulatory activity, a kind of biological hindrance that must be tackled.

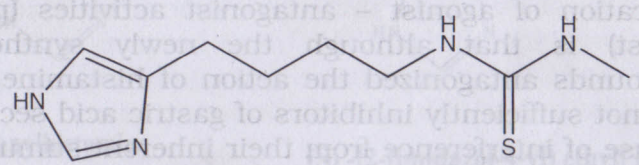
The quest for selectivity became rather critical. A further development involved the replacement of the guanidino group with thiourea group to give the compound code- named SKF 91581.



SKF 91581

SKF 91581 demonstrated exclusively antagonist activity, albeit weakly, a commendable step in the right direction.

With increase in the methylene side chain from 3 to 4 and subsequent methylation of the extant NH_2 group the drug **Burimamide** was the product.



Burimamide

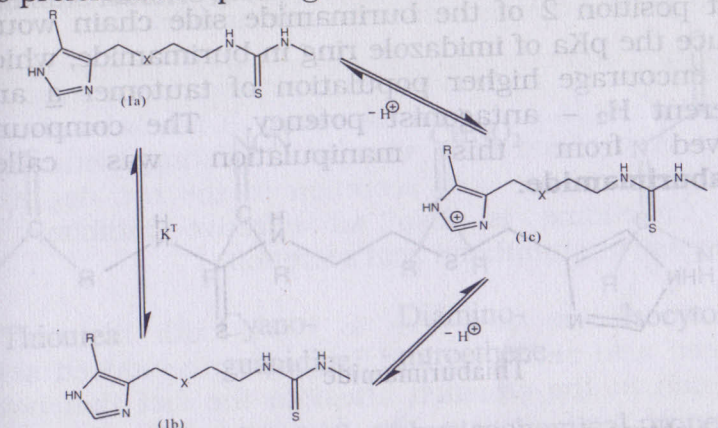
Burimamide demonstrated the desired potent pure competitive antagonist activity. Burimamide was an extremely important compound and it provided a vital breakthrough. It fulfilled all the criteria required for characterizing the existence of Histamine H_2 – receptor, other than H_1– receptors.

This discovery was announced in 1972 by Sir James Black's group after 6 years of intense research.

Burimamide antagonized the action of Histamine in stimulating gastric acid production in rat, cat and dog. When given intravenously in man, burimamide blocked the action of histamine as an inducer of gastric acid in man.

Burimamide had one drawback. On administering it orally to man, its potency waned, because of extreme ionization. The guanidino group conferred a high pKa on burimamide which ionized out at physiological pH 7.4 hence a decrease in absorption.

Attempts to restructure burimamide with a view to increasing its potency were embarked upon. Studies had showed that the pKa physicochemical attributes were of the essence, since it was realized that burimamide in aqueous solution was a mixture of many chemical species in equilibrium. At physiological pH there are three main tautomeric forms of burimamide (imidazole ring) and which form was the preferred entity with high population on the receptor was a question to answer. Dynamic structure - activity analysis (DSAA) was to suggest that tautomer **(a)** was the preferred receptor ligand.



$$\text{Log } K^T = 3.4\ (\sigma_m{}^{CH2XCH3} - \sigma_m{}^{R}) \quad \ldots\ldots 1$$

$$\text{Frac. (Ia)} = \frac{[Ia]}{[Ia] + [Ib]} \quad \frac{K^T}{1 + K^T} \quad \ldots\ldots 2$$

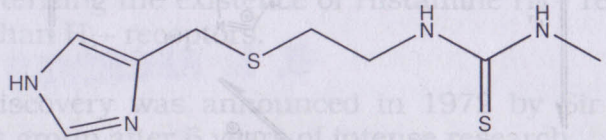
$$\text{Frac. (Ia + Ib)}^{7.4} = \frac{\text{antilog. } (7.4 - pK_a)}{1 + \text{antilog. } (7.4 - pK_a)} \quad \ldots 3$$

$$pA_2 \text{ (corr.)} = pA_2 - \log[\text{Frac.(Ia). Frac.(Ia + Ib)}^{7.4}] \ldots 4$$

Fig. 4: Tautomerism between Imidazole Species and Relationship to Physiological pH.

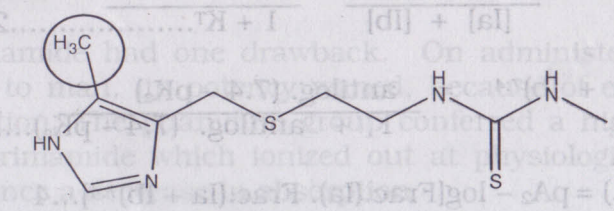
Considering physicochemical attributes and receptor affinity, for burimamide the ring pka (7.25 at 37°C) is greater than that of unsubstituted imidazole (pKa = 6.8), an indication that the side chain in burimamide was mildly electron contributing. In contrast for histamine the ammonium ethyl side chain was seen to be electron withdrawing, since it lowered the ring pKa (5.90).

To increase the population of unchanged tautomer of burimamide at the receptor site and hence its potency it was reasoned that an electron withdrawing atom e.g. **S** at position 2 of the burimamide side chain would reduce the pKa of imidazole ring in burimamide, which will encourage higher population of tautomer a and inherent H_2 – antagonist potency. The compound derived from this manipulation was called **Thiaburimamide**.



Thiaburimamide

For stereochemical reasons, a mild electron contributing radical, the methyl (CH_3-) group was now inserted on position 4(5) of the imidazole ring to give **Metiamide**.

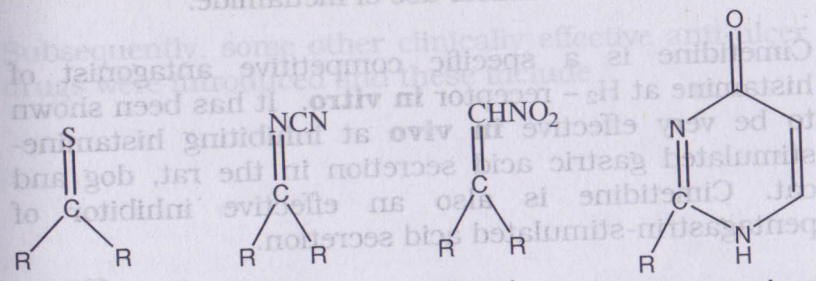


Metiamide

An optimum antagonist potency was observed with **metiamide** which was introduced into medicine for use in the treatment of gastric and duodenal ulcers.

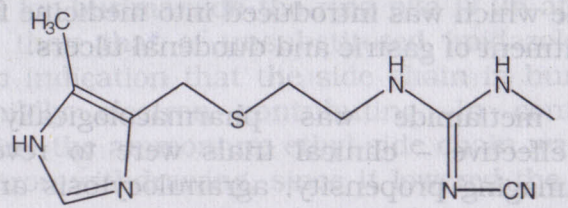
Although metiamide was pharmacologically and clinically effective – clinical trials were to reveal its kidney damaging propensity, agranulocytosis and low incidence of reversible granulocytopenia.

It was suspected that these demerits had to do with the **thiourea** group in the molecule. A consideration of available iosteric groups to thiourea i.e.



Thiourea | Cyano-guanidine | Diamino-nitroethene | Isocytosine

based on essentially similar physicochemical properties strongly identified the **cyanoguanidine** group for a possible isosteric exchange with the thiourea group. This structural modification (bioisosterism) gave rise to a clinically effective and highly successful H_2 - receptor antagonist **Cimetidine**



Cimetidine (Tagamet)

which is free from the side effect of granulocytopenia which limited the clinical use of metiamide.

Cimetidine is a specific competitive antagonist of histamine at H_2 – receptor **in vitro**. It has been shown to be very effective **in vivo** at inhibiting histamine-stimulated gastric acid secretion in the rat, dog and cat. Cimetidine is also an effective inhibitor of pentagastrin-stimulated acid secretion.

That cimetidine was able to block both histamine-induced acid secretion and pentagastrin-induced acid secretion in the stomach attest to the fact that both histamine and gastrin are somehow linked in the gastric acid process.

Cimetidine was extensively studied in man and its safety and efficacy have been established in the acute treatment of peptic ulcer. An oral dose of 0.8 – 1.2g/day was shown to relieve symptoms and promote healing of lesions in a majority of patients with peptic ulcer disease.

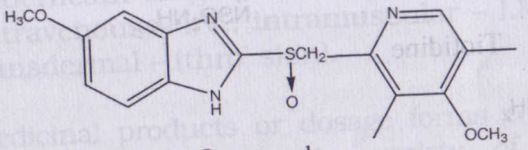
Cimetidine was marketed first in the United Kingdom in November 1976, in the USA in August 1977 and in Japan in 1982. By 1999 Cimetidine had become

known as Tagamet in over all the world. Cimetidine changed the medical management of peptic ulcer disease in the most successful manner.

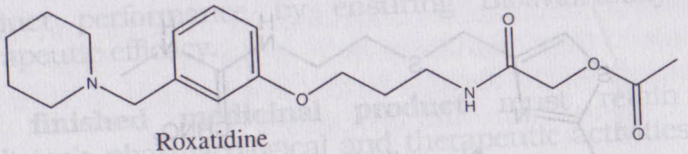
The research project was initiated in 1964 and the arduous exercise came to fruition in 1976 – in spite of **considerable difficulties** and **disappointments**. **A typical case study** in **Drug Design** and **Drug Discovery**.

In 1983 Cimetidine's (Tagamets) annual worldwide sales reached the level of nearly $100,000.000.00.

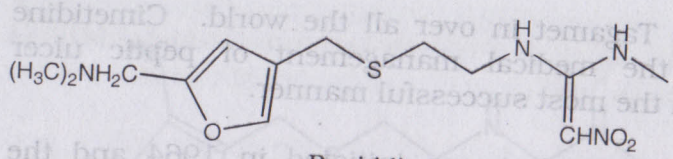
Subsequently, some other clinically effective anti-ulcer drugs were introduced and these include



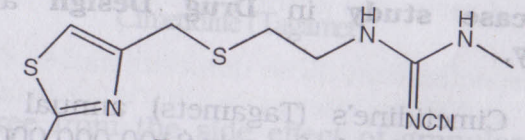
Omeprazole



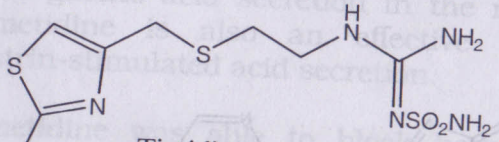
Roxatidine



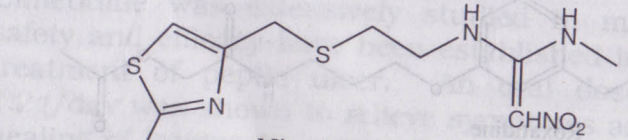
Ranitidine



Famotidine



Tiotidine



Nizatidine

8. FORMULATION AND PRODUCT DEVELOPMENT OF MEDICINES

The evolutionary stages of drug design and development involve identification of a Lead substance, e.g. **histamine**, the chemical synthesis of hundreds of analogues and variants, physiological, pharmacological and toxicological evaluation of these drug molecules. Further and advanced **in vitro** and **in vivo** tests may be conducted to determine the putative drug's selectivity for its proposed therapeutic action.

At the end of this stage the choice candidate e.g., Cimetidine must be formulated into a dosage form, **the medicinal product**, that can be easily handled and administered to the patient. The medicinal dosage forms range from **liquids** (solutions, syrups, suspension's), **solids** (tablets, capsules) to **parenteral** (suppositories – anal; pessaries – vaginal; sublingual – underneath tongue, inhalations – aerosols), **injections** (intravenous – I.V., intramuscular – I.M.) and of recent transdermal – (thro' skin).

Medicinal products or dosage forms contain the **native drug substance** plus a variety of additives called pharmaceutical excipients whose role is to enhance product performance by ensuring Bioavailability and therapeutic efficacy.

The **finished medicinal product** must retain the medicine's pharmacological and therapeutic activities and provide a predictable response in a patient.

The pharmaceutical product development process must ensure efficacy and long-term safety, devoid of any deleterious toxicity when administered in line with medical

recommendations. The development process must also ensure quality and stability.

The product must be correctly labelled and well-packaged in line with the government regulatory agency requirements of the proposed country of marketing, in terms of acceptable quality assurance levels.

The pharmaceutical development of a medicinal product is therefore a large undertaking requiring extensive resources.

Biopharmaceutic Considerations in Pharmaceutical Product Development

Bioavailability refers to the measurement of the rate and extent of drug delivery to the systemic circulation (i.e. the blood and organs of the body). Biopharmaceutic studies allows for **rational formulation** of medicinal products.

Biopharmaceutics is a discipline in the Pharmaceutical Sciences which relates the physicochemical properties of the drug substance and the finished medicinal formulation (as well as the excipients) to the systemic bioavailablility of the pharmacologically active drug substance.

Medicinal preparations intended for systemic circulation include orally administered drugs e.g., tablets and capsules, (solid dosage form), syrups and suspensions (liquid dosage form) and injectables.

Systemic Drug Bioavailability

For solid dosage forms – factors that may affect systemic bioavailability include

- **disintegration** of the solid dosage form in the aqueous physiological fluid of the gastrointestinal tract, git, thereby releasing the active drug constituent of the tablet or capsule
- **dissolution** of the drug substance released in the git fluid compartment, "solvation" and subsequent absorption through the villi of the small intestine into systemic circulation
- Physicochemical nature of the drug substance (weak acids, weak bases, salts, neutral compounds)
- Formulation factors affecting **disintegration** and **dissolution**.

Physicochemical Considerations in drug absorption processes

- solubility, pH and drug absorption
- stability, pH and drug absorption
- particle size and drug absorption
- polymorphic crystals, solvates and drug absorption
- formulation ingredients and drug absorption

A **poorly formulated** drug e.g. **paracetamol tablet** would result in **poor disintegration**, **incomplete dissolution**, **inadequate absorption**, **incorrect pharmacokinetics**, subtherapeutic or abnormal systemic drug concentrations and ultimately treatment failure or poor clinical response, the very last thing a physician would want.

It is the responsibility of the Physician and Pharmacist to ask intelligent questions and demand proof from pharmaceutical companies before yielding to pressure to prescribe a new drug, in order to avert an unwitting self inflicted blame for treatment failures.

TABLE 1: Common Excipients Used in Solid Dosage Forms (Tablet, Capsules)[7]

Excipient	Property in Dosage Form
Lactose	Diluent
Dibasic calcium phosphate	Diluent
Starch	Disintegrant, diluent
Microcrystalline cellulose	Disintegrant, diluent
Magnesium stearate	Lubricant
Stearic acid	Lubricant
Hydrogenated vegetable oil	Lubricant
Talc	Lubricant
Sucrose (solution)	Granulating agent
Polyvinyl pyrrolidone (solution)	Granulating agent
Hydroxypropylmethylcellulose	Tablet-coating agent
Titinium dioxide	Combined with dye as colored coating
Methylcellulose	Coating or granulating agent
Cellulose acetate phthalate	Enteric coating agent

TABLE 2: Common Excipients Used in Liquid Dosage Forms[7]

Excipient	Property in Dosage Form
Sodium carboxymethylcellulose	Suspending agent
Tragacanth	Suspending agent
Sodium alginate	Suspending agent
Xanthan gum	Thixotropic suspending agent
Veegum	Thixotropic suspending agent
Sorbitol	Sweetener
Alcohol	Solubilizing agent, preservative
Propylene glycol	Solubilizing agent
Methyl, propylparaben	Preservative
Sucrose	Sweetener
Polysorbates	Surfactant
Sesame oil	For emulsion vehicle
Corn oil	For emulsion vehicle

TABLE 3: Routes of Drug Administration[3]

Route	Advantages	Disadvantages	Product types
Parenteral	Exact dose, 100% compliance, unconscious patient	Pain, expensive, self-administration unusual, trained personnel	Solutions, suspensions,* emulsions, implants*
Oral	Easy, convenient, acceptable, painless self-administration	Nausea/Vomiting, stability, interactions (food), low availability, conscious Patient	Solutions, syrups, suspensions, emulsions, powders, granules, capsules, tablets
Rectal	Avoids stability in GI tract, no first pass metabolism, useful if no oral administration	Unpopular, inconvenient, erratic absorption, Irritation	Suppositories, enemas (solutions, suspensions, emulsions), foams, ointments, creams
Buccal	Rapid onset, no first pass, dosage form recoverable, convenient	Taste, low dose drugs only	Tablets, mouthwashes
Inhalation	Convenient, local or systemic effects, no first pass	Irritation, embarrassing, difficult technique	Gases, aerosols (solutions, suspensions), powders
Trans-dermal	Convenient, local or systemic effects, no first pass	Irritation, potent drugs only, absorption Affected by site	Solutions, lotions, sprays, gels, ointments, creams, powders, patches
Eye	Local action only	Hard to administer, inefficient, irritation	Solutions, ointments, injections
Vaginal	Local or systemic effects (hormones), no first pass metabolism	Inconvenient, erratic absorption, irritation, lack of data	Creams, ointments, foams, tablets

* Not for intravenous administration.

TABLE 4: Approximate pK_a Values for Selected Acidic Drugs and Protonated Forms of Basic Drugs

Acids	pK_a	Protonated bases	pK_a
Acetaminophen	9.5	Allopurinol	9.4
Ascorbic Acid	4.2, 11.6	Amantadine	10.4
Aspirin	3.5	Amphetamine	9.9
Barbiturates	7.8	Antipyrine	1.4
Cephalosporins	2.7	Atropine	9.2
Ethosuximide	9.3	Benzocaine	2.8
Fluorouracil	8.0, 13.0	Carbachol	4.8
Furosemide	3.9	Carbinoxamine	8.1
Hippuric acid	3.6	Chlordiazepoxide	4.8
Ibuprofen	5.2	Chlorpheniramine	9.0
Indomethacin	4.5	Cimetidine	6.8
Mandelic acid	3.4	Codeine	8.2
Nalidixic acid	6.7	Dextromethorphan	8.3
Nicotinic acid	4.9	Erythromycin	8.8
Nitrofurantoin	7.1	Heroin	7.8
Penicillins	2.6	Histamine	5.9, 9.8
Phenylbutazone	4.5	Isoniazid	2.0, 3.9
Phenytoin	8.3	Isoproterenol	8.6
Salicylamide	8.2	Lidocaine	7.9
Salicylic acid	3.0, 13.4	Procaine	8.8
Sulfamethoxazole	5.6	Pseudoephedrine	9.7
Tolbutamide	5.4	Quinine	4.2, 8.8
Warfarin	5.0	Reserpine	6.6

TABLE 5: Physicochemical Properties for Consideration in Drug Product Design[3]

pK_a and pH profile	Necessary for optimum stability and solubility of the final product.
Particle size	May affect the solubility of the drug and therefore the dissolution rate of the product.
Polymorphism	The ability of a drug to exist in various crystal forms may change the solubility of the drug. Also, the stability of each form is important, because polymorphs may convert from one form to another.
Hygroscopicity	Moisture absorption may affect the physical structure as well as stability of the product.
Partition coefficient	May give some indication of the relative affinity of the drug for oil and water. A drug that has high affinity for oil may have poor release and dissolution from the formulation.
Excipient interaction	The compatibility of the excipients with the drug and sometimes trace elements in excipients may affect the stability of the product. It is important to have specifications of all raw materials.
pH stability profile	The stability of solutions are often affected by the pH of the vehicle; furthermore, because the pH in the stomach and gut are different, knowledge of the stability profile would help to avoid or prevent degradation of the product during storage or after administration.

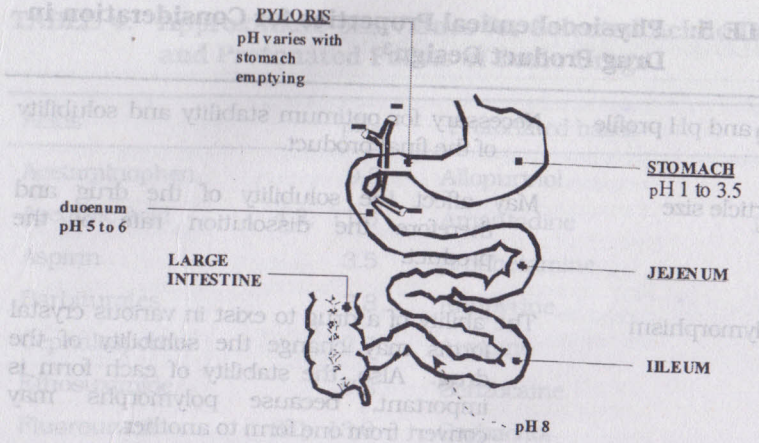
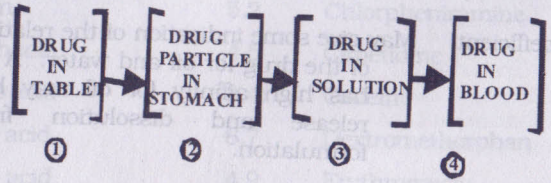


Fig. 5: Diagram illustrating the pH of various regions in the g.i. tract.



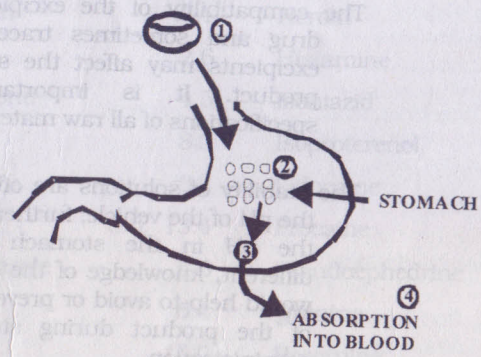


Fig. 6: Illustration of the usual steps involved in the absorption of a drug following oral administration of a tablet: disintegration, dissolution, and absorption.

