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Inaugural Lecture Series 149

**DRUGS: - INTO, AROUND
AND OUT**

BY

FESTUS ADIO OGUNBONA

Professor of Pharmaceutical Chemistry

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PREAMBLE

I) PHARMACEUTICAL CHEMISTRY IN PHARMACY

It is indeed a great pleasure for me today to have the honour and privilege to inaugurate, for the first time in this great University, the Chair of Pharmaceutical Chemistry. Pharmaceutical Chemistry is a discipline which is regarded as the backbone of Pharmacy but often considered by the students (erroneously though) as too abstract. A Pharmaceutical Chemist is a versatile pharmaceutical scientist who can engage in several areas of research such as synthetic chemistry, natural product chemistry, Pharmaceutical analysis, quality assurance and pharmacokinetics to mention but a few. In Synthetic Chemistry, he engages in the synthesis of new drugs or in the study of the structural modification of known drugs or templates from natural products. Many Pharmaceutical Chemists have made their mark in the area of quantitative structure activity relationship (QSAR) or contributed their quota to our understanding of the mode of action of drugs through their research activities in synthetic chemistry. In the area of natural product chemistry, there are many Pharmaceutical Chemists engaged in the isolation of active ingredients from natural sources like medicinal plants, terrestrial and marine animals *etc.* Using isolated compounds from these sources as templates, he can make several derivatives for testing as drug candidates. In the field of Pharmaceutical analysis and quality assurance, the expertise of the Pharmaceutical Chemist is challenged in the development of new methods of analysing drugs and other pharmaceuticals not only in raw materials and drug preparations but also in various biological fluids. He can engage himself in the area of Pharmacokinetics, a clinically oriented research endeavour. It is relevant to state very clearly that a reputable Pharmaceutical Chemist, given his versatility and usual bundle of energy (high), invariably distinguishes himself in two or more of the areas mentioned above without losing his focus. I venture to say that all the above-named areas of research are receiving adequate attention in our Department which has established strong linkages with various laboratories in many parts of the globe like Britain, Germany, Sweden, Canada and the United States of America. I am proud to belong to a Department of Pharmaceutical Chemistry which has grown over the years to become the strongest of its kind in Africa, particularly in terms of the quality and quantity of the human resources on ground.

III) PHARMACOKINETICS

A drug can be defined as an agent in use for the diagnosis, mitigation, treatment, cure or prevention of diseases in man or his economic species. It has been asserted that the vast array of effective medicines available today represent indeed one of man's greatest scientific accomplishments. There are over 2,000 drugs (over 20,000 drug products) in circulation in the world today. For example, the 1993 British Pharmacopoeia (BP) describes 2,040 monographs of drugs. There is need to state very clearly that we Pharmacists do recognise the fact that drug discovery and development involves the collective contributions of many scientific specialists including Chemists (organic, physical and analytical), biochemists, physiologists, pharmacologists, toxicologists, pathologists, physicians, biostatisticians and computer scientists.

When a drug is administered to man, the patient and his physician or therapist are interested in the relief expected in terms of the action of the drug on man. It is easy to neglect the fact that man himself has to act on the drug. Indeed, with only a few exceptions, it is the action of man on the drug which precedes the action of the medicine on man. For example, considering a drug given by the oral route (the most common route of administration of medicines) the drug has to move invariably from the gut into the blood stream before it can be effective. The movement of the drug around in the body involves its interaction with various parts of the body at molecular level. The monitoring of such an interaction requires the development of highly sophisticated analytical tools which will evaluate the interaction in a qualitative and quantitative manner. While traditional Pharmacology deals with the action of drugs on man, Pharmacokinetics is the science involved in such an investigation of the action of man on drugs and it is a discipline which now attracts pharmaceutical scientists, analytical chemists, clinical pharmacologists and other scientists. A combination of the Greek word "Pharmakon" meaning drug and kinetics, pharmacokinetics is a pharmaceutical science which involves a study of the kinetics of absorption, distribution and elimination of drugs.

Such studies are carried out in laboratory animals such as rats, mice and rabbits, in monkeys, dogs, sheep and other man-mimetic animals as well as in man himself.

Pharmacokinetic studies are essential in drug development at both pre-clinical and clinical phases, in drug quality assurance, therapeutic drug monitoring and toxicological evaluation of medicines to mention but a few. For example, in therapeutic drug monitoring, an understanding of the knowledge of the pharmacokinetics of a drug can be utilized in the individualization of dosage regimen of the drug. This has proven to be very essential and invaluable in the management of patients undergoing acute or chronic therapy with life-saving drugs such as digoxin, a cardiac glycoside, lidocaine, an anti-arrhythmic agent (indicated in severe ventricular arrhythmias), gentamicin, an aminoglycoside antibiotic, usually reserved for treatment of serious gram-negative bacterial infections.