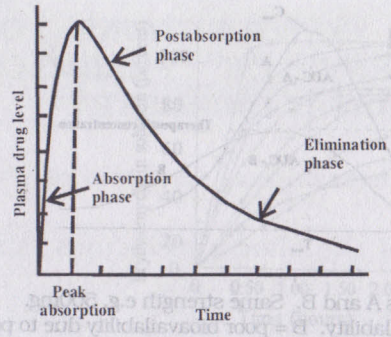


Fig. 7: Plasma level-time curve for a drug given in a single oral dose. The drug absorption and elimination phases of the curve are shown.

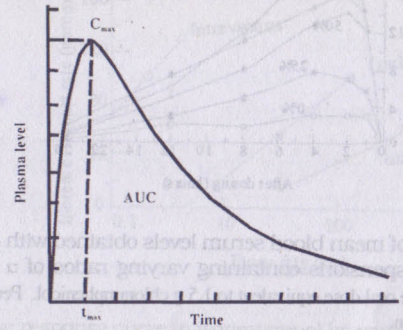


Fig. 8: Typical plasma level-time curve for a drug given in a single dose.

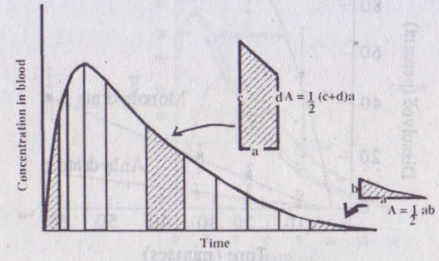


Fig. 9: The total area under the concentration time course (AUC) following oral administration may be estimated by summing the areas of the trapezoids and triangles which approximately comprise it. This is illustrated for intravenous administration.

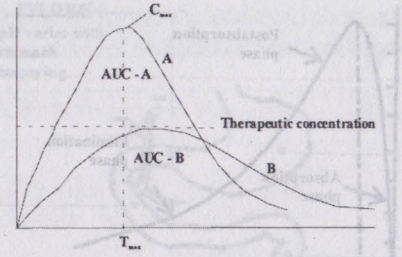


Fig. 10: Two drug tablets A and B. Same strength e.g. 500mg.
A = good bioavailability. B = poor bioavailability due to poor formulation.

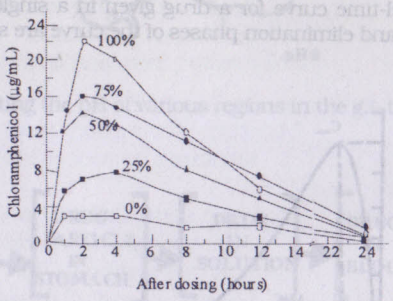


Fig. 10a: Comparison of mean blood serum levels obtained with chloramphenicol palmitate suspensions containing varying ratios of α and β polymorphs, following single oral dose equivalent to 1.5 g chloramphenicol. Percentage polymorph β in the suspension.

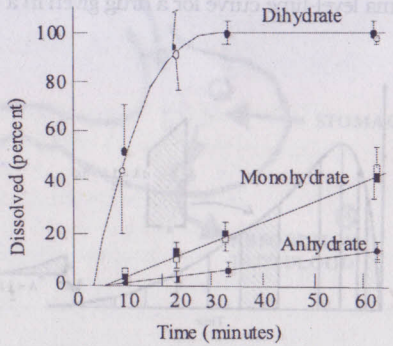


Fig. 10b: Dissolution behaviour of erythromycin dihydrate, monohydrate, and anhydrate in phosphate buffer (pH 7.5) at 37°C.

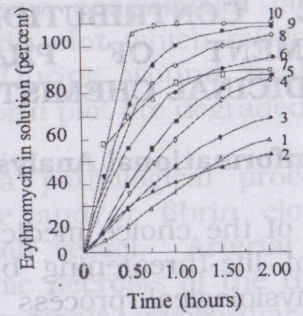


Fig. 11a: Dissolution profile of various lots of erythromycin stearate as a function of time (0.05 M pH 6.6 phosphate buffer).

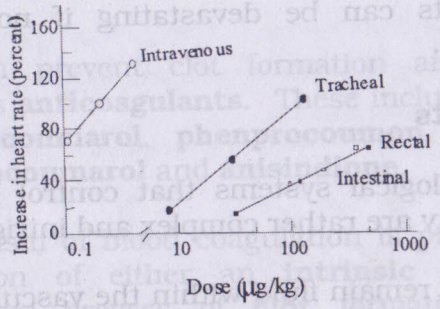


Fig. 11b: Dose response curve to isoproterenol by various routes in dogs.

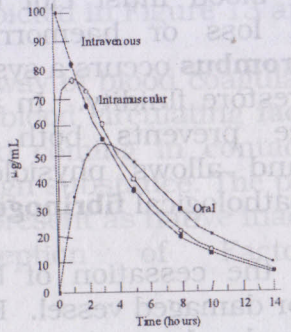


Fig. 12: Plasma concentration of a drug after the same dose is administered by three different routes.

9. HUMBLE CONTRIBUTIONS OF THE DEPARTMENT OF PHARMACEUTICAL AND MEDICINAL CHEMISTRY

1. Solution Conformational Analysis of Warfarin

Warfarin is one of the choice medicines employed for the treatment of life-threatening blood clots. Blood clotting is a physiological process leading to extra-thickening of the blood, coagulation, and thereby impairing normal blood flow to vital organs and tissues of the body. The medical complications arising from such events can be devastating if not expediently attended to.

Blood Clots

The physiological systems that control blood fluidity and viscosity are rather complex and intriguing.

Blood must remain fluid within the vascular system, to enable vital oxygen and nutrients be carried to tissues and organs of the body. However during vascular injury such as a cut, blood must clot quickly to prevent excessive blood loss or haemorrhage. When an intravascular **thrombus** occurs a system of **fibrinolysis** is activated to restore fluidity. In normal situation a delicate balance prevents both **thrombosis** and **haemorrhage** and allows physiological **fibrinolysis** without excess pathological **fibrinogenolysis**.

Haemostasis is the cessation of blood loss from a vascular injury or damaged vessel. Blood platelets first adhere to macromolecules in the subendothelial regions of the injured blood vessel; they then aggregate to form the primary haemostatic plug. Platelets stimulate local

activation of plasma **coagulation** factors, leading to generation of **fibrin clot** which reinforces the platelet aggregate plug. During wound healing the platelet aggregates and fibrin plot are degraded.

Thrombosis is a pathological process in which a platelet aggregate and/or fibrin clot intravascularly occludes the blood vessel. Arterial thrombosis may result in ischaemic necrosis of the tissue supplied by the artery. For example, myocardial Infarction (which can result to death) is due to thrombosis of the coronary artery which supplies blood to the heart muscle.

Drugs which prevent clot formation are generally referred to as **anticoagulants**. These include **heparin**, **warfarin**, **dicoumarol**, **phenprocoumon**, **Indan-1,3-dione**, **acenocoumarol** and **anisindione**.

The mechanism of blood coagulation is predicated on the activation of either an **intrinsic** pathway (a relatively slow process of **clot** formation) or the extrinsic pathway with a faster rate of **Fibrin** formation. A summary of the processes involved in blood clot formation is as depicted in Figure 13 and Table 7.

The intrinsic pathway of blood coagulation occurs from the interaction of blood circulating **factors**. Activation is sequel to blood coming in contact with damaged vessel wall or foreign substance. The plasma circulating blood factors are present as native inactive proenzymes, with the exception of Factor III (tissue **thromboplastin**).

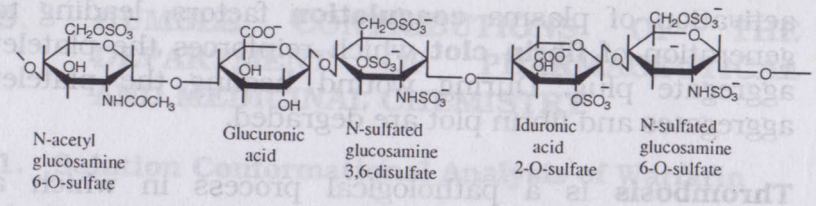


Fig. 13a: The antithrombin-binding structure of heparin

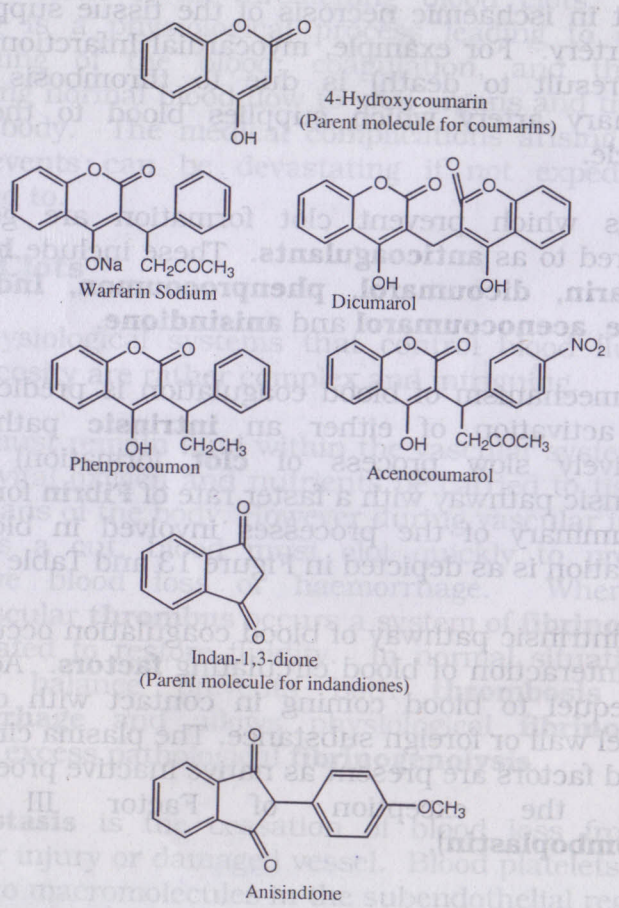


Fig. 13b: Structural formulae of the oral anticoagulants

TABLE 7: The Roman Numerical Nomenclature of Blood-Clotting Factors and Some Common Synonyms[7]

Factor	Synonyms
I	Fibrinogen
II	Prothrombin
III	Thromboplastin; tissue factor
IV	Calcium
V	Proaccelerin; accelerator globulin; labile factor
VI	(This number is not now used)
VII	Proconvertin; stable factor; autoprothrombin I, SPCA
VIII	Antihaemophillic factor; antihaemophillic globulin; platelet Cofactor I; antihaemophillic factor A
IX	Plasma thromboplastin component (PTC); Christmas factor; platelet cofactor II; autoprothrombin II; antihaemophillic factor B
X	Stuart-Powder factor, Stuart Factor, autoprothrombin III
XI	Plasma thromboplastin antecedent (PTA);
XII	Hageman factor
XIII	Fibrin stabilizing factor; Fibrinase Laki-Lorand factor

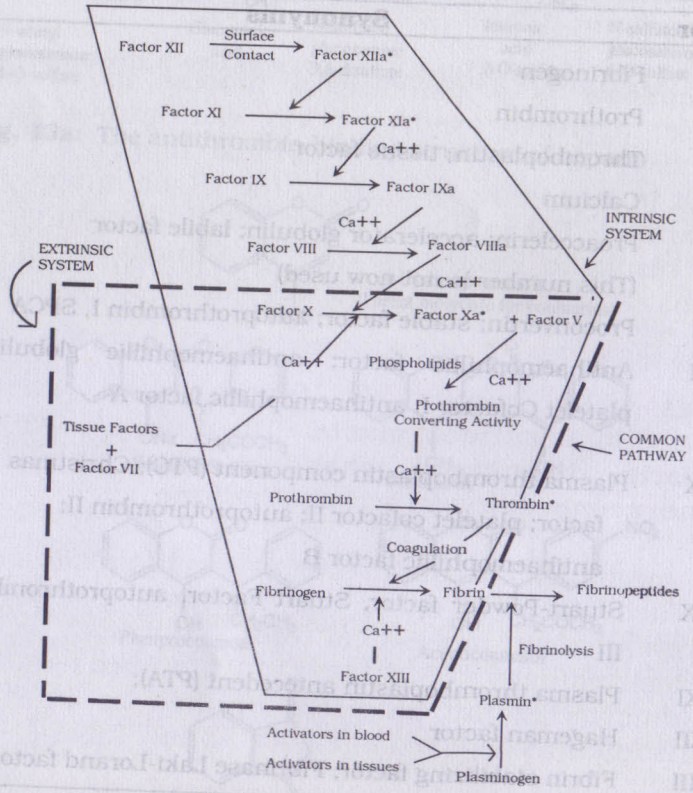


Fig. 14: Scheme of blood coagulation and fibrinolysis. Reactions enclosed by the solid line are of the "intrinsic system," while those enclosed by the dotted lines are of the "extrinsic system." The asterisk denotes a serine protease.[7]

The factors (except **fibrinogen**) are activated by the enzymic removal of a small peptide in the cascade of sequential events leading to clotting.

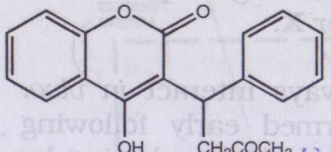
The extrinsic clotting system involves a mechanism by which **thrombin** is generated in plasma after the addition of tissue extracts. When various tissues such as brain or lung (containing **thromboplastin**) are added to blood, a complex between thromboplastin and factor **VII** in the presence of calcium ions activates factor **X**, thereby bypassing the time-consuming steps of the intrinsic pathway which form factor **X**.

The intrinsic and extrinsic pathways interact *in vivo*. Some amounts of **thrombin** formed early following stimulation of extrinsic pathway accelerate clotting by the intrinsic pathway by activating factor **VIII**. **Thrombin** also speeds up the clotting rate by activation of factor **V** located in the common pathway.

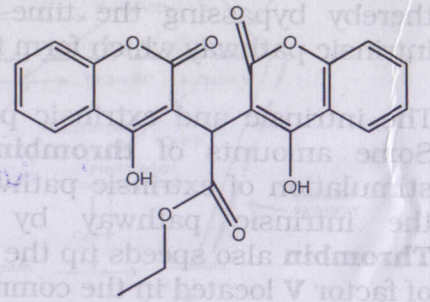
Thrombin then converts the soluble protein, **fibrinogen**, into an insoluble **fibrin gel** and also activates factor **XIII**, which stabilizes the **fibrin** gel in the presence of calcium by inducing the formation of cross-linking between the chains of the fibrin monomer.

In 1943 the Nobel Prize for Physiology and Medicine went to Denmark's Henrik Dam and Edward Doisy of the USA for their characterization of vitamin K — so named because a lack of this vitamin causes a defect in blood **Koagulation** (the Scandinavian spelling). The immediate benefit of this discovery was that fatal bleeding and deaths in infants as a result of vitamin **K** deficiency was now averted by administering vitamin K to pregnant women and newborns.

Meanwhile it had been observed that cows fed with mouldy sweet clover hay all died as a result of bleeding. It was Karl Link who in 1940 identified the fungal coumarin product — **dicoumarol**, which antagonized vitamin **K**. Dicoumarol became the template for the discovery of **Warfarin** as a potent medicinal drug. Link coined "**warfarin**" after the **W**isconsin **A**lumni **R**esearch **F**oundation, to which he assigned the patent rights. (Evan Sadler – 2004).



Warfarin



Dicoumarol

Vitamin **K** deficiency impairs blood clotting by preventing the carboxylation of essential glutamic acid residue in several blood clotting proteins. Usually, the carboxylation reaction is catalyzed by vitamin K-dependent **carboxylase**, which uses oxygen and a reduced form of vitamin K to add a molecule of **carbon dioxide** to glutamic acid, producing γ-carboxyglutamic acid. This modification facilitates the binding of calcium ions on to clotting factors which now associate with membrane surfaces to initiate clotting of blood.

Vitamin K 2,3-epoxide, an important byproduct of this catalytic pathway, is recycled to reduced vit. **K** by vit. **K** epoxide reductase.

Warfarin brings about its anticoagulant activity by inhibiting the activity of vit. K epoxide reductase thereby breaking the cycle of events leading to **blood clotting**.

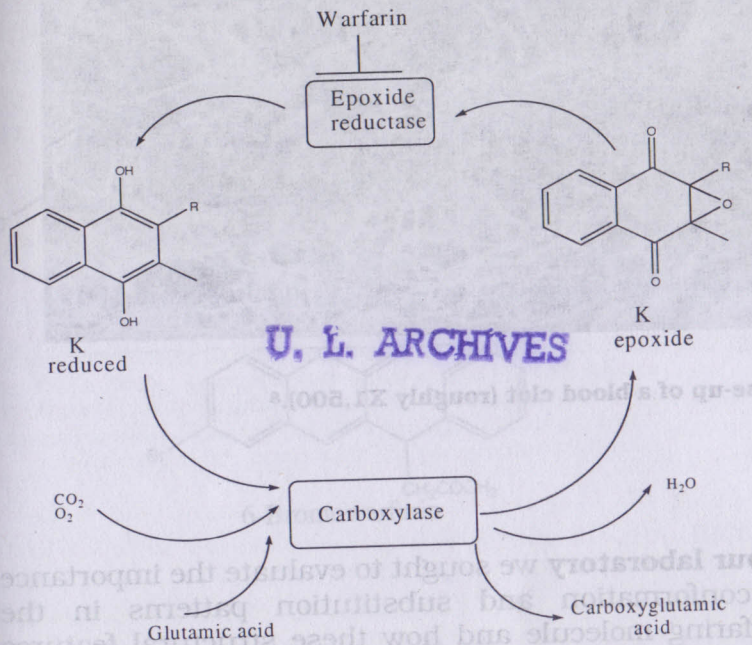
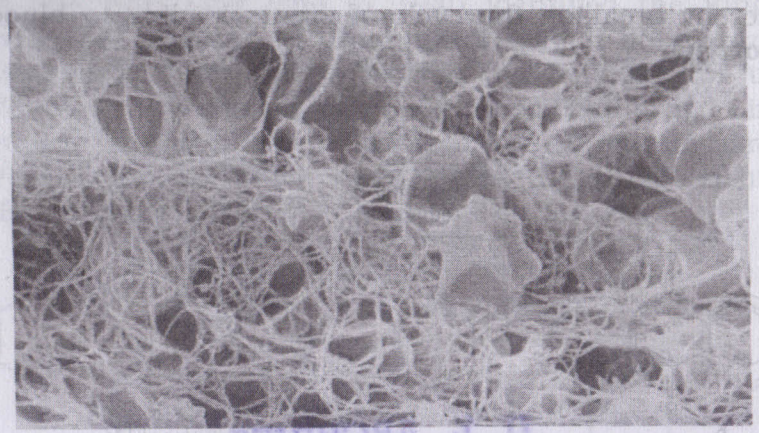


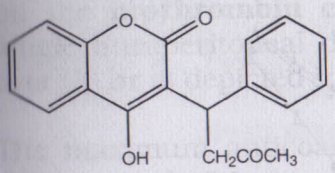
Fig. 15: The vitamin K cycle, Vitamin-K-dependent carboxylase uses reduced vitamin K and oxygen to add a carbon dioxide molecule to the side chain of glutamic acid in certain blood-clotting proteins, producing γ-carboxyglutamic acid and vitamin K 2,3-epoxide. Vitamin K epoxide reductase regenerates reduced vitamin K for another cycle of catalysis. **Warfarin** inhibits the reductase, impairing the synthesis of clotting factors. A deficiency in multiple clotting factors can also be caused by mutations in either vitamin-K-dependent carboxylase or epoxide reductase.



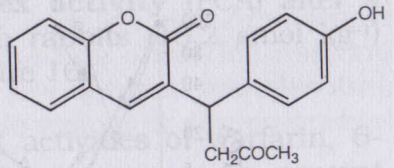
Close-up of a blood clot (roughly X1,500).[8]

In **our laboratory** we sought to evaluate the importance of conformation and substitution patterns in the warfaring molecule and how these structural features affect the anticoagulant activity of warfarin, using the laboratory rabbit as animal model.[7]

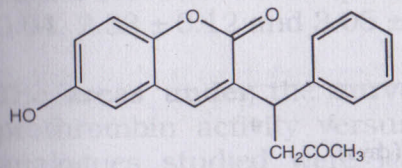
We employed the following compounds – warfarin, 4′-hydroxywarfarin, 6-hydroxywarfarin, 7-hydroxywarfarin, 8-hydroxywarfarin, 6-chlorowarfarin and 6-Bromowarfarin.



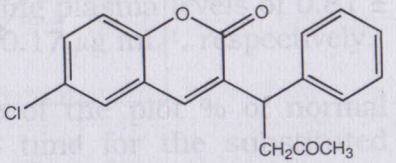
Warfarin



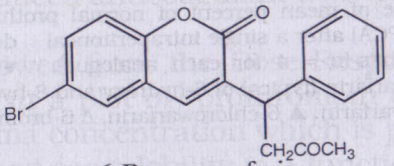
4'-Hydroxywarfarin



6-Hydroxywarfarin



6-Chlorowarfarin



6-Bromowarfarin

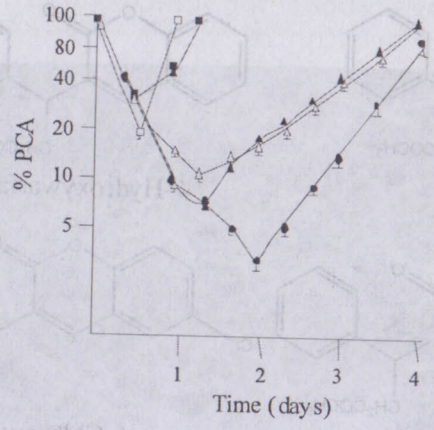


Fig. 16: Time course of mean percent of normal prothrombin complex activity (% PCA) after a single intraperitoneal dose (16.2 μmol kg^{-1}) in rabbits (n = 4 for each analogue): • (±)-warfarin, ◙ 7-hydroxywarfarin (typical of 6-hydroxy and 8-hydroxywarfarin), , 4'-hydroxywarfarin. ▲ 6-chlorowarfarin, Δ 6-bromowarfarin.

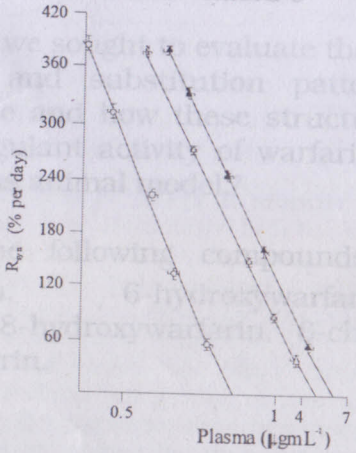


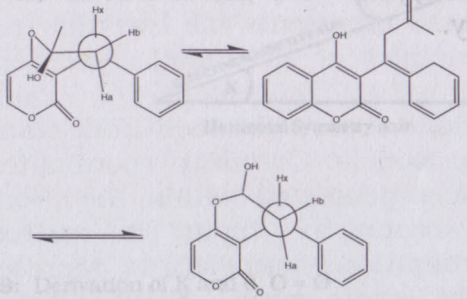
Fig. 17: Mean synthesis rate of prothrombin complex activity as a function of plasma concentration in rabbits (n = 4): O (±)-warfarin, Δ 6-chlorowarfarin, ▲ 6-bromowarfarin.

The mean time course of the effect of these analogues on the **prothrombin complex activity** (PCA) after a single intraperitoneal dose in rabbits (16.2 μmol kg^{-1}) over 96 hr is depicted in (Figure 16).

The maximum anticoagulant activities of warfarin, 6-chloro- and 6-bromowarfarin expressed as percent normal prothrombin activity were 3.1 ± 0.2, 6.0 ± 0.4, 10.2 ± 0.5% with corresponding plasma levels of 0.81 ± 0.04, 2.33 ± 0.12 and 3.05 ± 0.17 μg mL^{-1}, respectively.

The **areas under** the **curve** of the plot % of normal prothrombin activity versus time for the substituted analogues studied were less than that of **warfarin**. ($P<0.05$), indicating that **substituents** on the warfarin molecule reduced anticoagulant activity.

We also showed from the Dose-Response relationship as depicted in a plot of "prothrombin complex activity" versus plasma concentration which is predicated on the fact that blood coagulability is a function of the rates of clotting factor synthesis (Rsyn) and degradation (Rdeg) in the body, it becomes obvious that when Rsyn (a measure of potency) is correlated with log of analogue plasma concentration, halogenation (6-chloro-and 6-bromo) significantly reduces the 'real' anticoagulant activity of warfarin; plots are shifted to the right (Figure 17).



Scheme I: Solution conformation and rotamer average of Warfarin.

From all indications it was obvious that stereochemically speaking a perfect conformational "fit" between substrate and enzyme receptors for optimum anticoagulant activity was provided by the **intact** 4-hydroxycoumarin moiety of **warfarin** itself.

Since its discovery and introduction into medicine warfarin has remained the most widely prescribed anticoagulant drug to date.

As a matter of fact science literature has it that when US President Dwight Eisenhower had a heart attack in 1955, warfarin came to the rescue.

We had also explored the possibility of using **nuclear magnetic resonance** (nmr) studies at unraveling solution conformations of Coumarins and guaiacol ethers. Advantage was taken of the fact that the lanthanide shift reagent, $Eu(fod)_3$ could complex with certain electron-rich centres of organic compounds. The induced paramagnetic shifts experienced by protons on the nmr time scale in the organic substrates can be used to compute the solution conformations of these compounds.

We synthesized a series of substituted coumarins, guaicol ethers, diguaicol ethers and subjected these to conformational analysis with the aid of $Eu(fod)_3$ and nmr spectroscopy.

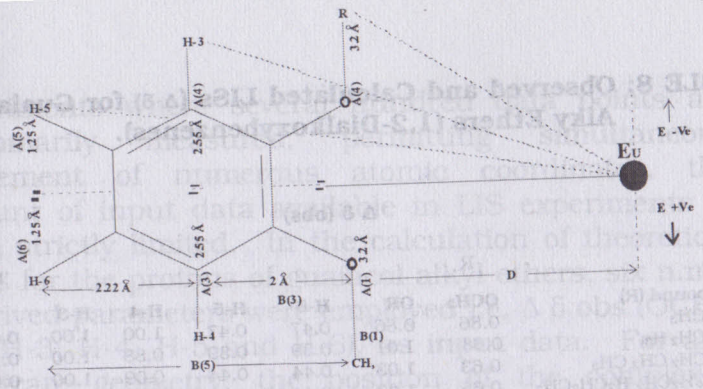


Fig. 18: Representation of two-dimensional E complex of 1,2 dialkoxybenzene and Eu (fod).

A (1) = Distance of R from midline, 3.2Å.
A (2) = Distance of CH_3 from midline, 3.2 Å.
A (3) = Distance of H-3 from midline, 2.55 Å.
A (4) = Distance of H-4 from midline, 2.55 Å.
A (5) = Distance of H-5 from midline, 1.25 Å.
A (6) = Distance of H-6 from midline, 1.25 Å.
B (1) = 0, i.e. R—— CH_3 Line
B (3) = 2 Å Distance from H-3: H-4 ⟷ R: CH_3.
B (5) = 4.22 Å, Distance from H-5: H-6 ⟷ R: CH_3.

These parameters were employed in the programme E.U.F.-4.

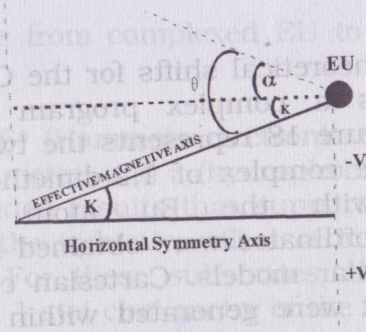


Fig. 19: Derivation of K and θ, O = Ø

TABLE 8: Observed and Calculated LISs (Δ δ) for Guaiacol Alky Ethers (1,2-Dialkoxybenzenes).

Δ δ (obs)

Compound (R)	R						'R'
	OCH_3	OR	H-6	H-5	H-4	H-3	
1. – CH_3	0.86	0.86	0.47	0.47	1.00	1.00	**0.01**
2. – CH_2H_3	0.63	1.01	0.39	0.39	0.88	1.00	**0.14**
3. – $CH_2CH_2CH_3$	0.63	1.03	0.44	0.44	0.09	1.00	**0.03**
4. – CH_2CH_2 $H_2CH_2CH_3$	0.65	1.03	0.44	0.44	0.86	1.00	**0.11**
5. – CH_2 $(CH_2)_4$ CH_3	0.61	1.06	0.41	0.41	0.88	1.00	**0.13**
6. – $CH(CH_3)_2$	0.32	1.29	0.33	0.33	0.70	1.00	-
7. – $CH_2CH(CH_3)_2$	0.38	1.02	0.41	0.41	0.83	1.00	**0.12**
8. – $C\text{-}(CH_3)_2$	0.06	1.25	0.44	0.44	1.0	1.00	-
9. – $CH_2CH\text{-}CH_2$	0.67	0.97	0.41	0.41	0.90	1.00	**0.04**
10. – $CH_2C_6H_3$	0.59	0.90	0.40	0.40	0.85	1.00	**0.04**

Δ δ (calc.)

Compound (R)							'R'
	OCH_3	OR	H-6	H-5	H-4	H-3	
1. – CH_3	0.86	0.86	0.51	0.51	0.00	0.00	**0.01**
2. – CH_2H_3	0.63	1.05	0.59	0.57	1.07	1.00	**0.14**
3. – $CH_2CH_2CH_3$	0.63	1.01	0.54	0.55	1.01	1.00	**0.03**
4. – CH_2CH_2 $H_2CH_2CH_3$	0.65	1.06	0.59	0.57	1.07	1.00	**0.11**
5. – CH_2 $(CH_2)_4$ CH_3	0.61	1.07	0.62	0.61	1.06	1.00	**0.13**
6. – $CH(CH_3)_2$	-	-	-	-	-	-	-
7. – $CH_2CH(CH_3)_2$	0.36	1.06	0.57	0.59	1.04	1.00	**0.12**
8. – $C\text{-}(CH_3)_2$	-	-	-	-	-	-	-
9. – $CH_2CH\text{-}CH_2$	0.67	0.82	0.54	0.55	0.96	1.00	**0.04**
10. – $CH_2C_6H_3$	0.59	0.80	0.51	0.54	0.88	1.00	**0.04**

In computing theoretical shifts for the Coumarins and guaiacol ethers a complex program E.U.F.-4 was employed. Figure 18 represents the two dimensional structure of the complex of 1,2-dimethoxybenzene in coordination with the Eu atom of $Eu(fod)_3$. Interactomic coordinates were obtained from standard Dreiding molecular models. Cartesian coordinates for the LS complex were generated within the program, EUF-4, which accepts as input a matrix of bond lengths, coordination parameters as represented in Figure 19. Unlike single-crystal X-ray diffraction

experiments where several hundred data points are customarily measured, permitting simultaneous refinement of numerous atomic coordinates, the amount of input data available in LIS experiments is often strictly limited. In the calculation of theoretical shifts for the protons of guaiacol alkyl ethers, six n.m.r - derived parameters were employed i.e. Δ δ obs (OCH_3, OR, H-3, H-4, H-5 and H-6), as input data. For any substrate geometry, the position of the complexed lanthanide, EU, was varied with respect to the horizontal distance D, the vertical distance E, and the angle of "approach", Ø, (i.e. the angle which the effective magnetic axis makes with the symmetry axis) to give a "best fit" between calculated and observed data (Table 7).

For each position of Eu, theoretical shifts were evaluated from the McConnell-Robertson equation.

$$\Delta\delta \text{ calc.} = K_{ax}\left(\frac{3\cos^2\theta - 1}{r^3}\right) + K_{nonax}\left(\frac{\sin^2\theta \cos 2\emptyset}{r^3}\right)$$

r_H is the distance from complexed EU to a particular nucleus.

Various plots of 6* (Hammets electronic constant), Es (Taft's steric parameter) and π (hydrophobic parameter) versus Δ δ B yielded results that support the findings that the greater the inductive effect of R, the less the shift of OCH_3. For these substrates, the important assumption of 1 : 1 stoi-cheiometry of the L : S complex was made. However the assumption of magnetic axiality of the electronic 'g' tensor in the L : S complexes is questionable.

$$\text{Log } \frac{1}{C} = K_1\pi - K_2\pi^2 + K_3\sigma + K_4Es + K_5$$

C = effective concentration eliciting Biological Response

π = governs lipophillic nature of drug during pharmacokinetic movement of drug from point of administration to receptor site

π^2 = governs lipophillic component at pharmacodynamic interaction of drug and receptor protein

σ = electronic component of pharmacodynamic phase

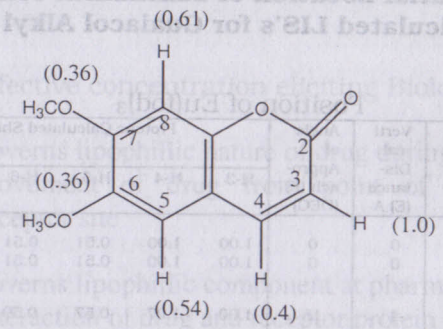
Es = steric component of pharmacodynamic phase

$$\text{'R'} = \left[\frac{(\delta \text{ obs} - \delta \text{ calc.})^2}{(\delta \text{ obs})^2} \right]^{1/2}$$

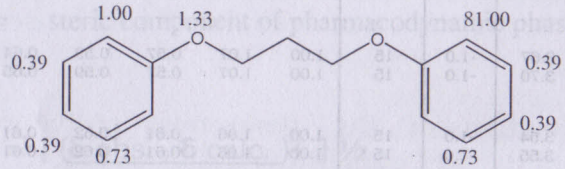
TABLE 9. Spatial Location of Lanthanide Ion and Calculated LIS's for Guaiacol Alkyl Ethers

Position of $Eu(fod)_3$

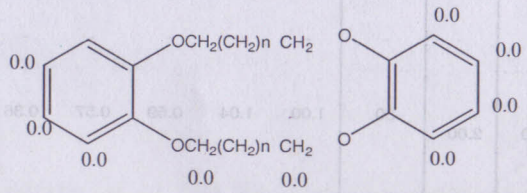
	Horizontal Position (D) A	Vertical Distance (E) A	Angle of Approach (K) (DEG)	Protonc Calculated Shifts Δ δ C					
				H-3	H-4	H-5	H-6	OCH.	OR
1. Veratrole	3.88 3.90	0 0	0 0	1.00 1.00	1.00 1.00	0.51 0.51	0.51 0.51	0.86 0.86	0.86 0.86
2. Guaicol Ethyl Ether	3.66	-1	15	1.00	1.07	0.57	0.59	0.63	1.05
3. Guaiacol N-Propyl Ether	3.8	-1.75	20	1.00	1.01	0.55	0.54	0.63	1.01
4. Guaiacol N-Pentyl Ether	3.67 3.70	-1.0 -1.0	15 15	1.00 1.00	1.07 1.07	0.57 0.57	0.59 0.59	0.64 0.65	1.05 1.06
5. Guaiacol N-Octyl Ether	3.54 3.55	-1.0 -1.0	15 15	1.00 1.00	1.06 1.06	0.61 0.61	0.62 0.62	0.61 0.61	1.07 1.07
6. Guaiacol Iso-Propyl Ether	-	-	-	-	-	-	-	-	-
7. Guaiacol Iso-Butyl Ether	3.60	-2.00	30	1.00	1.04	0.59	0.57	0.36	1.06
8. Guaiacol T-Butyl Ether	-	-	-	-	-	-	-	-	-
9. Guaiacol Allyl Ether	3.40 & 3.41	-0.75	10	1.00	0.96	0.55	0.54	0.67	0.82
10. Guaiacol Benzyl Ether	3.39 & 3.40	-1.50	20	1.00	0.88	0.54	0.51	0.59	0.80



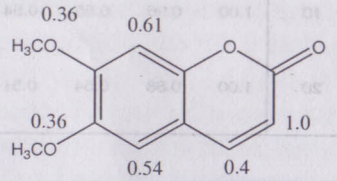
Relative shifts (Δ δ obs) for proton substituents of scoparon.



(II) Diguaiacoloxyalkane



(III) Dibenzotetraoxacyclodecadiene



(IV) 6,7-Dimethoxycoumarin

Fig. 20: Δ δ (obs) for substituents of compounds II, III and IV.

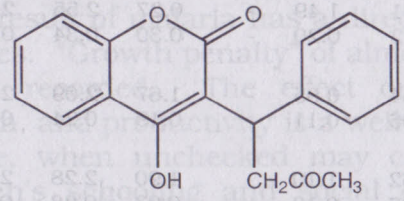
The complexation mode between $Eu(fod)_3$ and diguaiacol ethers was bidentate and simultaneous at both O-ether groups. No complexation was observed for the **diebenzotetraxocyclodecadienes**, and this was attributed to severe steric constraints to the approach of $Eu(fod)_3$.

The **Coumarins** demonstrated complex binding patterns allowing for intramolecular competitive binding between the carbonyl function and the ethereal function.

With the aid of more refined programmes incorporating numerous coordinates and cartesian parameters we were able to determine preferred conformation of the molecules, population analysis and species stoicheiometry during binding phenomenon.

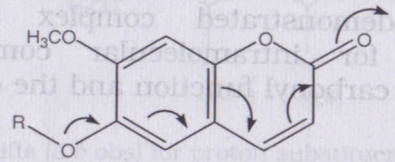
The results so obtained demonstrate that given the aggregate contribution of **electronic**, **steric** and **solubility** factors most of the substituents adopt in-plane rather than out-of-plane conformation.

From all indications, for **optimum anticoagulant activity** the preferred solution conformation, that is the probable rotamer average of **warfarin** is the graphical structure shown below.



Warfarin

TABLE 10: Bound (δ B) and observed (δ obs) shifts for 6-alkoxy-7-methoxycoumarin derivatives during interaction with Eu(fod)$_3$. δ B values were computed from points within L_o/S_o = 0.4. δ B (H-3) is assigned the value of 1, and other proton shifts (δ B) expressed relative to H-3, i. e. δ obs.



Compound (R)	OCH_3	OR	H-6	H-5	H-8	H-4	H-3	δ
CH_3	2.68	2.68	-	3.95	4.18	2.59	6.21	δ B
	0.43	0.43	-	0.63	0.67	0.41	1.00	δ obs
Et.	1.22	1.91	-	2.60	2.73	2.41	7.32	
	0.16	0.26	-	0.35	0.37	0.32	1.00	
n-Pr.	0.9	1.43	-	2.20	2.52	2.45	7.50	
	0.12	0.19	-	0.29	0.33	0.32	1.00	
n-Bu.	0.96	1.54	-	2.34	2.70	2.63	8.24	
	0.11	0.18		0.28	0.32	0.31	1.00	
n-Pen.	0.73	1.42	-	2.13	2.43	2.36	7.27	
	0.10	0.19	-	0.29	0.33	0.32	1.00	
n-Oct.	0.91	1.49	-	0.27	2.55	2.43	7.45	
	0.12	0.20	-	0.30	0.34	0.32	1.00	
iso-Pr.	0.54	0.95	-	1.67	2.09	2.53	8.38	
	0.06	0.11	-	0.19	0.24	0.30	1.00	
iso-Bu.	0.62	1.10	-	1.90	2.28	2.49	8.05	
	0.07	0.13	-	0.23	0.28	0.30	1.00	
Allyl-	1.22	1.79	-	2.46	2.75	2.36	6.84	
	0.17	0.26	-	0.35	0.40	0.35	1.00	
Herniarin	0.59	-	1.2	0.69	2.28	2.70	9.02	
(RO = H)	0.06	-	0.13	0.18	0.25	0.29	1.00	

10. THE MALARIA SCOURGE

The malaria scourge continues to remain a vexatious issue inspite of the efforts of the World Health Organisation (WHO), and the United Nations Children's Education Fund (UNICEF) through various eradication programmes.

The disease's occurrence traverses the entire tropical and subtropical regions of the world.

It is estimated that there are about **300 million acute cases** of malaria each year globally, resulting in more than **a million deaths**. About 90% of these deaths occur in Africa, and mostly in young children.

Malaria is Africa's leading cause of under-five mortality (20%) and constitutes 10% of the continent's overall disease burden. It accounts for about 40% of public health expenditure, 30 – 50% of inpatient admissions, and up to 50% of outpatient visits to the hospital.

Malaria has been estimated to cost Africa more than US $10 billion every year lost in GDP and presents major obstacles to social and economic development.

Morbidity as a result of malaria has a direct impact on human resources. "Growth penalty" of almost 1.5% per year has been recorded. The effect on GDP and economic growth, and productivity is a well-known fact. Malaria disease, when unchecked may cause death, hamper children's schooling and social development through both absenteeism and permanent neurological disorders associated with severe episodes of malaria.

Malaria, together with HIV/AIDS and TB, is one of the major public health challenges undermining

development going by the high morbidity and mortality rates especially in children.

The disease in the developing countries is a disease of poverty and the cause of poverty. It is responsible for potential medical complications such as low birth weight in infants, increase in unexplained sudden abortion and stillbirths by pregnant women, resulting from malaria during pregnancy.

Concern for this debilitating scourge galvanized some political commitment by African Leaders for action on Malaria and this led to the founding of the Roll Back Malaria (RBM) global partnership in 1998. In the year 2000 African Heads of State met in Abuja Nigeria to further strengthen the RBM's goal of reducing the African malaria burden to less than 40% by the year 2010. The Abuja declaration signed in April 2000 endorsed a concerted strategy to tackle the problem of malaria across the entire Africa.

We must commend the Federal Ministry of Health for restrategising efforts at meeting the challenges posed by this disease scourge headlong.

Professor Eyitayo Lambo, the Honourable Minister of Health, Dr. Mrs Edugie Abebe, the Director of Public Health, and Dr. Mrs O.G. Sofola, coordinator of the Roll Bank Malaria initiative must be commended for the progress made so far in stemming the march of malaria on Nigeria.

The Federal Ministry of Health in collaboration with WHO and UNICEF has embarked on certain intervention measures meant to create awareness in Nigeria of possible preventive measures, and reduction of the disease burden.

Some of the steps already taken include:

- provision of insecticide treated mosquito nets (ITNs) and making them affordable by encouraging Government to reduce the tariffs on the ITNs.
- encouraging local production of quality long – lasting ITNs.
- establishment of Country Strategic Plans (CSP)
- organizing public enlightenment campaigns in various areas of the country
- embarking on improved vector control and other associated environmental measures.
- prompt access to effective treatment by all citizens plagued by the malaria disease.
- prevention and effective management of malaria in pregnancy.

The resolve and courage of the ministry chieftains in encouraging the government and people of Nigeria in adopting the change in drug treatment policy along with WHO, UNICEF and the malaria world deserve our collective support. In the face of overwhelming evidence, the Ministry of Health has created an enabling environment whereby to avert **catastrophy** arising from treatments failure due to parasite resistance to commonly used drugs, Artemisinin-based combination Treatments (ACTs) have been strongly proposed.

Combinations such as **Artemisinin + Amodiaquine** and **Artemisinin + Lumefantrine** have been shown to return about 98% efficacy.