Absorption of a drug is a process involving the movement of a drug from the site of administration into the systemic circulation *i.e.* into the blood stream. This movement into the blood occurs in most cases by a passive diffusion process dependent on the characteristics of the drug product, the drug substance as well as the membrane being penetrated. The amount of the drug absorbed and the rate at which it does so have important bearing on the action of the drug on man. The blood carries the drug around to various parts of the body in what is termed a *distribution process*. The movement into the tissues and other body fluids depend on same factors as those controlling the absorption process. The organs, tissues and other body fluids which take in the drug during the distribution process and the rate at which they do so greatly influence both the intensity and duration of action of the drug in question. It is pertinent to note that it is in the course of this process of distribution that a drug may "strike" at its site of action (receptor sites). Presently, our understanding of the detailed knowledge of membrane characteristics coupled with high technology, employed in drug manufacturing, are being exploited to produce target drugs.

A drug is a foreign agent (a xenobiotic) in the body. It is one of the various xenobiotics to which man is exposed. Other xenobiotics include pesticides, food additives, smoke and many other environmental pollutants. A drug, like any other xenobiotic, is cleared out of the system as fast as the body can do so, depending on the nature of the drug and the formulation of presentation as well as the pathophysiological conditions of the patient.

Thus, the pharmacokinetic parameter used to account for drug elimination (loss) from the system is known as *clearance*. Elimination of a drug can be by metabolism usually by the liver and by excretion usually through the kidney as a consequence of which drugs and their metabolites are found in urine. However, drugs are also lost through faeces (biliary excretion), sweat, breath and breast milk. It is relevant to mention here the distinction between a drug properly formulated, administered, absorbed and lost through faeces and a poorly formulated drug product lost in faeces as tablets or capsules without undergoing any of the processes of absorption or distribution.

B. CONTRIBUTION TO DRUG METABOLISM

Some of the key areas of Pharmacokinetics include: metabolism, bioavailability and toxicokinetics. My contribution to Pharmacokinetics began in the area of metabolism. *Drug metabolism* is the process by which the body converts drugs usually into more polar and water-soluble derivatives in order to facilitate their excretion from the body. The most common routes of drug metabolism are oxidation (the major route of metabolism of many drugs), reduction, hydrolysis (all termed Phase I reactions) and conjugation (Phase II). Given the fact that most drugs are usually lipid soluble compounds, such a chemical interaction with macromolecules in the system is required to eliminate them from the body. For example, Brodie (1964) stated that without such processes as drug metabolism, it would take the body about a hundred years to terminate the action of pentobarbitone (a highly lipophilic sedative-hypnotic) in man. It can only be imagined if all the drugs one had ingested say in the past twenty years still remain in circulation in the body till the present time. Hence, the importance of such a process which facilitates the movement of drugs *out* of the body cannot be overemphasized.

My initiation into this interesting area of pharmaceutical sciences occurred during my days as a graduate student in Professor Beckett's laboratory at the University of London. It is known that drugs are mostly weakly basic or acidic compounds with the former group invariably possessing one or more nitrogen atoms in their molecules. Amphetamines and derivatives form one of such groups of basic drugs. Amphetamines used to be notorious in those days as drugs of abuse in sports in the developed world but was better known here in Nigeria to

students of those days in form of dexamphetamine, a bad drug of choice for keeping awake till day break (TDB)! In the early seventies, Beckett's laboratory at Chelsea College was in the forefront in unravelling the disposition of this group of drugs in man employing mainly the *in-vitro* methods of studies. It is pertinent to note that the laboratory was also famous as the dope testing centre in Britain at that time particularly for horse racing. All graduate students in the laboratory had to come to work, in shifts, on Saturdays to analyse urine samples from the winning horses and their jockeys for any drugs of abuse. This marked my first encounter with drugs of abuse in sports. There is no doubt that the pioneering efforts in that laboratory coupled with the vigorous campaign by Prof. Beckett on the dangers of such drug abuse led to dope testing in sports world wide. The consequence of such an abuse on sportsmen can be exemplified at the last World Cup competition, tagged USA 94, during which Diego Maradona of Argentina tested positive to ephedrine and four other related drugs including pseudoephedrine after the Nigeria/Argentina encounter on June 25, 1994. This ended his participation in that competition while also earning him a 15-month worldwide ban from any FIFA organised tournaments. At the 15th Commonwealth Games held in Canada in August 1994, a member of the Nigerian quartet in the 4 x 400m relay was sent back from the Vancouver International Airport in Canada when he was found on arrival (with the Nigerian contingent) to be in possession of some steroid injectables, syringes and needles. He was not even allowed to get to the Games village in Victoria, B.C. (the venue of the competition). Such examples underscore the seriousness attached to dope testing in sports at international level. It is unfortunate that Nigeria has not found it necessary to start running such tests on our sportsmen, if only at national competitions. One hopes that we will not wait until we are further embarrassed at such occasions abroad before we tap the resources available to embark on dope testing in sports in Nigeria. Our Department, if provided the necessary facilities, has the human resources capable of carrying out such tests. The same is true of some other laboratories in our Schools of Pharmacy in the country.