The ministry has also taken measures aimed at making the ACTs affordable by the ordinary citizen. There are also plans to encourage the different zones of Nigeria

start cultivating *Artemisia annua* (Quinqhaosu plant), to provide ready availability self-sufficiency in the processing of **arteminsinin** from the natural source.

In its usual and characteristic manner the Minister and his lieutenants have involved all stakeholders, including all relevant professional bodies and the Pharmaceutical Manufacturers Group of Nigeria in the transition implementation committee to assist the government in this compelling and onerous task of reducing the malaria disease burden in Nigeria.

Chemotherapeutic Interventions

Drug resistance is the greatest challenge facing Africa and Nigeria in the fight against malaria.

Antimalarial drugs in current use include Chloroquine, Amodiaquine, Quinine, the antimebolites or antifolates (Fansidar = Sulphadoxine + pyrimethamine SP), Holofantrine, Mefloquine, Artemisinin, Artemether Artesunate, Dihydroarteminsinine (DHA).

In the event of problems arising from treatment failure and idiosyncratic adverse drug reactions, certain drug combinations could be considered.

Fasimef (mefloquine + salphadoxine + Pyrimethamine)
Malarone (atovaquone + Proquanil)
Quinine + Tetra cycline
Quinine + Doxcycline
Lapdop (dapsone + Proquanil)

Classification of Treatment Outcome

- ❒ Early Treatment Failure (ETF)
- ❒ Late Treatment Failure (LTF)
- ❒ Adequate Clinical Response (ACR)
- ◆ Late Parasitological Failure (LPF)

Adequate Clinical and Parasitological Response (ACPR)

National Antimalarial DET: Study Outcome - Chloroquine

	Calabar	Enugu	Ibadan	Jos	Kaduna	M'duguri
Number analysed	44	54	44	47	53	59
ETF - No.	10	27	9	1	3	5
%	22.7	50	20.5	2.1	5.7	8.5
LTF - No.	12	2	7	8	6	3
%	27.3	3.7	15.9	17.0	11.3	5.1
ACR - No.	22	25	28	38	44	51
%	50	46.3	63.6	80.9	83.0	86.4
LPF - No.	18	23	10	13	3	21
%	40.9	42.6	22.7	27.7	5.7	35.6
ACPR-No.	4	2	18	25	41	30
%	9.1	3.7	40.9	53.2	77.3	50.8

Courtesy: L. A. Salako et al.

National Antimalarial DET: Study Outcome - FANSIDAR

	Calabar	Enugu	Ibadan	Jos	Kaduna	M'duguri
Number analysed	47	47	45	52	52	54
ETF - No.	10	17	2	3	2.	2
%	21.3	36.2	4.4	5.8	3.8	3.7
LTF - No.	6	2	2	1	1	3
%	12.8	4.3	4.4	1.9	1.9	5.6
ACR - No.	31	28	41	48	49	49
%	65.9	59.6	91.1	92.3	94.2	90.7
LPF - No.	27	21	7	5	0	14
%	57.4	44.7	15.6	9.6	0	25.9
ACPR-No.	4	7	34	43	49	35
%	8.5	14.9	75.6	82.7	94.2	64.8

Courtesy: L. A. Salako et al.

Chloroquine has been the most effective drug against malaria disease for over 5 decades. Current statistics show that the efficacy of chloroquine in malaria management has waned below 40% in Nigeria, due to acquired resistance by the offending parasite, plasmodium falciparum.

Results emanating from pilot studies carried out in the six geopolitical zones in Nigeria painted a very gloomy picture for chloroquine medication.

The second line antimalarial medication sulphdoxine-pyrimethamine (SP) combination, was also reported to have suffered serious knocks.

The introduction of newer chemotherapeutic agents have not helped much, and are plagued by one demerit or the other.

The Roll Black Malaria Initiative appears to be the most ambitious of all the eradication programmes mounted by the WHO, UNICEF and concerned country living in malarious regions of the world.

Newer treatment guidelines and chemotherapeutic interventions were to usher in the Arthemisinin – based combination therapies (ACTs) which include the use of Artesunate + Amodiaquine Artemether + Lumefantrine

The advantages of this mode of chemotherapy include:

- established high efficacy, as a result of rapid reduction of parasite population and fever abatement. Artesunate is a rapid membrane acting antiplasmodial (including merozoites, trophozoites and parasite qametocites); Amodiaquine is a highly effective schizontocide (erythrocytic forms).
- rapid resolution of clinical symptoms
- effective against multidrug- resistant plasmodium falcipara
- adverse drug reactions to the Artemisinin are very few.
- Artemisinin combination therapies (ACTs) are a classical case of **therapeutic synergism.**
- Chloroquine combined with Artemisinin would not be favoured for obvious reasons of cross - resistance.

Malaria and the Drug Resistance Phenomenon

Chloroquine has remained the first line drug in the management of malaria for over five decades. Its success and usefulness are attested to by the avalanche of published research works and books on chloroquine.

The World Health Organization posits that plasmodial drug resistance is the ability of a parasite strain to survive and / or multiply despite the administration and absorption of a drug given in doses equal to or higher than those usually recommended but within the limits of tolerance of the subject.

The main mechanisms advanced so far for the development of chloroquine resistance in *p. falciparum* include: drug pressure effect, extensive use of subcurative doses, transmigration and increased virulence of the resistant parasites.

Chloroquine resistance in malaria infection stems from the fact that chloroquine **resistant plasmodia** accumulate significantly less chloroquine than do **susceptible strains**, arising from rapid efflux of chloroquine from the resistant parasite. And where efflux far exceeds influx of chloroquine, steady state sublethal chloroquine concentrations subsist, a condition favouring survival and thriving of the parasites.

There is also the strong suggestion that mutation of the plasmodium probably results in the alteration of the parasitized **red blood cell** (rbc) membrane receptors, thus leading to reduced binding affinity for chloroquine: hence the markedly reduced uptake of chloroquine by the **rbcs** infected by the chloroquine – resistant parasite.

Some malariologists have attributed the enhanced chloroquine efflux from the **rbcs** infected by the CQ – resistant parasite to the mediating influence by a multiple drug resistance (mdr) protein, or p-glycoprotein as obtains in some drug resistant cancer cells. This observation was predicated on the fact that **verapamil**, known to reverse drug resistance in cancer cells by interfering with the activity of the mdr – glycoprotein, was found to reverse chloroquine resistance in-vitro in *P. falciparum* malaria.

Chloroquine resistant strains of *P. falciparum* tend to demonstrate one biological advantage over chloroquine susceptible strains by virtue of preferential or exclusive survival in the absence of drug pressure. Resistance once acquired is transmitted to progeny in accordance with mendelian genetics, when homologous or cross-fertilization of susceptible and resistant gametes occurs in the stomach of the mosquito. The fusion of gametes resistant to two different drugs may result in the presence of biresistent sporeozoites in the progeny.

Cross resistance between chloroquine, mefloquine, halofantrine and also quinine has been attributed to mutations in the pf mdr-1 and also the presence of parasitized RBC membrane receptors shared commonly by the drugs.

The anitmetabolites such as the Sulphonamides, Pyrimethamine, Proguanil and Cycloguanil are also known to demonstrate acquired activity lag against *P. falciparum*. These drugs are known to attack all growing stages of the malarial parasite in the erythrocyte and the hepatic apparatuses. They also show some antisporogonic activity in the mosquito.

The type 1 antifoloate sulphonamides block the biotransformation activity of the enzyme dihyropteroate synthase, DHPS, while the type IIantifolates, pyrimethamine and Cycloguanil, inhibit a second and subsequent enzyme, dihydrofolate reductase, DHFR.

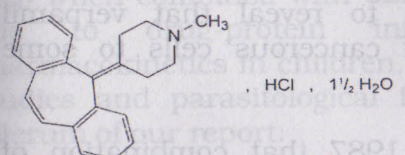
DHPS and DHPP are essential complementary enzymes and tetrahydrofolate co-factors essential for the biosynthesis of deoxythymidylate for DNA. This double sequential blockade of DHPs and DHFR as demonstrated by the antiplasmodial action of sulphadoxine / pyrimethanime is akin to what obtains in the antibacterial action or Sulphamethoxazole/Trimethoprim combination (CO-trimoxazole). It has been muted that *P. falciparum* resistance to these drugs apparently depends largely on point mutations in the DHPS and DHFR genes.

Sulphadoxine – Pyrimethamine (SDX – PM, Fansidar) for a long time proved very active against *P. falciparum* malaria as a first line antimalarial drug, with time it became a second line drug and recent reports confirm that *P. falciparum* resistance to SDX – PM is now worldwide.

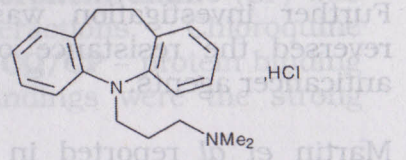
Reversal of Chloroquine Resistance

The concept of chloroquine resistance-reversal had dawned on man as far back as 1988 when Peters, Ekong, Robinson and Warhurst reporting in the annals of Tropical Medicine and Parasitology on the chemotherapy of rodent malaria observed the reversal of chloroquine resistance in rodent and human plasmodium by certain classical antihistamines – Cyproheptadine, Ketotiten, Pizotyline, Azatadine and

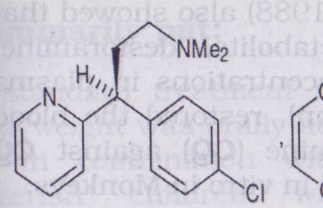
Loretidine and relatively recently promethazine and chlorpheniramine. These antihistamines were reported to have produced a marked reversal of chloroquine resistance both in-vivo and in-vitro.[8]



Cyproheptadine

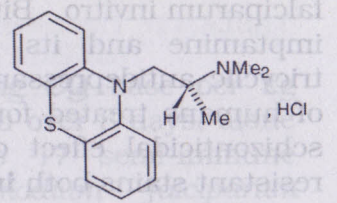


Imipramine



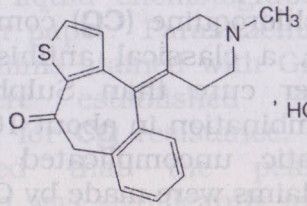
and enantiomer

Chlorpheniramine Maleate



and enantiomer

Promethazine



Ketotifen

Fig. 21: CQ-resistance reversal agents: desipramine; cyproheptadine; ketotifen; pizotyline; azatadine and loratadine.

The use of non-antimalaria compound to reverse resistance to chloroquine in *p. falciarum* may have taken a cue from the observation that certain anticancer drugs had their chemotherapeutic activity potentiated by concomitant administration with **verapamil**, an orthodox calcium blocker.

Further investigation was to reveal that verpamil reversed the resistance of cancerous cells to some anticancer agents.

Martin *et al* reported in 1987 that combination of verpamil and chloroquine inhibited the growth of p. falciparum invitro. Bitoni *et al* (1988) also showed that imptamine and its major metabolite, desipramine, tricyclic antidepressants (at concentrations in plasma of humans treated for depression), restored the blood schizonticidal effect of chloroquine (**CQ**) against **CQ** resistant stains both **in vivo** and in vitro in Monkeys.

In a more clinical setting Sowunmi, Oduola, Ogundahun and Salako reporting in the Transactions of the Royal Society of Tropical Medicine and Hygiene (1998) observed that chloroquine (**CQ**) combined with chlorpheniramine (**CP**), a classical antihistamine H_1 blocker provided better cure than Sulphadoxine – Pyrimethamine (SP) combination in about 100 children with acute symptomatic uncomplicated falciparum malaria. The same claims were made by Oduola *et al* in *American Journal of Topical Medicine and Hygiene* (1998).

The Molecular mechanisms associated with such therapeutic observations and reports were not evinced by these gentlemen.

The report of **Okonkwo**, **Coker et al**[12] in the Transactions of the Royal Society of Tropical Medicine and Hygiene (1999, 93, 306 – 311), Nig. Journ. Pharmacy (2000, 31, 30 – 34)[12], Nig. Journ. Pharm. (1999, 30, 23 – 27)[12], Okonkwo (Ph.D. Thesis)[13] showed that the enhanced antimalarial efficacy of **chloroquine** (CQ) when combined with **chlorpheniramine** (CP) was due to drug-protein interactions. Chloroquine pharmacokinetics in children, **CQ/CP** – protein binding studies and parasitological findings were the strong fulcrum of our report.

Summarily put:

A standard treatment with 25 mg **CQ** base per kg bodyweight was orally administered over 3 days, alone or in combination with **CP**, to 17 semi-immune Nigerian children with *Plasmodium falciparum* parasitaemia attending a hospital in Lagos, Nigeria, and observed for 28 days. Whole-blood **CQ** concentrations were monitored 14 times during the follow-up by high-performance liquid chemotography analysis of blood dried on filter paper. Parasitaemia was determined on thick blood films stained with Giemsa, and treatment failures were established following the WHO classification for **CQ** resistance. Our pharmacokinetic data showed that the peak whole-blood **CQ** concentration was significantly increased ($P < 0.05$) by **CP** administration, and the time to achieve the peak was reduced in the presence of CP. The area under the first-moment drug-concentration-time curve was also significantly increased ($P < 0.05$) by CP administration.

Treatment with **CQ – CP** combination resulted in a shorter parasite clearance time (2.0 ± 0.5 days) and a higher cure rate (87.5%) compared to treatment with **CQ** alone (3.5 ± 0.5 days; 66.7%). Our data suggest that **CP** enhanced the efficacy of **CQ** against resistant *P. falciparum* in acute uncomplicated malaria by increasing the uptake/concentration of **CQ** in resistant parasites.

TABLE 11: Treatment Outcome and Sensitivity Profile in Patients with Acute Uncomplicated Malaria Treated with CQ Alone

Patient Study No.	Treatment Group	Parasite Density, (per ul blood) – during 28 Days								Response Code
		Day 0	Day 1	Day 2	Day 3	Day 7	Day 14	Day 21	Day 28	
CQ1 AM 97	CQ	43,789 (100%)	641 (2.2)	475 (1.1)	33 (0.1)	-	-	-	-	S
CQ3 IQ 97	CQ	10,789 (100%)	1,925 (17.8)	N. D.	-	-	35,589+ (329.9)	297 (2.8)	-	RI
CQ4 SS 97	CQ	9,365 (100%)	N. D.	N. D.	271 (2.9)	204 (2.2)	174 (1.9)	-	-	RII
CQ12 NT 97	CQ	5,886 (100%)	827 (14.1)	570 (9.7)	45 (0.8)	-	-	-	-	S
CQ13 AK 97	CQ	48,176 (100%)	40,170 (83.4)	2,719 (5.6)						S
CQ14 SO 97	CQ	5,884 (100%)	1,220 (20.7)	420 (0.1)	-	-	-	-	-	S
CQ17 AS 97	CQ	512 (100%)	388 (75.8)	350 (68.4)	98 (19.1)	-	-	-	-	RI
CQ21 TO 97	CQ	2,640 (100%)	1,260 (47.7)	610 (23.1)	-	-	1,880 (71.2)	160 (6.4)	-	S
CQ22 BA 97	CQ	6,854 (100%)	1,680 (24.5)	220 (3.2)	-	-	-	-	-	

Values in parenthesis are percentage parasite density relative to the pre-treatment value.

TABLE 12: Treatment Outcome and Sensitivity Profile in Patients with Acute Uncomplicated Malaria Treated with a Combination of CQ-CP

Patient Study No.	Treatment Group	Parasite Density, (per ul blood)								Response Code
		Day 0	Day 1	Day 2	Day 3	Day 7	Day 14	Day 21	Day 28	
CP1 OK 97	CQ	2,563 (100%)	340 (13.3)	-	-	-	-	-	-	S
CP2 AA 97	CQ	21,327 (100%)	14,129 (17.8)	N. D.	-	-	8,280+ (85.7)	2,406 (2.8)	-	RI
CP5 DM 97	CQ	640 (100%)	-	-	-	-	- (1.9)	-	-	S
* CP6 OS 97	CQ	28,976 (100%)	7,540 (26.0)	20 (0.1)	-	-	-	-	-	S
CP7 AA 97	CQ	26,661 (100%)	8,943 (33.5)	34 (0.1)	-	-	-	-	-	S
CP9 IO 97	CQ	1,911 (100%)	69 (3.6)	-	-	-	-	-	-	S
* CP10 OO 97	CQ	4,860 (100%)	180 (3.7)	-	-	-	-	-	-	S
CP16 DD 97	CQ	26,480 (100%)	670 (2.5)	120 (0.5)	-	-	-	160 (6.4)	-	S
								-	-	S

*** Cases with history of consistent relapse after previous treatment with CQ**

Parasite Clearance Time: CQ = 3.5 ± 0.5 d Cure Rate (%): CQ Treatment 66.7%
CQ = CP = 2.0 ± 0.5 d CQ-CP Treatment.....87.5%

TABLE 13: Pharmacokinetic Quantities for Groups of Malarial Children Following Treatment with 25mg CQ Base/Kg BW Alone or in Combination with Chlorpheniramine

CQ Pharmacokinetic Parameters	CQ Group N=9	CQ – CP Group N=8	Significance Level
C_{max} (ng/mL)	819	888	P < 0.01
T_{max} (h)	2.5	2	NS
AUMC (days 0 – 28) (ng x day^2 /mL)	931,615	1,614,519	P < 0.001

[a] Data are given as mean
[b] Abbreviations:
C_{max} = Maximum drug concentration
T_{max} = Time to reach maximum concentration
AUMC = Area under the first-moment blood-level-time curve

Scatchard analysis of the **CQ – Protein** binding data demonstrated a 3-fold decrease in the affinity of **CQ** for plasma proteins.

We deduced from these results that chlorpheniramine, **CP**, enhanced the efficacy of chloroquine **CQ** *in vivo* against resistant *Plasmodium falciparum* in acute uncomplicated malaria by decreasing the affinity of CQ for binding protein sites and increasing the concentration of **free circulating CQ**.

We inferred that improved clinical response and outcome when malaria sufferers are administered the combination of CQ and CP is due to **changes** in **plasma protein binding**.

Chlorpheniramine competitively displaces Chloroquine from protein binding site by virtue of its physicochemical attributes such as pK_a and lipophilicity; thus making more chloroquine available for entry into the erythrocyte.

Chloroquine is known to be highly selective and has great affinity for parasitized erythrocytes. Chloroquine and quinine injure schizonts (trophozoites) only in erythrocytes and are harmless to exoerythroeytic schizonts and also mosquito-borne sporogenic (asexual) gametes. The clue to this differentiation seems to lie in the fact that parasitized erythrocytes concentrate these drugs about one thousand-fold. Thus a patient under chloroquine may have only 10^{-8} M of this drug in his blood stream, but as much as 10^{-3} M inside the erythrocytes.

TABLE 14a: Protein Binding Data

Day of Treatment	Total Protein P_T g/dL	Control n = 8 [CQ] ng/mL	% Bound g/dL	P_T ng/mL	CQ Group n = 9 [CQ]	% Bound g/dL	P_T ng/mL	CQ-CP Group n = 8 [CQ]	% Bound
D0	7.5	N.D	-	8.2	N.D	-	8.3	N.D	-
D1	8.1	106.7 ±27.5	58.9 ±2.2	8.6	27.17 ±12.66	85.59 ±3.62	8.5	136.88 ±29.04	85.39 ±4.09
D3	8.4	111.67 ±21.92	59.4 ±2.4	8.7	134.28 ±15.26	82.47 ±4.14	8.4	153.75 ±22.33	82.24 ±4.31
D7	8.5	155.83 ±10.96	59.2 ±3.3	8.9	31.40 ±11.57	77.93 ±2.75	8.4	66.38 ±20.96	77.45 ±3.89
D14				8.8	25.62 ±9.16	79.44 ±9.07	7.6	55.88 ±17.55	76.98 ±5.62
D21				8.2	19.0 ±6.53	75.09 ±7.86	7.3	43.0 ±15.93	72.88 ±5.9
D28				7.6	16.86 ±5.27	70.22 ±5.3	7.1	24.88 ±6.94	67.03 ±4.18

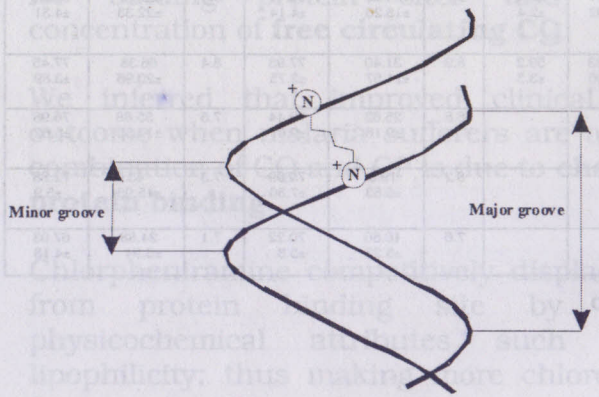
N.D.: NOT DETECTED

TABLE 14b: Kinetics of Protein Binding

Time Post-Treatment (day)	Total $(D)_T$ Drug		Bound Drug $(D)_B$		Free Drug (D)		$(D)_B$ / $(D)_T$ - B		B / (D)	
	CQ	CQ-CP	CQ	CQ-CP	CQ	CQ-CP	CQ	CQ-CP	CQ	CQ-CP
1	12717	136.88	93.23	101.70	33.94	35.18	0 733	0.743	0.0216	0.0211
3	134.28	53.75	99.23	112.08	35.05	41.67	0 739	0.729	0.0211	0.0175
7	31.40	66.38	23.69	47.395	7.71	18.985	0 754	0.714	0.0978	0.0376
14	25.62	55.88	19.33	40.35	6.29	15.53	0.754	0.722	0.1199	0.0465
21	19.0	43.0	13.99	29.97	5.01	13.03	0 736	0.697	0.1499	0.0535
28	16.86	24.88	10.47	14.60	6.39	10.28	0 621	0.587	0.0972	0.0571

Values are reported as mean concentration

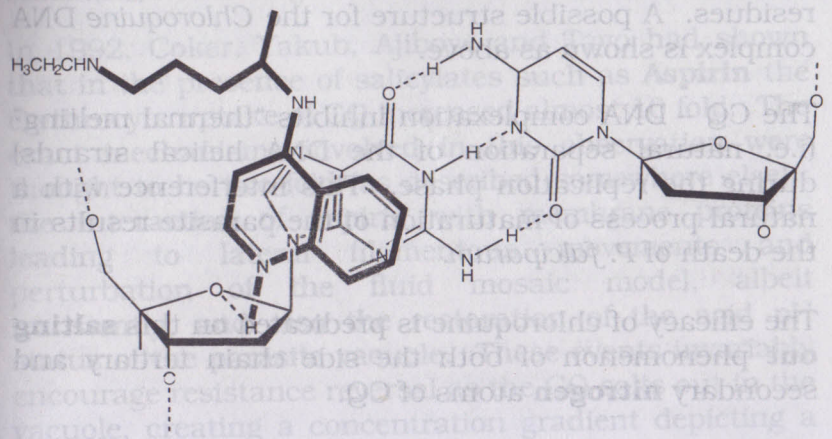
The molecular mechanism of the antiplasmodial action of chloroquine is thought to be by intercalation of the quinoline ring in the DNA in the parasite and the basic group forming and an ionic link with phosphate groups across the double helical strands of the DNA.



CQ - DNA Complex

CQ side chain nitrogen atoms ionically bonded to phosphate groups of base pairs across the helical strands of the protozoal DNA.

Chloroquine-DNA Complexation



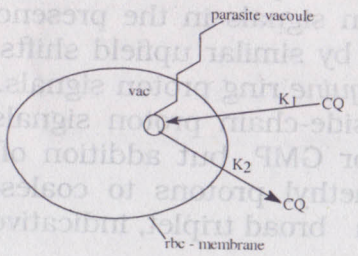
The quinoline antimalarial, *Chloroquine* is considered to act as a result of intercalation between a proportion of the base pairs of the DNA double helix, stabilized by charge-transfer interactions. ***Chloroquine* is linked primarily by ionic bonding of its diamino side-chain across the minor groove of DNA.** This, however, permits intercalation of the heteroaromatic nucleus which occurs preferentially adjacent to guanine or adenine. PMR studies have established charge-transfer interactions between *Chloroquine Phosphate* and both AMP and GMP, which support the view that DNA complexes may be similarly stabilized. Thus, both AMP and GMP show upfield shifts in the H_8, H_2 and H'_1 (ribose) proton signals in the presence of *Chloroquine*, accompanied by similar upfield shifts due to shielding of the *Chloroquine* ring proton signals. No shifts in the *Chloroquine* side-chain proton signals were seen with either AMP or GMP, but addition of ATP caused the side-chain methyl protons to coalesce from a sharp quartet to a broad triplet, indicative of electrostatic

interaction with the additional charged phosphate residues. A possible structure for the *Chloroquine* DNA complex is shown as above.

The CQ – DNA complexation inhibits "thermal melting" (i.e. natural separation of the DNA helical strands) during the replication phase. This interference with a natural process of maturation of the parasite results in the death of *P. falciparum*.

The efficacy of chloroquine is predicated on this **salting out** phenomenon of both the side chain tertiary and secondary **nitrogen** atoms of CQ.

To the biological chemist, chloroquine failure may very well be described as a situation when "salting out" state of CQ is neutralized; the CQ gets disengaged from CQ – DNA complex and is expelled from inside of the vacuole in the parasite and finally from the erythrocyte.
To avoid death, the parasite over a period of time had evolved a mechanism for preventing such CQ – DNA complexation either by enzymic action which increases the pH (alkalinisation) of the vacuole, or through gene manipulation of the DNA line expression. The resultant effect is efflux of CQ from the erythrocyte.



To the **biological chemist "Resistance"** to chloroquine medication may be described as the state in which CQ efflux ($\mathbf{K_2}$) becomes greater than influx ($\mathbf{K_1}$).

In 1992, Coker, Yakub, Ajiboye and Tayo had shown that in the presence of salicylates such as **Aspirin** the erythrocyte uptake of CQ increased almost 10 fold. The exact mechanisms involved in this observation were thought to be two-fold (as described somewhere else) : the interaction of aspirin with membrane proteins leading to lateral filamentous movements and perturbation of the fluid mosaic model, albeit transiently; and also the restoration of the acid pH status of the parasite vacuole. These events invariably encourage resistance reversal as the CQ salts out in the vacuole, creating a concentration gradient depicting a situation when $K_1 >> K_2$.

Further studies in our laboratory have shown that incorporating ascorbic acid, vitamin C, into the melieu further improves treatment outcome. Fever is cleared within 24 hours of the administration of **Vitamin C**, 1 gram daily along with **chloroquine** and **chlorpheniramine**.

The rational explanation for this observation is that Vitamin C not only makes the parasite vacuole acidic, it also acts as a powerful **antioxidant** neutralizing the effects of injurious **oxygen centred free radicals** on the thermoregulator residing in the midbrain of the central nervous system. During "malaria burst" the lysed (broken) rbc releases a host of metabolites including plasmodial merozoites, haemoglobin degenerates and a host of injurious free radicals. These along with some prostaglandins, leucotrienes and cytokines in a seeming high-energy state accentuate pyrexia (body temperature) and fever. This state of 'oxidant stress' is abolished by the concomitant presence of an **antioxidant**.

Paracetamol, an antipyretic, crashes body temperature but does not remove the causative agents of pyrexia. In feverish conditions, especially arising from malaria disease, the combined regimen of **Paracetamol** and **Vitamin C** is a far better option than paracetamol alone.

The Medicinal Chemistry Laboratory, Faculty of Pharmacy, University of Lagos posits and advises that a **better chemotherapy** for malaria is achieved by the use of the regimen.

Chloroquine + Chlorpheniramine + Paracetamol + Vit. C (Piriton)

or

Chloroquine + Piriton + Aspirin + Vit. C

However, I share in the sentiments of WHO that such regimen as posited above may not satisfy the WHO definition of Drug **Combination** Therapy.

Our laboratory proposes that the above regimen may very well be described as Chloroquine Antimalarial Enhancement Therapy (CAET).

Our regimen is effective and readily affordable. Where this regimen fails, I sincerely would recommend the physician goes for **Artesunate + Amodiaquine** or **Artemether + Lumefantrine**, in the overall interest of the patient.

These Artemisine-based Combination Therapies are classical cases of Therapeutic Synergism. I equally share in the strong sentiments that **environmental factors and vector control** hold the ace as **intervention measures** aimed at stemming the devastating march of malaria on poor Nigerians.

11. CARDIOVASCULAR CHEMISTRY

Mefloquine and Cardiovascular Apparatus

In the attempt at unraveling some of the reported untoward effects of certain antimalaria drugs. Adegunloye, Sofola and Coker have shown that **Mefloquine** at 1.6×10^{-4} mol. l^{-1} relaxed aortic rings precontracted with both **noradrenaline** (10^{-7} mol. l^{-1}) **potassium chloride**, **(kcl)**, and **calcium chloride**, **($CaCl_2$)**, in physiological salt solution.

The relaxation was attenuated by removal of endothelium. These results suggested **mefloquine** relaxes vascular smooth muscle via mechanisms which are partly **endothelium dependent**, and which is also associated with inhibition of Ca^{2+} influx from extracellular medium.

Anigbogu, Coker and Obaseki further showed that mefloquine caused a significant fall in both systolic and diastolic blood pressure in a dose dependant manner in anaesthetized rabbit. There was a more pronounced fall in mean arterial pressure in vagatomised rabbit.

These findings translate to possible cardiovascular influences, and when combined with the extra-pyrimidal CNS effects reported for **mefloquine**, physicians and pharmacists are strongly advised to exercise caution when recommending mefloquine for the treatment of acute malaria, or as prophylaxis, especially in patients with cardiac problems or people engaged in intense vocational stress.

Halofantrine, Artemether, Amodiaquine, Atovaquone, Levamisole and Fluconazole.

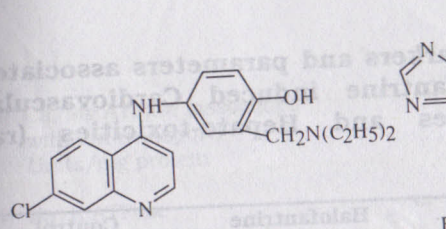
Halofantrine, a phenanthrene methanol, (Halfan) has proved very efficacious, but not without observed notable side effects. Deaths from halofantrine intake have been reported, especially in **patients with cardiac problems**. Halofantrine has been implicated in some cardiac insults resulting in torsade de pointer ventricular tachycardia and prolongation of the QT interval as reflected in electocardiograms.[15]

Certain **deaths** due to halofantrine intake in some humans with cardiac problems were definitely **avoidable**, though unwitting in nature.

In our laboratory we thought we could develop animal models, and using physiological chemistry and biochemical markers we could lend some explanation to these observed abnormalities when these drugs are in use. We were not oblivious of the fact that not all animal laboratory studies can be extrapolated to humans. But then, in **drug development**, results from animal studies are necessary **pointers** to areas needing caution and emphasis during clinical trials.

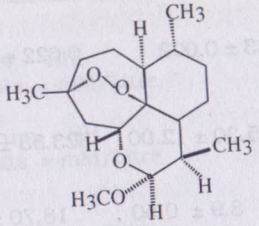
With the aid of investigational markers commonly employed in Biological Chemistry and Free Radical Chemistry we were able to monitor the influence of commonly used tropical drugs such as Halofantrine, Artemether, Amodiaquine, Levamisole Fluconazole on cardiovascular Chemistry, using rat model.

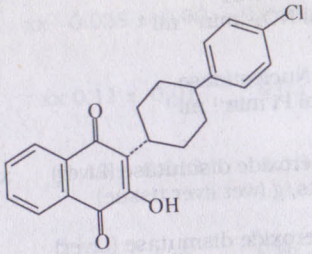
Prolonged administration of Halofantrine demonstrated significant differences in the values of these free radical markers.



FLUCONAZOLE

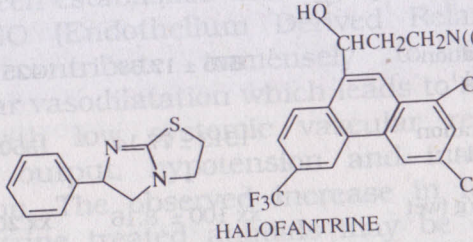
AMODIAQUINE





ATOVAQUONE

ARTEMETHER



HALOFANTRINE

LEVAMISOLE

TABLE 15: Enzyme markers and parameters associated with Halofantrine induced Cardiovascular abnormalities and Hepato-toxicities (rat model)

Parameters	Halofantrine Treated Rats	Control
(1) Serum NO_2-/NO_3- μmol NO_2-/NO_3- min^{-1} ml^{-1}	16.71 ± 0.041	78 ± 0.00
(2) Plasma NO_2- μmol NO_2- min^{-1} ml^{-1}	xx69.25 ± 0.03	23.50 ± 0.74
(3) 5'- Nucleotidase μmol Pi min^{-1} ml^{-1}	0.023 ± 0.002	0.022 ± 0.007
(4) Superoxide dismutase (Liver) Units/g (wet liver tissue)	xx 235.30 ± 12.00	323.53 ± 13.89
(5) Superoxide dismutase (Liver) Linearization method units/ml	xx 8.9 ± 0.50	18.70 ± 2.40
(6) Superoxide dismutase (Heart) units/g (wet heart tissue)	83.32 ± 24.50	71.42 ± 14.87
(7) Superoxide dismutase (Heart) Linearization method units/ml	2.13 ± 0.77	1.71 ± 0.25 n = 3
(8) Liver O_2- generation n mole min^{-1} ml^{-1}	675 ± 17.68	425 ± 40.82
(9) Heart O_2- generation n mole min^{-1} ml^{-1}	1313 ± 77.14	1350 ± 80.86
(10) Catalase/units/g (wet liver tissue)	xx 100 ± 8.16	xx 200 ± 8.16
(11 Lipid Peroxidation (x 10^{-4}) units/mg protein	0.15 ± 0.00	0.13 ± 0.00
(12) α - Amylase (associated with renal failure and uremia) Units/100ml Serum	724.16 ± 7.00	709.48 ± 9.85
(13) Ca, Mg ATPase (associated with ion transport) Units/mg protein	0.26 ± 0.010	0.31 ± 0.041
(14) Na, K ATPase Units/mg protein	xx 0.42 ± 0.013	0.49 ± 0.11
(15) NADPH-Cytochrome C reductase Units/mg protein	xx 0.16 ± 0.009	0.12 ± 0.002
(16) Cytochrome b_5	xx 0.038 ± 0.00	0.018 ± 0.000
(17) Liver – SH, Units = mM/Litre	xx 0.11 ± 0.01	0.05 ± 0.01
(18) Serum – SH, Units = mM/Litre	1.19 ± 0.013	1.15 ± 0.02
(19) Monoamine Oxidase Units/100ml Serum	xx 0.63 ± 0.01	1.12 ± 0.03

It has been established that high plasma levels of nitric oxide NO (Endothelium Derived Relaxing Factor – EDRF) contribute immensely to the peripheral arteriolar vasodilatation which leads to a hyperdynamic state with low systemic vascular resistance, high cardiac output, hypotension and inadequate tissue perfusion. The observed increase in levels of NO in halofantrine treated animals may be connected with possible biochemical and metabolic mechanisms involved in certain halofantrine reported cardiac abnormalities.

Halofantrine pretreatment enhanced 5'- Nucleotidase activity. Adenine, a metabolic product of 5'-nucleotidase activity, is known to be a vasodilator. The mechanism of action is thought to be mediated through

the anrrioventricular AV node, causing a reduction in impulse conduction. The participation of adenine in the metabolic regulation of a host of cardiac functions was reported by Itoh *et al.*, (1986). The effect of long-term treatment with halofantrine on the *in vivo* status of adenine and the subsequent slowing of the cardiac apparatus is hereby, implied.

The increased superoxide dismutase (SOD) activity in the heart tissue after halofantrine pretreatment is probably the result of a biochemical mechanism aimed at prolonging the high levels of nitric oxide (NO) since SOD has been shown to prolong the half life of NO by scavenging any available superoxide ion (O_2-). The high levels of superoxide ion (O_2-) in the liver and the NO in the serum and plasma of the halofantrine treated rats are necessary prerequisites for the formation of peroxynitrite (O.NO.O), a known toxic intermediate. The reaction pathway of the O_2- and NO radicals is thought to be through rapid pairing of the unpaired electrons leading to the formation of the non-radical O.NO.O. In addition, the activity of SOD in the liver of halofantrine treated rats, which is supposed to reduce the level of superoxide ion, O_2-, was low and this also contributes to the high level of peroxynitrite, which in turn augments, in no small way, the cytotoxic effects of halofantrine.

The low level of catalase activity obtained after halofantrine pre-treatment suggests little or no effect on catalase activity.

α-Amylase activity was not significantly increased. A rise in α-Amylase has been associated with renal insufficiency and pancreatitis, and also renal failure has been associated with NO generation (Midgley *et al.*, 1991). Our result does not suggest an impairment of

the renal apparatus and/or pancreas with halofantrine.

The activity of Ca^{2+} Mg^{2+} ATPase was not significantly influenced by halofantrine pretreatment. In the present study we have observed a decrease in Na^+, K^+ ATPase activity in halofantrine rats. A decrease in potassium conductance has been shown to be a property of many drugs such as quinidine that alter cardiac repolarization and clinically prolonged QT-intervals (Schwartz *et al.*, 1990). Castot *et al.*, (1993) reported that halofantrine probably has the same effect on smooth muscle repolarization as the structurally related nitrogenous quinidine.

Halofantrine enhanced the activity of the xenobiotic metabolizing microsomal enzymes, NADPH cytochrome C reductase and cytochrome b. Both enzymes have been implicated in superoxide ion generation, and substantial homology between NADPH cytochrome C reductase and nitric oxide synthase NOS was reported (Moncada and Higgs, 1993). Nitric oxide is rapidly oxidized to higher oxides of nitrogen, such as peroxynitrite resulting in nitrosation of melecules or substrates containing sulfhydryl groups, -SH, such as glutathione, cysteine and albumin. The observed increase in thiol groups (-SH) in the liver homogenates of halofantrine treated rats lends credence to this metabolic activity of halofantrine. MAO was higher in the control and also significantly different from the corresponding halofantrine treated rats.

NAG or N-acetyl-β-D-glucosaminidase and Monoamine oxidase (MAO) have been implicated as enzyme markers for monitoring Liver Fibrosis and Cirrhosis with serum as the enzyme source. Compared with NAG, Monoamine Oxidase is diagnostically more specific for

Liver Cirrhosis/Fibrosis but its diagnostic sensitivity is low.

What is obvious to us is that significant perturbations in some of these biological markers may necessarily explain the cardiac toxicities and hepatoxicities is seen after prolonged use of halofantrine, or when used in unnecessarily high dose, or even when adequate doses are applied in abnormal physiological conditions.

Artemisinin up to doses equivalent to 200mg/70kg body weight have not shown significant effects on some of these parameters in short-term administration.

Neurotoxicities have been reported for Artemisinin, however these are usually idiosyncratic in nature or when administration is indiscriminate.

Levamisole and Fluconazole demonstrated marked effects on nutrient and drug metabolizing enzymes as shown in animal models and in humans, using pharmacokinetic models.

TABLE 16: Effect of Fluconazole Administration on Lipid Peroxidation, Superoxide Radicals and Antioxidant Enzymes

Parameters	Fluconazole pretreatment (n=4)	Control
i. Lipid peroxidation Units/mg protein	+0.019 ± 0.002	0.005 ± 0.001
ii. Superoxide radicals nanomoles x 10-4 min-1	+45.00 ± 8.70	18.00 ± 6.20
iii. Superoxide dismutase Units/g fresh wt. of liver	+225.02 ± 4.3.31	87.50 ± 33.07
iv. Catalase Units/g fresh wt of liver	100.80 ± 7.88	143.55 ± 21.29
v. NADPH-	+0.21 ± 0.031	0.036 ± 0.005
vi. Cytochrome C Reductase Units/mg protein		
vii. Cytochrome b_5 Units/mg protein	+0.94 ± 4.3.31	0.19 ± 0.02
viii. Alkaline Phosphate UL-1	+ 1881 ± 134.05	1254 ± 85.21
ix. 5'-nucleotidase Units/mg protein	0.028 ± 0.007	0.014 ± 0.001
x. α-amylase Units/100ml	+754.76 ± 18.59	642.62 ± 29.19

+ Statistically different at ($P < 0.05$) using the Student's t-test from the corresponding control value.
Results are expressed as mean ± standard error of mean (S.E.M.)
n = number of determinations made.

TABLE 17: Fluconazole Modulation of Tolbutamide Pharmacokinetics

Pharmacokinetic Parameters	Control	Fluconazole-Pretreatment
$t_{½}$	5.70 ± 4.85	12.0 ± 4.85
CL (ml min^{-1} kg^{-1})	0.276 ± 0.08	0.16 ± 0.04
AUC (μg-h. ml^{-1})	0.750 ± 0.25	1.7448 ± 0.85
Vd ($ml.kg^{-1}$)	0.1366 ± 0.05	0.142 ± 0.04

Results are mean ± SD for the subjects.
Statistical analysis was carried out by paired student t-test and P = 0.05 was taken as the minimum level of significance.

TABLE 18: Pharmacokinetic Parameters of Tolbutamide and Antipyrine before (B) and after (A) pre-treatment with Levamisole (n = 10 on each occasion; mean ± SD)

Object Drug	Treatment	$AUC_{0-\infty}$ $mg.hr.L^{-1}$	$t_{½}$	Vd. L.	CL ml. min^{-1}
Tolbutamide	Control B Levamisole, A	2421.2 ± 20 807.97 ± 15.5	15.2 ± 4.1 6.24 ± 1.25	8.69 ± 1.2 7.69 ± 0.8	6.61 ± 0.55 14.1 ± 1.82
Antipyrine	Control, B Levamisole, A	393.97 ± 10.3 176.87 ± 8.5	9.8 ± 1.2 4.8 ± 0.7	32.79 ± 2.5 29.41 ± 1.7	38.65 ± 4.2 70.77 ± 6.2

TABLE 19: Pharmacokinetic Parameters of Tolbutamide before (B) and after pretreatment with cimetidine (C) and rantidine (R) in healthy volunteers

Subject	$t_{1/2}$ (h)			V (1-kg^{-1})			CL (ml – min^{-1} . kg^{-1})		
	B	C	R	B	C	R	B	C	R
1	6.39	6.63	6.64	0.152	0.147	0.154	0.27	0.26	0.27
2	7.69	7.65	27.75	0.168	0.166	0.169	0.25	0.25	0.25
3	5.77	6.79	6.86	0.176	0.180	0.179	0.35	0.31	0.30
4	7.15	7.75	8.20	0.126	0.131	0.134	0.20	0.20	0.19
5	4.58	4.81	5.46	0.134	0.140	0.176	0.34	0.34	0.37
6	7.48	8.37	7.85	0.145	0.154	0.149	0.22	0.21	0.22
7	5.42	8.00	7.19	0.129	0.124	0.115	0.27	0.18	0.19
8	5.81	5.45	5.84	0.089	0.087	0.092	0.18	0.18	0.18
Mean	6.29	6.93	6.97	0.140	0.141	0.146	0.26	0.24	0.25
± SD	1.09	1.27	0.97	0.027	0.028	0.031	0.06	0.06	0.07

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We also reported our observed interaction between Fluconazole and plasma circulating sex hormones after prolonged administration in rats.

TABLE 20: Effect of Fluconazole on Plasma Levels of Some Circulating Hormone

Hormone	Control ± SEM	Test ± SEM
Progesterone (ug/ml)	3.7±0.78	1.05 ± 0.18
Estradiol (ug/ml)	313.5±132.58	135 ± 16.26
Testosterone (ug/ml)	1.85±0.46	0.25 ± 0.4
FSH (i.u/L)	1.1±0.14	1.95 ± 0.11
LH (i.u/L)	1.4±0.28	1.05 ± 0.18

Progesterone and testosterone levels in treated animals were reduced by as much as 72%. These results are consistent with the findings of Echkoff *et al* (1988) and Hanger *et al* (1988).

Noticeable decreases were found with LH and oestradiol while FSH showed an increase of about 75%. This pattern of differential elevation/reduction in circulating hormonal values were also reported by Eckhoff *et al* (1988). There is a paucity of information on the exact mechanisms of action of fluconazole on the circulating hormonal levels. There is the possibility of an interplay of steroidogenesis inhibition and the microsomal metabolizing enzyme inhibition and induction. The fall in progesterone, oestradiol, testosterone and luteinizing hormone levels may be attributable to a direct inhibitory effect of fluconazole on steroidogenesis, while the rise in FSH level may be due to a direct substrate specific inhibition for metabolic disposition of FSH, a

polypeptide hormone. The varying extents of hormonal level alteration may not be unconnected with the dose and duration of administration of fluconazole as was demonstrated for ketoconazole (Graybill *et al*, 1983; pont *et al*, 1984) or an evidence of ovarian failure caused by inhibitory effect on steroidogenesis, since elevated FSH occurs in ovarian failure with low LH.

Studies have shown that fluconazole could influence human as well as fungal cytochrome-P450 dependent enzymes and that it is a potent and specific inhibitor of fungal sterol synthesis thus having the potential to interfere with mammalian steroidogenesis. Ketoconazole, a compound closely related to fluconazole has been shown to block testosterone synthesis (Graybill *et al*, 1983; Grasso *et al*, pont *et al*, 1984).

Pont *et al* (1984) further showed that ketoconazole may block cortisol secretion and the adrenal response to corticotrophin may be suppressed, the effect becoming more intense with higher doses. In a comparative study of the effect of fluconazole and ketoconazole on 17 B-oestradiol production in rat ovaries ketoconazole produced a more pronounced reduction in the levels of oestradiol (Latrile *et al* 1989). Eckhoff *et al* (1989) reported a similar effect of these two agents on steroidogenesis in rat adrenal cells *in vitro*. They observed an inhibition of ACTH stimulated corticosterone and aldosterone secretion, enhanced 11-deoxy-corticosterone output at low concentrations and reduced it at higher concentrations. Hanger *et al* (1988) using rat Leydig cells and male volunteers respectively reported a reduction in testosterone levels due to the effect of fluconazole.

Calcium Antagonists and Cardiovascular Chemistry

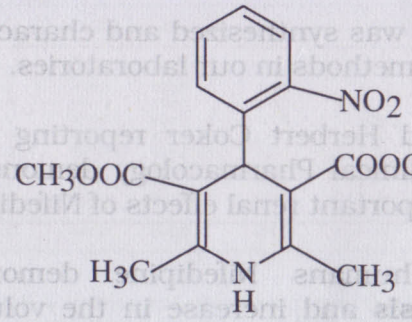
Nifedipine (Adalat) is a calcium blocker used for the treatment of certain types of high blood pressure (hypertension).

The mechanism of action is predicated on the interaction of Nifedipine and 1,4-dihydropyridine receptors in the heart muscles.

This blockade prevents entry of excess calcium (Ca^{2+}) into the heart muscle and thereby reducing sacolema contractility, myocardial force of contraction and peripheral pressure.

At the Medicinal and Biological Chemistry unit we synthesized the water-soluble Calcium-drug complexes of Nifedipine.

We rationalized out that, apart from Calcium entry inhibitory effect of Nifedipine, it was not impossible that sequestration of some cations by Nifedipine might be additional means of lowering blood pressure.



Nifedipine: 4-(2´-nitrophenyl)-2,6-dimethyl-3,5-dicarbomethoxy-1,4-dihydropyridine

The possible complexation of Ca^{2+} ion with Nifedipine. 4-(2-nitrophenyl)-2,6-dimethyl-3,5-dicarbomethoxy-1,4-dihydropyridine), a calcium antagonist and an established anti-hypertensive drug has been investigated. Water-Soluble complexes have been synthesized in protic (ethanol) and aprotic (toluene) solvents. Spectroscopic characteristics are reported and a possible additional mechanism of antihypertensive action of Nifedipine has been postulated.

The Nif-CO complex was synthesized and characterized by physicochemical methods in our laboratories.

Canin Adepeyo and Herbert Coker reporting in the Fundamentals of Clinical Pharmacology demonstrated exciting and very important renal effects of Nifedipine.

In normotensive humans Nifedipine demonstrate **natriuresis**. **Kaliuresis** and increase in the volume of **urine output**. Diuresis was accentuated with the concomitant administration of chlorothiazide diuretic.

It may obviate as a Biological Chemist, was sought – I know suggest of the physician and the cardiologist that in treating hypertensive patients with calcium antagonists the physiology and chemistry of the patient are to equal essence.

Caution is of immense importance it a diuretic must be co-administered, of **using** excessive dehydration and potassium depletion which very give rise of complications.

TABLE I: Sodium excretion (8-h^{-1}) and urine volume (8- h^{-1}) in 10 healthy normotensive volunteers following intake of slow-release formulation of Nifedipine

Subject	Sodium excretion (mmol)				Urine volume (liters)			
	Control	Initial	7 days	14 days	Control	Initial	7 days	14 days
1	29.6	40.6	34.9	41.8	0.527	0.600	0.624	0.840
2	46.4	59.4	47.4	49.8	0.466	0.693	0.480	0.490
3	41.5	57.9	57.8	25.7	0.421	0.815	0.760	0.350
4	58.2	71.4	65.8	52.6	0.566	0.882	0.642	0.448
5	32.7	30.6	39.1	30.4	0.231	0.205	0.308	0.200
6	27.6	51.3	35.7	42.5	0.428	0.980	0.712	0.772
7	64.2	127.5	60.9	50.9	0.691	1.305	0.600	0.727
8	48.9	45.1	46.2	64.4	0.521	0.489	0.556	0.605
9	46.3	86.2	44.4	41.0	0.351	0.805	0.300	0.368
10	58.8	134.2	72.6	60.9	0.571	1.078	0.820	0.476
Mean	45.4	70.4*	50.5+	46.0	0.477	0.785**	0.58+	0.528
SD	12.7	35.5	13.1	12.3	0.129	0.311	0.175	0.205

+ $P < 0.05$; * $P < 0.025$; ** $P < 0.005$, compared with control
+ $P < 0.05$ compared with the respective value after the initial dose

TABLE II: Sodium excretion (8-h^{-1}) and urine volume (8- h^{-1}) in 8 healthy normotensive subjects before (control) and after intake of a single 20-mg slow-release formulation of Nifedipine (Sf), 10-mg (10-cf) or 20-mg (20-cf) of the conventional formulation

Subject	Sodium excretion (mmol)				Urine volume (liters)			
	Control	Sf	10-cf	20-cf	Control	Sf	10-cf	20-cf
1	38.6	61.8	62.4	54.4	0.401	0.562	0.506	0.511
2	49.4	103.2	90.8	40.6	0.635	0.889	0.801	0.438
3	20.2	25.8	17.2	24.6	0.209	0.274	0.304	0.321
4	30.8	53.4	68.4	56.4	0.320	0.449	0.514	0.462
5	28.9	41.6	41.4	30.8	0.301	0.588	0.626	0.382
6	32.4	76.2	48.8	25.2	0.337	0.627	0.701	0.246
7	48.6	127.2	112.6	73.4	0.600	1.118	0.884	0.688
8	26.8	61.4	48.6	20.2	0.214	0.522	0.410	0.196
Mean	34.5	68.8**	61.3+*	40.7	0.377	0.629**	0.593 +	0.406
SD	10.4	32.9	29.8	19.0	0.161	0.263	0.197	0.157

** P < 0.005; * $P < 0.01$; + $P < 0.001$ compared with the control + $P < 0.025$ compared with the respective value after a 20-mg single dose of the conventional formulation (20-cf)

TABLE III: Sodium excretion (8-h^{-1}) and urine volume (8- h^{-1}) before (control) and after a single dose of the 20-mg slow-release formulation of Nifedipine (NIF), chlorothiazide (CTZ), and their combination (NIF/CTZ) in 6 normotensive volunteers

Subject	Sodium excretion (mmol)				Urine volume (liters)			
	Control	NIF	CTZ	NIF/CTZ	Control	NIF	CTZ	NIF/CTZ
1	53.3	65.2	136.8	134.2	0.581	0.908	1.155	1.118
2	25.4	54.6	124.8	159.5	0.356	0.707	0.850	1.430
3	42.6	59.1	90.4	164.8	0.470	0.610	0.760	1.446
4	42.8	56.3	180.7	217.3	0.488	0.736	1.246	1.961
5	45.4	49.6	103.3	164.8	0.518	0.583	1.131	1.364
6	34.8	67.9	131.3	146.9	0.337	0.740	1.018	1.232
Mean	40.7	58.8*	127.9**	164.6***	0.458	0.714**	1.027+	1.425***
SD	9.6	6.8	31.3	29.3	0.095	0.116	0.189	0.291

* $P < 0.025$; ** $P < 0.005$ compared with the control. + $P < 0.01$; + + $P < 0.005$ compared with Nifedipine (NIF) alone; *** $P < 0.025$ compared with chlorothiazide (CTZ) alone.

TABLE IV: 8-h excretion of potassium and chlorothiazide after a single dose of 20-mg slow-release formulation of Nifedipine (NIF) chlorothiazide (CTZ) and their combination (NIF/CTZ) in 6 normotensive volunteers.

Subject	Potassium (mmol)			Chlorothiazide (mg)	
	NIF	CTZ	NIF/CTZ	CTZ	NIF/CTZ
1	23.3	42.6	49.2	30.5	20.7
2	16.7	58.6	47.6	22.3	26.4
3	12.1	31.7	35.4	19.6	14.9
4	26.4	51.7	60.5	61.3	48.3
5	17.8	40.8	34.1	19.7	26.9
6	22.0	55.8	51.8	24.7	34.7
Mean	**19.7**	**46.9***	46.4	29.7	28.6
SD	5.2	10.3	10.1	16.0	11.7

* $P < 0.001$ compared with Nifedipine (NIF) alone.

Drug Biotransformation Reactions

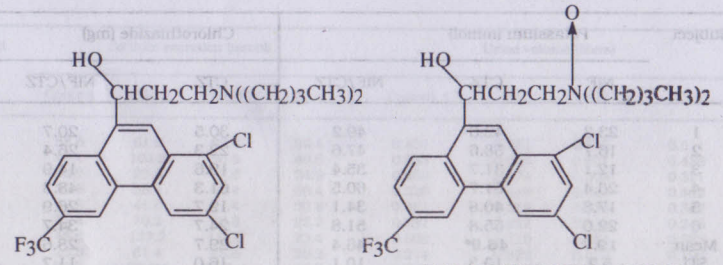
Under the watchful eyes of Professor Etienne E. Essien, the Foundation Dean of School of Pharmacy, University of Lagos.

At the medicinal chemistry unit we explored the interactions between the hepatic cytochrome P450 group of enzymes and numerous medicinal agents and the influence of these interactions on the safety and toxicities of drugs.

We were the first group to report the N-oxide metabolites of some tropical drugs when administered to man.

Halofantrine N-oxide was isolated and characterized with the aid of nmr spectroscopy and Mas spectroscopy.

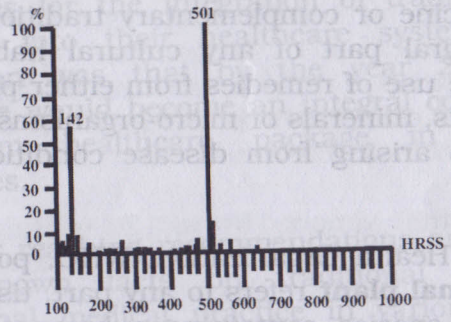
Metronidazole N-oxide, Tinidazole N-oxide and mefloquine N-oxide were isolated and characterized using nuclear magnetic resonance spectroscopy and high performance liquid chromatography.



HALOFANTRINE

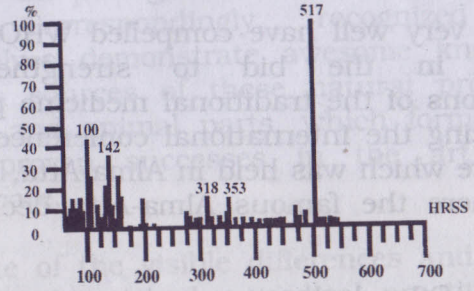
HALOFANTRINE N- **OXIDE**

Halofantrine, δ (CD_3 OD_3) 0.99 (6H, t), 1.39(4H, m), 1.72(6H, m), 3.2 (H, s), 3.35(H, t), 3.55(6H, t), 7.8(H, s), 8(H, d), 8.5(H, d), 8.7(H, s), 8.85(H, s), 9(H, s), ppm., M.



Fast Atomic Bombardment Mass Spectrum of Halofantrine (Mol. Wt. = 501).

Halofantrine N-oxide, m.p. 187 - 189°C (decomposition); (Found C, 62.2; H, 6.01; Cl, 14.11; F, 11.25; N, 2.68% $C_{26}H_{30}Cl_2F_3NO$ requires C, 62.4; h, 6.04: Cl, 14.16:F, 11.38: N, 2.78%). δ (CD_3 OD_3) 0.99 96H, t), 1.39 (4H m); 1.72 (6H, m), 3.2 (H, s), 3.35 (H, s), 3.35 (6H, t), 7.8 (H, s), 8(H, d), 8.5(H, d), 8.7(H, s), 8.85 (H, s), 9.1(H, s) ppm; M517.



Fast Atomic Bomdardment Mass Spectrum of Halofantrine N-oxide Mol. Wt. = 517).

12. COMPLEMENTARY TRADITIONAL MEDICINE AND NATURAL PRODUCT CHEMISTRY

Ethnomedicine or complementary traditional medicine is an integral part of any cultural habitat and its people. The use of remedies from either plant sources, animal parts, minerals or micro-organisms for the relief of illnesses arising from disease conditions predates history.

The World Health Organization, WHO, posits that — the **medicinal plant** refers to any part, tissue or organ of a plant species containing substances usable for therapeutic purposes, or which serve as templates for the synthesis of more useful drugs with minimal side effects (WHO, 1978).

WHO has long been aware of the very vital role traditional medicine practitioners and birth attendants from member states play in health delivery systems, more importantly in the rural areas of African countries.

This may very well have compelled WHO to take the initiative, in the bid to strengthening these contributions of the traditional medicine practitioners, in organizing the international conference on primary health care which was held in Alma-Atta, in the Soviet Union where the famous Alma-Atta declaration was adopted.

The spirit of the declaration was to encourage member states in the use and exploitation of all available resources in tackling primary healthcare.

As a matter of fact, in December 1999, the World Health Organization (WHO) at a 3-day consultative

interaction by experts on the Strategy for Traditional Medicine for African Region (2000 – 2001) in Harare, Zimbabwe, urged African Member States to develop strategies for the integration of traditional medicine practice into their healthcare systems. The WHO projection was that by the year 2000 traditional medicine would become an integral component of the minimum healthcare package in most African countries.

This far reaching recommendations are predicated on well known facts on traditional medicines and traditional medical practice in various parts of the world. There is no doubting the fact that in most countries in Tropical Africa almost 70 – 80% of the population patronize traditional healers for their medical care. In the rural communities the herbalists or traditional healers are usually the first port of call in the event of illness. More so, in terms of primordial history, members of a community tend to have more confidence in these rural doctors and birth attendants because of years of established track records which are usually the prerogatives of known families through the ages. Correspondingly, recognized practitioners themselves demonstrate awesome knowledge of the various sources of these natural products, notably plants and animal parts, which forms the basis for their proven successes in the art of traditional healthcare.

In spite of the visible differences and high suspicion between the orthodox medical practitioners (Western trained medical doctors) and traditional medicine practitioners, or herbalists (or ethnomedical practitioners), ethnomedicine keeps enjoying increased acceptance all over the world.

There is now the strong compelling need to preserve the natural biodiversity for continuity sake and also taking cognizance of the fact that the very vast flora in Nigeria remain a source for future drug discovery and new ethnopharmaceuticals. As a matter of fact the developed countries of the Western world have been at the forefront of research into development of natural resources and ethnomedicine.

It is estimated that almost 75% of 120 useful bioactive plant derived pharmaceuticals used worldwide were discovered by systemic investigation of leads from traditional medicine.

It has been reported that only 10 - 15% of about 250,000 – 500,000 known higher plants have been investigated for the presence of bioactive compounds. Tropical rain forest plants constitute only 7 -10% of the land surface of earth. The tropics are naturally endowed with about 150,000 seed plants with 120,000 found in the tropical rain forests alone, an indication of the rich ethnomedicinal attributes of the rain forest plants.

The study of naturally occurring compounds has evinced impressive advances in pharmacology, physiology and clinical medicine. Tropical plants will continue to provide mankind with a dynamic natural laboratory as sources of important medicines, food, cosmetics, natural pharmaceutical excipients and also will serve as an essential elements in the stabilization of the ecosystem and biodiversity.

Pharmaceutical development from ethnobotanical sources in the forested areas offers great potential for contributing to sustained growth. Consequently there

is an urgent need to conserve tropical forests as biological resources in order to ensure the future availability of known and yet undiscovered medicinal substances for future generations. Success in this direction must of necessity incorporate community participation. Return of benefits to local communities will go a long way as economic incentives for continuous cooperation in conservation purposes.

There is no doubt that **Nigeria** is richly blessed with abundant natural resources within the Nations biodiversity and ecosystems.

Documentation and reviews abound to attest to the fact that extracts from a host of flora and fauna from diverse areas of Nigeria have found good use in disease conditions such as malaria, diabetes, epileptic lesions, convulsion, dementia of various grades, e.g. Alzheimer, sickle cell disorders, pyrexia, inflammatory conditions, pains, microbial infections including HIV and AIDS.

At the Department of Pharmaceutical and Medicinal Chemistry we have made impressive studies in natural product chemistry in spite of the relatively young age.

Ekpenyong *et al* have demonstrated the antihypertensive properties of the leaf water extracts of *Persea americana* (Avocado pear). The active metabolites flavonols, quarcetin and Isorhamnetin, were isolated and completely characterized using ^{1}H and ^{13}C nmr, IR, UV, MS, DEPT and elemental analysis. Attempts are being made to quantitatively encapsulate and patent these natural products.

Ogbonnia *et al* have proved beyond any doubt that the plant *Sihumanniophyton magnificum* is a valuable herbal remedy for epilepsy and convulsions.

Adegunloye, Soga, Sofola and Coker have demonstrated the antihypertensive and cardioprotective properties of *Isapa* (*Hibiscus sabderifa*). Little wonder our folks in the hinterlands who feed on these natural products live longer and healthier lives.

Adesegun *et al* have convincingly proved the antihypertensive properties of the stem extracts of *Lecaniodiscus cupanoides* a plant commonly found in the Southwest of Nigeria. The isolated active principles are being developed into suitable dosage forms.

Adesegun has helped the Unit identify and enlist over 40 land-based plant materials shown to be effective against malaria.

The treatise of Adesegun, Ajayi, Olagbende-Dada and Coker have enlisted about 50 marine-based organisms, notably sponges whose extracts have demonstrated differing measures of anti-HIV properties.

Limited financial support has always been the bane of progress in these important areas of medicinal plant research.

Mr. V.C. sir, we have commenced combing the entire flora of Badagry/Ipokia - Ilaro - Ifo – Abeokuta axis for definite anti-HIV natural metabolites, as part of our ongoing humble contributions to healthcare in Nigeria.

I must thank all those who have been collaborating with us in this regard.

13. ENVIRONMENTAL CHEMISTRY AND HEALTH HAZARDS

Environmental pollution and especially food contamination have long been associated with health hazards. Over the past decade, countries all over the world have invested huge amounts of money in developing measures aimed at stemming the extent of environmental pollution.

Human toxicological hazards such as tumours and cancers of various tissues of the body have been associated with exposure to any of a host of toxicants and pollutants.

Sources of human carcinogens include ingestible food items, inhalation of toxic fumes from exhaust, industrial emissions, asbestos, percutaneous or mucosal absorption of certain industrial wastes and even cosmetic preparations.

The ecosystem in some parts of Nigeria have been subjected to gross spoilage because of petroleum pollution. Marine life has been devastated just as well as vast areas of farmlands and ecohabitats have laid waste and infertile due to incessant insults from environmental pollutants and petrochemicals.

Potential hazardous agents include soots, tars, tobacco, aromatic amines, nickel, chromium, cardmium, lead, arsenic compounds found chiefly in industrial wastes.

Others are carbon monoxide fumes from auto exhausts and power generating sets, asbestors implicated in lung and oesophageal cancers, fluorohydrocarbons, mycotoxins (aflatoxins) naturally existing in mouldy cereals, polyaromatic hydrocarbons the main culprits

in petrochemical spillage in the coastal regions of Nigeria.

These toxicants have all been implicated in malignancies and other debilitating disease conditions in man.

The Pharmaceutical and Medicinal Chemistry laboratory of the University of Lagos have made modest contribution toward the identification, quantification, assessment of extent of environmental and food contamination and also in the epidemiological survey of malignant diseases arising from these suspected carcinogens.

With the aid of advanced spectroscopy, HPLC, GC – MS we have been able to estimate some of these **toxicants** in various sources in the country.

TABLE 21: Total level of N-nitroso compounds obtained in local products in Lagos area of Nigeria

Products	n	N-nitroso compound as NDELA (mg/kg)	
		Range	Mean
Tobacco products	10	0.10 - 0.30	(0.20)
Diary products	5	0.01 - 0.01	(0.01)
Borehole water	4	0.02 - 0.10	(0.05)
Industrial effluent	6	1.50 - 1.90	(.175)
Treated industrial Effluent	6	0.02 - 0.05	(0.03)
Alcoholic beverages	10	0.01 - 0.02	(0.01)
Raw meat products	5	0.14 - 0.30	(0.20)
Cooked meat products	5	0.01 - 0.01	(0.01)
Smoked fish products	5	0.10 - 0.20	(0.16)
Pre-grilled meat (spiced)	10	0.90 - 1.60	(1.30)
Post-grilled meat (spiced)	10	0.80 - 0.09	(0.83)
Skin cream products	10	0.20 - 1.30	(0.80)
Body lotions	5	0.03 - 0.24	(0.14)
Hair cream	5	0.01 - 0.03	(0.02)

Samples		Total Aflatoxin Values mcg.g-1 ± SEM		
		Methanol/Water Extract (3 : 1)	Acetonitrile/ Water Extract (3 : 1)	Dichloromethane/ Water Extract (10 : 1)
GN	A	61.24 ± 0.67	47.04 ± 0.42	23.29 ± 0.10
	B	54.83 ± 0.51	53.76 ± 0.27	30.74 ± 0.04
	C	62.16 ± 0.83	64.52 ± 0.65	42.24 ± 0.09*
Type	B1	82.42 ± 0.55*	79.12 ± 0.93*	36.58 ± 0.08
	B2	80.62 ± 0.58*	77.01 ± 1.63*	35.34 ± 0.72
	B3	71.27 ± 0.47*	72.65 ± 0.70*	46.57 ± 0.64*
	B4	75.72 ± 0.60*	65.25 ± 1.32	53.49 ± 0.14*

Results are expressed as mean and Standard error of mean (SEM).
* Significantly different ($P < 0.05$) from the corresponding value using student's t-test

TABLE 22: Priority Polyaromatic Hydrocarbons (PAHs) concentration in the Delta area of Nigeria

Compound	Water (μg/ml)	Fish (μg/ml)	Sediment (μg/ml)	R.S.D. (%)
Naphthalene	0.55	8.1	1.25	4.76
Acenaphthylene	0.34	0.42	0.32	1.70
Acenaphthene	0.4	0.53	0.37	0.89
Flourene	0.33	1.92	0.66	6.20
Phenanthrene	1.46	3.77	1.99	7.17
Anthracene	0.35	0.93	1.07	4.92
Flouranthene	0.54	2.08	1.65	2.48
Pyrene	0.67	1.53	1.53	4.40
Benz[a]anthracene	0.56	1.79	1.28	5.36
Chrysene	1.32	2.79	1.17	4.26
Benzo[b[flouranthene	2.38	6.5	3.88	1.69
Benzo[k]flouranthene	1.82	2.21	2.88	2.71
Benzo[a]pyrene	1.72	6.78	5.91	2.11
Dibenz[a,h]anthracene	0	13.8	18.32	10.16
Benzo[ghi]perylene	0	34.48	21.32	15.79
Indeno[1,2,3-cd]pyrene	0	12.57	11.45	4.77

[a]*Department of Pharmaceutical Chemistry, University of Lagos, Surulere, Lagos, Nigeria.*
[b]*Department of Chemistry and Biochemistry, San Francisco State University, CA, USA.*

TABLE 23: The pH of Four Water Fronts in Midwestern Region of Nigeria

Water Fronts	Phosphate Concentration (mg/ml)			
	Inorganic	Organic	pH	Total
Main Market (4)	16.00±0.00[a]	27.50±0.30[d]	5.80±0.04[a]	43.50±0.30[a]
Ogunu (4)	7.00±0.00[a]	28.30±0.20[c]	5.90±0.03[a]	5.30±0.00[b]
Pessu Jetty (4)	17.00±0.00[a]	27.00±0.00[b]	5.80±0.06[a]	44.00±0.00[a]
Refinery Jetty (4)	20.00±0.00[b]	26.50±0.20[a]	6.80±0.03[b]	6.50±0.30[c]

TABLE 24: Sodium and Potassium Ions Concentration of Four Water Fronts in Midwestern Region of Nigeria

Water Fronts	Na^+ Concentration	K^+ Concentration
Main Market	5.10±0.00[a] (4)	2.40±0.10[d] (4)
Ogunu	10.50±0.06[b] (4)	2.00±0.08[d] (4)
Pessu Jetty	5.30±0.40[a]	1.70±0.03[a]
Refinery Jetty	9.00±0.20[c] (4)	2.1±0.04[c] (4)

The health hazards posed by these noxious pollutants, contaminants and toxicants are real and should be a matter of concern to health authorities of Nigeria. Some of these toxicants have been heavily implicated in malignances.

We must confess though, that data are lacking in any epidemiological survey.

The good news is that the Nigerian government has shown some positive reactions to environmental pollution and hazards.

14. What has the Chemist got to do with healthcare delivery?

The **Chemist** is of necessity, a member of the healthcare team. He is a professional who must bring **Chemistry** to bear on health related issues, amongst many other things.

However, he does not have to indulge in **legendary quarrels** with other members of the team or any association, since the Lord Almighty has helped to conquer **hunger** the usual source of most human misunderstandings.

All the **Chemist** needs do is to learn how to identify the agreeable gentlemen and ladies in the polity, and together carry on with the days work and assignment, realizing there is so much to do for the country and mankind.

The **Chemist** must continuously sharpen his skills in organic chemistry, inorganic chemistry, analytical chemistry, biological chemistry, clinical chemistry, biochemistry and biotechnology and be ready to apply such endowment in lending explanation to untoward events in Physiology, Pharmacology, Biology, and health related matters.

The **Chemist** must provide ready answers on the rational and irrational actions of drugs, nutrients and phytomedicines on macromolecular protein receptors.

The **Chemist** must be intellectually enterprising — he **must** attend and contribute productively at Seminars in related disciplines; he must endeavour to participate at Ground Rounds in Medicine and Chemical Pathology.

If he must keep the frontiers of knowledge nascent; he must of necessity be an accredited member of the **Lagos University Medical Society** and must participate actively.

The Chemist must attend **ward rounds** on invitation and must be ready to provide answers to beguiling issues on medications gone awry, or non-discernible idiosyncratic observations by the medical practitioner.

The **Chemist** must employ his residuals in medicinal chemistry, biopharmaceutics, pharmacokinetics and pharmacodynamics in explaining to the physician the possible demerits associated with drug-drug interactions, drug-food interactions, poor absorption and disposition profile of medications which may result in treatment failure.

For example: — Dr Elain Azinge once expressed her displeasure with the use of Artemisinin in managing malaria disease in patients. She had already concluded that "resistance" had crept in and Artemisinin was failing.

A cursory look into some medication prescriptions reveal the co-existence of Artemisinin, Vitamin C and multivitamin preparations containing trace elements and minerals.

Artemisinin in its chemical structure contains a fragile di-oxygen bridge. Its **antiplasmodial** action is predicated on the generation of an oxygen centred free radical due to transient cleavage of the 0-0 bridge.

The last thing a Biological Chemist would want is the presence of an **antioxidant** such as Vitamin C. The antioxidant will mop up the free radical, thereby incapacitating the drug molecule for effective antiprotozoal action.

For this reason the Biological Chemist would advise that Artemisinin-based antimalarial drugs should not be prescribed along with antioxidant vitamins such as Vitamin C, β-carotenes and Vitamin E.

Some multivitamin preparations contain some amounts of minerals and trace elements. Species of the Transition series such as Zinc (Zn), Copper (Cu^{2+}), Iron (Fe^{2+}) will catalyze the physiological breakdown of the dioxygen bridge through auto-induced hydrolytic cleavage (RO – OR ⟶ RO-H + R-OH), thus rendering the drug useless.

Lest we forget, the doctor meant well. He meant to prime and reinvigorate the enzyme system, improve the patients appetite and speedy recovery. But the intricate chemistry of the attendant circumstance would dictate otherwise.

The Biological Chemist would suggest that where the doctor must treat malaria with Artemisinin he should avoid multivitamin overload. Simple B-complex will do.

It is the place of the **chemist** to bring to the awareness of the authorities that environmental factors such as **global warming** (arising from ozone layer depletion due to man-made events such as gas flaring, release of industrial emissions) contribute detrimental havoc to drug stability and shelf-life of drugs, going by the **Arrhenius** concept.

Surreptitious increase in the Earth's surface temperature may be responsible for the faster degradation of drugs on the shelf. A microscopic examination of "substandard pharmaceutical preparations" may not necessarily be the fault of the manufacturer, but that of the **Chemist** who has failed to factor in the incremental rate of temperature rise —

on drug stability when determining the **shelf-life and expiry date** of a particular drug.

Global warming (and of course the NEPA syndrome) may be responsible for the decomposition of many thermolabile compounds such as Insulin preparations. The unsuspecting **diabetic** keeps jabbing himself with Insulin that has lost almost 10 - 30% potency.

Little wonder — diabetes is on the increase and appears uncontrollable, not completely because of bad eating habit or metabolic complications, but also the unwitting use of substandard antidiabetic drugs.

The challenges indeed are plethora. Mr Vice Chancellor sir, it stands to reason that the **Chemist** can contribute meaningfully and productively to healthcare delivery. But he must realize that, as with all professionals, the post of honour lies in proving his mettle at all times.

Humble Recommendations

The Faculty of Pharmacy is a relatively young chap on the block. It is not impossible some other colleagues in the establishment may have muted the idea of **a Central Research Laboratory Complex** which will house every conceivable and relevant research equipment such as the NMR spectrometer 250 MHz, assorted HPLCs, HPTLCs, GCs, GC-MS, AAS etc. Such a complex shall have constant electricity and water supply.

The University of Lagos has the boys and girls, and I am pretty sure there are couple of professors who would prefer to remain in the laboratories. It is possible to encourage regular meetings of all researchers in the Chemical Sciences, Biological Sciences, Pharmaceutical Sciences and Medical Sciences. Such rubbing of minds will engender fresh ideas, refocus thrusts in research with a view to making outputs relevant to the needs of the immediate society and the country.

Duplication of research endeavours, which is very common in these disciplines, will be minimized. Resources, both financial and human can be better utilized and managed. Inter-faculty seminars and science-driven workshops will do the youngsters a lot of good.

University researchers, at times, can embark on joint research projects with a view to helping solve important national problems akin to what obtains in countries like China, Indonesia, Malaysia etc.

For example Nigeria will soon receive seedlings of *Artemisia annua* plant (Quinghaosa) from China for cultivation in the geopolitical regions of the country.

There is no reason why the University of Lagos should not participate in this scheme. The University should make acres of land available, our botanists and Professor – farmers should supervise the planting, nurturing and cultivation of the *Artemisia annua* plant (as a matter of fact — all lecturers living on Akoka campus should come out on Environmental days and plant *Artemisia annua*, Quinghaosa). Chemists would harness **Artemisinin** material from the plants by the usual chemical processes of extraction, isolation and compound characterization.

The University of Lagos could then dispense this invaluable antimalarial to Pharmaceutical Companies in Lagos and its environs, and generate huge income from such venture. This must be done on a professional setting, devoid of any clandestine politics.

Such a scheme would form the template for further – Pharmaceutical and ethnobiological adventurisms.

Many researchers here at Unilag have links with overseas concerns who would be willing to assist with aids in the form of research equipment and grants.

Mr. Vice Chancellor sir, we hope when success comes the "Akoka faction" will not pull the rug from underneath our feet.

I hold the view that endeavours of this nature are not unethical and the University will not be misconstrued as violating any professional regulations.

I expect the Pharmacists Council of Nigeria to encourage and pronounce Unilag as the only Institution

in the Lagos area with the **academic** and **technological Know-how** to produce an industrial grade **Artemisinin raw material** suitable for manufacturing processes (given the caliber of our Chemists on ground).

Mr. Vice Chancellor sir, I would have loved to help in such a committee, but as you can see age is not on my side. Also, I am going on a retreat to the mountains of Jerusalem, in readiness for the 2007 Lagos State Governorship elections (according to the directive of the Holy Spirit).

- University of Lagos **should** put in place a **Cassava plantation** – for the purposes of harvesting and refining Cassava starch which is becoming a gold mine. Starch is a multipurpose – commodity. It is used in the pharmaceutical industry for **tabletting** technology and a host of other applications. For example our own Dr. (Mrs) Mercy O. Odusote (nee Ifaturoti), the foundation coordinator of the School of Pharmacy and the Department of Pharmaceutics and Pharmaceutical Technology, after almost 30 years of research has been able to put up a cottage industry. Her produces include MAO – yam powder, MAO – Gari, MAO – Elubo, MAO – Lafun, MAO – Ogi, etc., products from sheer industry and personal enterprise. FIIRO must be commended for helping to mould most of Mama's machines.

Mama is yet to be made a Professor. Her mistake? She spent time and energy running from pillar to post helping to develop and cordinate the nascent School of Pharmacy, forgetting that the only known edible material in the University is academic publications. But God Almighty looked down and having seen Mama's services and contributions, decided to bless

her with proceeds from Cassava starch with which Aunty Mercy has trained five children single-handedly – Doctors, Engineers and Pharmacists, scattered in Ireland, Canada and the USA. Mama (aunty Mercy) – is not happy because her children are not around to take over her business. The only child on ground Funmi, (the 6th horse), a Pharmacist, is a Senior Superintendent with Christ Embassy. Funmi is not interested in Cassava industry and she cleverly dodges her mum. She is more interested in winning souls for Christ.

Mr. Vice Chancellor – the University of Lagos Science Forum or Unilag Consult can go into partnership with Mama – take over and expand the Cassava business, send Mama Odusote back to Ondo, make some starch related products available for Lagosians to consume.

Such plantation will also be used for processing **Corn starch, Plantain starch, Yam starch and Cocoa-yam starch** whose value has not caught the awareness of the country yet.

Mr. Vice Chancellor sir, I humbly submit that productive ideas are no one's prerogative, there is the imperative need for an **all-inclusive committee** to help develop a strong proposal on ventures of this nature. Other experts on Starch in the Faculty include Prof. Igwilo, Prof. Ifudu, Prof. Adeyeye and Dr. Abioye.

There are a host of other areas to look into, a position paper would be a more appropriate information organ.

- Kindly use your position sir, to investigate the loss of acres of land in Ikorodu – belonging to the University of Lagos. The Governor of Lagos State has some respect for University of Lagos. We may be lucky to retrieve this landed property or have an alternative dispensed to the University.

The entire staff of the Faculty of Pharmacy continue to express **gratitude** for the support received from the University authorities to date. The Faculty has taken custody of new teaching materials and numerous items of laboratory equipment. The University has increased student intake and enrolment in Pharmacy. This is a welcome development. The Faculty must grow and should be seen to match any other institutional Pharmacy establishment in the country. As a matter of fact, the Faculty of Pharmacy, University of Lagos is number one in the country. Kindly disregard the NUC ranking which placed Unilag Pharmacy behind Uni-Ibadan Pharmacy.

The Faculty of Pharmacy, University of Lagos in the short span of existence has produced over 20 Ph.D holders. The **rate** of Ph.D candidature development is highest at Unilag Pharmacy (Chemistry, Pharmacognosy, Pharmaceutics, Pharmaceutical Microbiology etc). Unilag Pharmacy is the first Pharmacy Faculty to introduce the Clinical Pharmacy programme both at undergraduate level and postgraduate level. The first institution to produce masters holders, M. Pharm in Clinical Pharmacy, in Africa is Unilag - Pharmacy. The over thirty M. Pharm graduates have either joined various state Hospitals and University Teaching Hospitals. Others have joined the teaching staff of other Pharmacy institutions with a view to helping develop Clinical Pharmacy programmes in these institutions. In the next two months and by the grace of God, the Faculty of Pharmacy of the University of Lagos will be the first Pharmacy Institution in Africa and the entire tropical world to produce a Ph.D in Clinical Pharmacy (Mrs. Bola Aina).

May we seize this opportunity to thank numerous consultants from the School of Clinical Sciences,

College of Medicine, University of Lagos who have served as associate lecturers in this programme. The Faculty has indeed benefited tremendously from the **multidisciplinary nature** of the College Campus.

Lest we forget, the chieftain, guru and mastermind behind these strings of successes is the man – The Very Revd. Professor Fola Tayo (Ph.D Strathclyde). Of course only "special mortals" and products of the University of Strathclyde, Glasgow, can perform such feats.

Mr. Vice Chancellor sir, it may please you to know that of all the Pharmacy graduates from Universities all over the world who write the Foreign Board Examinations in the USA, Canada and Britain, none of our graduates in the past 20 years has failed any of these examinations. As a matter of fact some have gone on to win State Scholarships and have become professors in some of these foreign universities. Sir, the element of decency and deep sense of gratitude must compel me to say thank you to the University of Lagos (and especially the **College of Medicine** – Idi-Araba) for providing the enabling environment which has accentuated these lofty achievements.

The NUC ranking caught us unawares. We must confess that we did not give the NUC circulars and questionnaires the seriousness they deserved and in some instances these memos arrived rather late at our end in Idi-Araba from Akoka. We sincerely promise this will never be the case again.

Mr. Vice Chancellor sir, may I recommend strongly that the University should sponsor the Chief Medical Director of LUTH, Prof. Tolu Odukoya and Chairman – MAC, Dr. David Oke (my very bosom friends) on a

visit to hospitals abroad – Great Britain, the USA and South Africa to understudy the functions of **Hospital Pharmacists** in a typical hospital setting. Part of their enquiries should cover renumerations for Pharmacists both in the hospitals and in the community at large. Hospital Pharmacists in Nigeria, are **underutilized**. Part of their traditional functions like cytotoxic-drug reconstitution, central sterilization management, drug utilization schemes, therapeutic drug monitoring, patient counseling, doctor-counseling, nursing staff counseling on drug use and utilization have been taken over by some "greedy people".

Hospital Pharmacists are grossly underpaid, they are not involved in hospital management decisions.

The Hospitals and the University of Lagos have **bluntly refused** to implement the allowances due Pharmacists working in Academia as directed by the Federal Government of Nigeria. These directives have already been implemented at the ABU, UNIJOS, and other institutions.

Can we really blame these children for running away to overseas countries after graduation?

Although I am supposed to discuss Chemistry, a man must shout out when the shoe overpinches.

Mr. Vice Chancellor the Faculty needs more staff and we need to catch them young. I thank you indeed for your effort in this regard.

Many other areas of the Faculty needing attention have already been discussed with you elsewhere.

Mr. Vice Chancellor I thank you for the opportunity given me to serve in numerous committees of the University. Most recently I was appointed into the Environmental Committee. I am an environmentalist, that is where I belong naturally and I promise to put in my very best. I left home for school one early bright morning when I was in Standard 4. I failed to do the morning chores before leaving home – I did not polish Pa's shoes, I failed to carry out and wash Pa's chamber pot, I failed to do the garden. That morning I saw the driver and Pa's house-help in my school. "Pa says to bring you home". I got the message. We drove back home, and after **eight heavy strokes** on my back I rushed out of the house. I looked towards heaven and asked God if this man was my father. Of course when I got back to school I told my friends that my father was a wicked man. Mr. Vice - Chancelllor sir, since that day I have **never failed** to **visit** the **garden every morning**. That is the source of my expertise on environmental matters.

I promise to bring a new brand of Christianity to this campus, Christianity tainted with esoteric flowers. But you have to settle me first.

Mr. Vice Chancellor sir, the Tai Solarin epitaph at Yaba Bus Stop is in a deplorable state. Uncle Tai does not deserve the level of neglect being meted out to "him". He did so much for education in this country. University of Lagos is the closest tertiary institution to that epitaph.

I, personally, do not think it is too much for the University of Lagos to take over the maintenance of that memorablia of an **ebullient** and **distinguished mortal.** Kindly mandate the Environmental Committee and Arts to look into this. The University may disagree with me if it so wishes.

Sir, kindly look into the possibility of including Professors of College of Medicine in issues like Commendation Service for the deceased. Gentlemen like the late Professor Olikoye Ransome-Kuti and Professor Akinrimisi should have been accorded deserving Senate Ceremonies.

Prof. Oye Ibidapo-Obe, it would be very glamorous and thoughtful of you if you would kindly put a Committee in place to enquire about the welfare of retired Professors living in Lagos and environs. It hurts some of us when we see aged Professors of the University of Lagos (Foundation Teachers like Prof. Ayodele Tella) coming to LUTH for medical treatment and struggling to get out of the car. Doctors in such Committee could visit them at home and this may reduce the ordeal, trauma and discomfort often experienced by these fathers of ours. Our culture encourages such thoughtful acts.

Acknowledgements

I thank the good Lord almighty for His grace, mercies and divine protection to this date. I thank Him for the enabling health bestowed on me which has been the very source of all my humble achievements to date.

I thank my parents Mr. & Mrs. Increase-Coker for bringing me into this world and for all the education, both domestic and academic, which they gave to me.

I thank my inalienable partner and chieftain of the Home front, Mrs. Margaret Mary Coker for tolerating all my inadequacies and excesses, and also for appreciating me as an invaluable gentleman of all times, the most glamorous man that ever came her way.

My very special and affectionate thoughts are extended to Samuel Coker, Alexander Coker and Lydia Coker.

I sincerely appreciate Mr. & Mrs. Engene Coker, Dr. & Mrs. Ernest Coker, Engr. & Mrs. Niyi Talabi and Mr. & Mrs. Patience Odiary for being there always.

Sincere and grateful thoughts of my teachers in School:

- The late Mrs Akajay-Macauley (nee Hamilton) of Ladilak Institute Yaba.
- The late Dr. J. A. Adegbite of Lagos Baptist Academy.
- Canon Emmanuel O. Alayande of Ibadan Grammar School.
- Prof. G. Osuide, Prof. Fola Tayo, Prof. Charles Nwambebe, Dr. G. Lahan, Prof. Elijah Sokomba - all formerly of Ahmadu Bello University.
- Prof. Peter Waterman, Prof. Gordon Smail, Prof. John B. Stenlake of the University of Strathclyde,

Glasgow.
and to my favourite teacher nd uncle - the late **Babajide Wickliffe** who put Physics through me. I wanted to be a **Physicist** like Bros. Jide but my parents dictated otherwise. I still read Physics Journals and I have a l... of interest in **nanoparticles** and protein **sens rs** such as prions.

My headmistress, Mrs. Akajay-Macauley popularly called Madam, initiated me into the School of Environmental Cleanliness. In the Kindergarten class (KG-2), at Ladilak Institute, I had dropped a piece of paper on the floor somewhere outside the classroom. She saw me from a distance and walked right down to my classroom where I had run into. Inspite of my pretence of looking into one of my books she moved close to me, drew my ears, then held my hands and walked me to the point where the dropped paper lay. She asked me to pick up that paper, she led me to a dustbin and requested I did the right thing. She bent down and said to my hearing "naughty boy", someone like you should know better. She explained to me why children should not litter the floor and as I looked her in the face I felt a kind of warmth and love for the first time in my life. I reasoned in me then that Madam scolded me so that I could be a better boy. Occasionally she would pass by to enquire how I was doing in class.

At the Obele Odan Municipal School, the very playful and rascally Engr. Pastor Femi Obembe was quite a contrast to Sereba and Ibinabo Aghiobu Kemmer — two sisters always spick and span in dressing and of quiet disposition.

Dr. J. A. Adegbite – of the Lagos Baptist Academy through his daily morning sermons in the School

Assembly – Shepherds Hill Baptist Church was the first mortal to instill the fear of God in me. Papa Adegbite was an expert on the Letters of Saint Paul. Reverence and godliness were to have a better grip on me through the sermons of the late Revd. Dahunsi, Revd. Ayorinde, Deacon Ajao and later Revd. Bolarinwa. I was temporarily converted into a Baptist. But for the fact that **Awe** is an Ilu Oke town, upcountry (due apologies to Prof. & Mrs O. O. Akinyanju, but not to Prof. (Mrs) Tayo Fagbenro-Beyioku) I was tempted to change town from Lagos to Awe. The discipline the Baptist mission instilled in me has remained with me till this day.

Canon E.O. Alayande made me go through the Christian rites of the Psalter and Prayer book inside out. The draconian cannings at Grammar School for failure to bring the Anglican Prayer book to morning and evening assemblies literally put the entire Psalter, (Psalms 1 – 150) and the Anglican liturgy into my grey matter. Mrs Edna Soyanwo sacrificed so much time to explain the music of the Psaltry and Church hymnals. Such exposure was to help me further appreciate essential Christianity.

The Scottish culture and education finally brought out the man in me. It was in Scotland, through the kind hands of Professors Peter Waterman and Gordon Smail that I came to appreciate the definition of the **Educated man**: that enlightened mortal, with developed mind and **character**, and liberated in knowledge.

Visits to Edinburgh, Aberdeen, Fyfe, Inverness, Lochlommond etc. enabled me to acquaint myself with the Scottish history. I saw the hometowns of those great names – David Livingstone, Mary Slessor, Mungo Park etc. When I returned to Nigeria – I changed my name from Coker to MacCoker (meaning son of Coker).

My very unreserved gratitude to Uncle Lateef Jakande, former Executive Governor of Lagos State and Uncle Bisi Onabanjo, former Executive Governor of Ogun State, for the sponsorship abroad that enabled me pursue a postgraduate course in Glasgow, Scotland.

Prof. Deji Femi-Pearse – I thank you once more for the offer of a Lecturer I job at the College of Medicine in Dec. 1984 when I arrived Nigeria from Scotland. I shall forget neither you nor your kith and kin.

I thank God that I have not disappointed your humble-self and the aforementioned noble mortals whom God used to anoint my chequered journey in this turbulent life of ours.

My continued unalloyed support and loyalty to Mr. Uwaga and Pius Abanum the President and General Secretary respectively of the **Pharmaceutical Society of Nigeria**.

I give kudos to Prof. Ogunbona, Alhaji Mora, Mr. Gar, Mrs. Oshoba and all the executives of the Pharmacists Council of Nigeria for the marvelous job rendered in the Council.

Sincere greetings to Dr. Leke Pitan, the Honourable Commissioner for Health, Lagos State and his very able and dynamic Permanent Secretary Dr. Jide Idris for the opportunities afforded me to serve Lagos State.

I must show due regards to my colleagues at the Faculty of Pharmacy – Prof. Fola Tayo, Prof. (Mrs) Igwilo, Prof. N.D. Ifudu, Prof. (Mrs) Adeyeye, Prof. (Mrs) Odusote, Prof. Mendie, Dr. Abioye, Dr. Silva, Ms Bukky

Dada, Mrs. Arin Joda, Dr. (Mrs) Ukpo, Dr. Chukwuani, Mrs. Adepoju-Bello, Dr. (Mrs) Owolabi, Mrs. Ogah, Mr. Akinleye, Mrs. Ajayi, Mrs. Olagbende-Dada, Mrs. Soremekun, Dr. (Ms) Odukoya, Dr. Adesegun, Dr. Ogbonnia, Mrs. Enwuru, Mr. Anyika, Mrs. Aina, Dr. Peters – together we have brought the fortunes of Pharmacy to its present state.

The full history of the Faculty of Pharmacy has been recounted elsewhere. A flash of insight and subsequent dexterous move by Professor Ade Elebute (former Provost of the CMUL) gave birth to the proposal for a School of Pharmacy. The wholehearted support of Professor Akin Adesola, former Vice Chancellor of the University of Lagos was to actualize this dream. It was a hectic struggle further championed by Professor Deji Femi-Pearse to reposition Pharmacy for recognition and accreditation by the Pharmacist Board of Nigeria (now PCN). The Foundation teachers: Prof. Bamgbose, Prof. Ayodele Tella, Prof. Onabanjo, Prof. El-Dahwi, Prof. Duma-Badu, Dr. (Mrs.) Odusote, Prof. Alade Akintonwa, Dr. Rasaki Ashorobi etc. – to all of you I say thank you for establishing a veritable means of employment for so many Nigerians.

The history of Pharmacy Unilag cannot be complete without the name of Professor Jelili Adebisi Omotola – the quintessential achiever. He laid the foundation seed of the Pharmacy Faculty Building and earmarked the financial wherewithal to complete the building within 6 months. Unforeseen circumstances of the day were to dictate otherwise.

My academic pursuits and exploits hav been made possible through the collaborative efforts of my former Ph.D students (and now my colleagues) Dr. (Mrs.) Ukpo, Dr. Charles Adeosun , Dr. Chinyere

Chukwuani, Dr. Gabriel Isamah, Dr. (Ms) C. Okonkwo, Dr. (Mrs.) Eduzie Thomas, Dr. (Mrs.) Owolabi, Dr. Adesegun and Dr. Ogbonnia. Hopefully in the nearest future we shall have Mrs. Glory Ajayi, Mrs. Ronke Adepoju-Bello, Mr. Akinleye, Mrs. Ogah and Mr. Kasim join the club of Ph.D holders.

Having to cope with **"13 children"** over the years is not the best of options. But when a teacher encounters willing students that teacher has no choice.

I say thank you indeed for the academic support all through the years.

I would like to acknowledge the over 50 M.Sc. graduates whose tutelage have kept me busy in the laboratories all through the years. I know your thoughts for me. Many of you would wish I crossed over to the US, Canada, South Africa.

If we all left the country who looks after the younger generations?

Many thanks indeed to May and Baker Nig. Plc, Boots Company Plc, GlaxoSmithkline Beecham whose company facilities and laboratories I have used over the years. God bless all the employees of these companies.

Mr. Vice Chancellor sir, I am quite pleased to say I am not an idle mind, I am working and productively engaged, and more importantly I am rendering the best of my humble services to the development of my country, Nigeria. my humble best to the development of my country.

I thank my academic mentors — my late father Mr. Increase-Coker, Mrs. Akajay-Macauley, Babajide Wickliffe, Professor E. E. Essien and Professor Fola Tayo. I learned from these mortals different attributes and virtues that have remained a beacon of light to me till this day.

I worked with the late Dr. Andrew Oserhenini Obaseki in the area of Biopharmaceutics, I have worked with Prof. Soga Sofola, Dr. Adegunloye and Dr. Anigbogu in the area of Physiology, Professor Alade Akintonwa and Dr. Ashorobi in the area of Pharmacology and Environmental Toxicology. Professor Tayo Fagbenro-Beyioku and I are inseparable in the area of Malariology, Ganiu Adebayo in Clinical Pharmacology, Dr. Tunde Taiwo and Dr. (Mrs) A.F.F. Banjo in the area of Histopathology. Dr. M.O. Kehinde, Dr. Temiye and Dr. Akanmu continue to guide me in the very interesting area of Sickle Cell anaemia research.

Papa Professor Joseph O. Sodipo has joined our group. I am sure he will bring a wealth of experience to bear on our research endeavours.

We have mounted war against HIV. The **cure** for HIV is in Nigeria, and hopefully somewhere in the Egba-Egbado-Awori-Egun conclave. I am going to catch that metabolite very soon.

In the areas of free radical Chemistry, Biochemistry and Biological Chemistry I shall never forget the late Dr. Mohammed Ibrahim of NIMER a very brilliant Kano gentleman. Coker, Isamah and Ibrahim played a lot with Enzymology and Biology. Dr. James Renner was to join us later and helped to demonstrate clinical manifestations of free radical injuries.

I learned so much from Dr. Molara Maboyoje and Dr. Felix Adetayo about the intricacies and techniques of Drug Clinical trials.

I say a big thank you to Prof. D. N. Osegbe for the milk of human kindness.

I must express sincere gratitude to Professor Tolu Odugbemi, former Provost of the College of Medicine of the University of Lagos. I served under him as Assistant Editor of the *Nigeria Quarterly Journal of Hospital Medicine*. Together we tried to improve the College landscape by planting flowers. When I took ill and had to go to England for treatment, Prof. Tolu Odugbemi approved the purchase of a return ticket and gave to me another 500 British pounds to help defray my expenses.

I say thank you Prof. and God bless you and the family.

I also wish to thank Prof. Olalekan Abudu the immediate past Provost. I served the College as the Deputy Provost. Some 2-3 years ago, under the barrage of continuous stormy winds and heavy downpour the entire roof of my apartment was yanked off the building and legoed behind the boys quarters. The heavens opened as the torrential deluge came down continuously for almost 2–3 months. As the level of water rose and gulped everything in the house, I prayed to God and wished it were fire, because fire does it in a jiffy and it is over with. Rainwater or local tsunami gives it to you painfully instalmentally. Of the almost ₦700,000.00 used in rehabilitating the house, the College made available about ₦350,000.00 using direct labour.

For circumstantial reasons, the University refused to help me out (laugh).

I must say thank you to these Catholic gentlemen, Prof. J. Taiwo Darocha-Afodu, Prof. Odeigha, Prof. Efe Ohwovoriole, Prof. Alloy Ejiogu, Prof. Jerry-Boy Adepoju — who came by and sympathized with me. However they left without giving me anything.

So the 500 year old war between the Roman Catholics — led by Dr. Amaeshi and Dr. Ngozi Osarenren, and the Anglicans led by Prof. Coker continues.

To all the **Consultants** and **young Doctors** at the College/LUTH who have always been helpful to me and to everyone — you are the best crop in the country. The age old tradition of discipline, professionalism, cultured enlightenment and love for mankind stand you out as primus interpares in Africa

Thank you indeed for everything Funmi Amodu our darling College Secretary. Kindly say hello to all the boys and girls in administration, Victor Isiekwenagbu, M.S. Jatto, Mrs. Ipaye, Mrs Lawal, Mrs Abanikanda *et al*. My brothers Mr. H.O.A. Taiwo, Lekan Lawal, Nofiu Sobande - members of the Egba abroad confraternity; All my former brothers and sisters from Igbogi — you can always count on me.

I shall never forget the boys - Ajirotutu, Bakare, Balogun, Aremu, Chukwu, Sunday, D.O., Ademulegun, Anjorin, Yoyo, Iyun *et al* — the Unionists and Engineering mafia. You have always stood by me in sunshine and in rain. God bless you all.

I salute all the cleaners at Idi-Araba, my sisters from Ilu Oke. I have not stopped praying for you and your families. Many of you travel all the way from Ifo, Ojokoro, Mowe, Ibafo, Akesan, Ipaja, Egbe, Ikotun etc. and arrive Idi-Araba before 7.00 a.m. so that Professor Coker and others may have clean environment to do their work. Almost 60% of your salaries is spent on transportation. Inspite of the scorching hardship in the land we are told Government still wants to embark on massive retrenchment.

The Vice Chancellor may want to look into this. Unilag should consider the harrowing plight of its junior workers and do something about their transportation within the metropolis of Lagos.

Prof. Ibidapo-Obe kindly put buses on the road to convey these hallowed children of God to comfortable places like Oshodi, Agege, Mile 2, Ojota from where they can continue their journey home.

Our country Nigeria is not done yet and Nigeria will never go under. We have pledged our lives for you – the down trodden masses and forgotten Nigerians. We will continue to work and till the ground until salvation, happiness, freedom and equity come to the ordinary citizen of this country. If Nigeria sinks we will sink with it, and if Nigeria floats we will float with it.

The Very Revd. M.E. Euler-Ajayi — the Chief Resident Minister and Chairman Chapel Committee, Chapel of the Healing Cross, CMUL/LUTH Idi-Araba — thank you indeed for the marvelous and glorious ministerial work in the Chapel, at CMUL/LUTH and environs. The very engaging weekdays' programmes, the different services and daily Eucharists, the vigils, seminars, workshops and missions continue to remain sources of blessings to thousands.

May the Lord continue to bless you and the amiable and industrious colleagues of yours Revd. Arch. Segun Kuti, Revd. Dr. Efunkoya, Revd. Dr. Sadare and Rev. Dr. Egbuonwu. And to our father — Ven. Professor Sam Ade Olaitan, Resident Minister Emeritus, the Rabbi at whose feet we must continue to imbibe the fountain of spiritual wisdom. May our good Lord continue to bless you as you continue to support, and watch over the Chapel with your fatherly gesture.

Professor G. Odia and other members of the Chapel Volunteer Singers — but for your company how would I have managed my spiritual life.

Revd. Dr Aggrey of Ghana in the early 20th century said "Churchianity is no Christianity and Religiosity is no morality", speaking to the pretences and colonial mentality of the whiteman.

But then in Prof. Odia, the CVS family finds a gifted and thoughtful leader who is so concerned about the salvation of the flock. May the good Lord continue to enrich your fatherly wisdom and the **weekly activities** of the CVS.

Mrs. Dele Awere, leader of **CODISA** (Committee for the Disabled), your very bright ideas are beginning to yield quantum dividends. May the good Lord grant you the spiritual strength to lead **us** in the group to greater heights and achievements (Cheshire home, Atunda Olu home, Modupe Cole home, SCIAN Centre etc). You are indeed a spirit – guided leader.

Professor Bode Gbenle — leader **Cheshire home**. The Lord is your strength, may He continue to bless you, Dr. (Mrs) Jane Ajuluchukwu and the others as you sacrifice time and effort for the sake of the less fortunate members of our society. And the National leader of the Bernard Cheshire Home Nigeria, Chief (Mrs) A. Y. **Oyediran** — may the good Lord recompense you in 100 fold measure the unimaginable exemplary care and contributions you have endowed on the **less fortunate** in Nigeria **all these years**.

Mrs. Bimbo Dada, Prof. (Mrs) Ogunlesi, *et al.* May the good Lord bless you richly for all the work and

leadership of the Hope and Anchor Fellowship group, Prof. (Mrs) Ogunlesi – those Bible expositions have been a source of blessing to us all in the fellowship.

Humility, respect for and service to the elders of the society are necessary rites of passage to graceful ageing. Show me a man without culture he is doomed for life. May I thank the following members of the Association of Egba Chiefs living in Lagos and Environs through whom I have learned so much about the culture of our land.

Chief (Dr.) M.A Majekodunmi (Life President), Sir Chief (Dr.) E.O. Smith, Wesleyan Knight of the Methodist, (1st Vice President), Chief A. Branco (Chairman), Chief (Mrs) A.Y. Oyediran (Past Chairman), Chief R.A.O. Oriade (Past Chairman), Chief (Dr.) T.A. Ogunmuyiwa (Past Chairman), Chief B.A. Olaogun (Past Chairman), Chief (Mrs) S.A. Lambo, Chief (Mrs) I.M. Ogunmuyiwa, Chief (Lady) Ayo Alakija, Chief (Lady) K. Smith, Chief (Mrs) F. Branco, Chief (Mrs) B.A. Akinwande, Chief I.O. George (Treasurer), Chief J.A. George, Chief A.A. Sanyaolu, Chief O. Sopeju (Gen. Secretary), Chief (Mrs) E.M. Sanyaolu, Chief O. Lucas, Chief (Mrs) A.O. Elliot, Chief T.O.O. Adetutu, Chief M.O. Bajulaiye, Chief (Mrs) M.B. Edu, Chief S. Fashanu, Chief (Mrs) O. Adetutu, Chief V.O. Odofin-Bello, Chief (Mrs) F. Fashanu, Chief J. Ola-Kogbodoku, Chief (Mrs) C.A. Odofin-Bello, Chief A.A. Soyoye, Chief M.A. Ishola Jagun, Chief O.A. Soetan, Chief R.O. Soyinka, Chief (Dr.) A.O. Ajayi, and Chief H.O. Taylor.

I promise the **Onigbogi** of **Igbogi** I will continue to support the Lagos branch of the movement with all God-given resources at my disposal. I shall make sure Igbogi, the lost tribe of Israel, the beloved children of God is carved out and given a separate State of their own to avoid pollution by the rest.

Debts of Honour

Mr. Vice Chancellor sir, please permit me to reflect some of the old man's wishes. He was penning down some names in his second book when the good Lord came calling him to the bosom of our Lord Jesus Christ: the late Pa Nathaniel Ladner, the late Very Revd. C.J. Patterson (former Archbishop of West Africa, Anglican Communion), the late Justice Peter Thomas, All Demgrites Past and Present, Pastor Pharmacist Ifeanyi Atueyi, the late Honourable Dr. Nnamdi Azikiwe, the Egbuche and Mba Kindred groups of Onitsha, the Aprekuma Kindred group of Brass, Bayelsa, His Excellency General Yakubu Gowon, Chief Tony Enahoro, the late Chief Abiodun Aloba, the late Chief Bola Shadipe, the late Chief Olubunmi Thomas, the late Chief Olabisi Onabanjo, the late Uncle Tai Solarin, Chief Lateef Jakande, Alhaji "Alade" Odunewu, the late Justice Adetokunbo Ademola, the late Prof. Saburi Biobaku, (former Vice Chancellor, University of Lagos), the late A.K. Blankson, the late Adewale Fashanu, the late Jimmy Adetutu, Chief Olu Akinfosile, the late Dr. Emma Phil-Ebosie, the late Prof. Miller Jaja, the late Dr. Nebo Graham-Douglas, Mr. Dove Edwin, the late Bobby Benson, Chief T.O.S. Benson, the late Mr. & Mrs. Midley-Scott, the late Mrs. Omolara De-Bordes, the late Revd. Col. Hunter, the Very Revd. Akinbobola, the Very Revd. T.A.J. Oluwole (All Saints Church – Yaba). The late Pa Nicole, the late Justice Akibo Salvage, Prof. and Mrs V.W. Fowler, Dr. & Mrs. Z.D. Brodie-Mends, the late Mr. Peter Anyansi, and Mrs Florence Anyansi, the Omoliyi Coker descendants of Popo Aguda, Chief 'Yinka Norman-Williams, Barrister & Mrs. Jide Oki, Prof.& Mrs. V. Akinsete, Engr. Akin Laguda, Mrs. Hilda Adefarasin, Alhaji Ogunsanya to mention but a few.....

May I say thank you **indeed** to Dr. Adeleke Adesegun, Dr. (Mrs) G. Ukpo, Dr. (Mrs) Owolabi, Mrs Adepoju-Bello, Dr. L. Kasim, Dr. Abioye, Mrs. Ajayi and Mrs. Olarewaju for helping to reproduce all the structural diagrammes in this lecture. Mr. T.A. Adetunji of Unilag Press, thank you for reading the entire manuscript and effecting necessary corrections. Thank you Miss 'Lara Johnson for typing the entire manuscript.

Mr. Vice Chancellor sir, Deputy Vice Chancellor (Academic and Research), Deputy Vice Chancellor (Management Services), our amiable Registrar (the exquisite Lady of Windsor, Buckingham, near Ikenne), other Principal Officers of the University, the entire **College of Medicine**, **Faculty of Pharmacy**, Members of the PSN, PCN, distinguished guests, ladies and gentlemen. I present to you.

My Inaugural.

Thank you and God bless you all.

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