Nitrene Formation - a Novel Route in drug metabolism

In the investigation into the metabolism of the amphetamines, the focus of research attention was on the nitrogen centre in the molecules of these amphetamines. Emphasis was also laid on the most important phase I reaction in drug metabolism *i.e.* oxidation. The publications by Beckett

& Al-Sarraj in 1972 on the metabolic oxidation of amphetamine seemed to have wrapped it all up with a comprehensive description of the oxidative pathways and the mechanism asserted to be followed by this group of compounds, as a general rule (Beckett & Al-Sarraj 1972 a,b). Results from other workers in the laboratory and other laboratories supported this great discovery. Those of us who were privileged to be working in the same laboratory at that time (graduate students and post-doctoral fellows) seemed happy enough to be part of the history. We all became involved in coining a name for the class of compounds produced by the action of chemicals (e.g. acids) rather than enzymes in the body. Hence, I was one of those who 'christened' metabolic products of non-enzymatic origin as 'metabonates'. Others who were part of the history that time included Professors Ron Coutts, Kamal Midha, Pierre Belanger, Bernard Testa, Peter Jenner, Ron Reid, Ettiene Essien, John Gorrod and many more. One thing in common about this group is that all are still active in pharmaceutical research up till today. Many, in fact, are notable scientists, authors and world renown authorities in pharmaceutical research, particularly in the area of Pharmacokinetics.

Amphetamine is a primary amine while the drugs I had for my Ph.D. project were secondary amine derivatives of the drug like ethylamphetamine and fenfluramine. It was expected that I would show that these compounds followed the same metabolic pathways as had been proposed in the classic papers under reference. After obtaining consistent pattern of results on this series of secondary (2°) amines I reported that my observations were at variance with the findings of the papers aforementioned. In essence, I observed that the major metabolic product of the secondary amines after incubation with microsomal preparations from various laboratory animals were not hydroxylamines but some other compounds totally unknown at that time. This position I took generated a lot of heat and controversy but I stood my ground. The words of the great Late Martin Luther King, Jr. re-echoed in my mind during those days when he said and I quote:

"The ultimate measure of a man is not where he stands in the moments of comfort and convenience but where he stands at times of challenges and controversy".

The controversy raged on for almost a year. It was in early 1973 that my supervisor, Professor Beckett, brought in Professor Ron Coutts, a chemist of high repute and a sabbaticant from the University of Alberta,

Edmonton, Canada, to wade into this matter. His interaction with me led to our proposal that the major route in the metabolism of this group of 2° amines involved the formation of nitrones (Beckett *et al.* 1973a). Hitherto, the only nitrones which have been isolated and reported in literature have been cyclic nitrones. Indeed, literature was quite assertive, at that time, that aliphatic nitrones of the type that was being proposed as having the structures of these metabolites were unstable and could never be isolated. The novelty of my findings, therefore, rested on the fact that not only had I isolated these compounds from *in-vitro* metabolic studies on this group of 2° amines but that I had also synthesized and fully characterized many of such nitrones as stable compounds using gas chromatography, gas chromatography-mass spectrometry, nuclear magnetic resonance *etc.* (Beckett *et al.* 1973 b,c,d). The results of the study blazed the trail in various areas of medicinal chemistry research *viz.* synthetic, analytical and metabolic. This led to my bagging the Ph.D. degree in a record time (exactly 3 years and 5 days); a record unequalled in the laboratory throughout the period of Professor Beckett's career as an academician and a supervisor.

I wish to place on record, at this juncture, my gratitude to the late Professor H.A. Oluwasanmi, the then Vice-Chancellor, who in his usual candour and commitment to excellence insisted that I had to go and work with Professor Beckett. In 1970, I had an AFGRAD scholarship to do my Ph.D. in North Dakota (on the recommendation of the University). All seemed set until sometimes later in that year when H.A. informed our Faculty that he had completed every arrangement for me and another colleague of mine to proceed to London and study in the laboratory of the No. 1 pharmaceutical chemist in the world at that time (*i.e.* Prof. Arnold H. Beckett). At first, we insisted that we would go to the USA even if it meant losing our job as Assistant Lecturer in the University because we were bent on having a new system of education other than the British type. He sent messages to us to make us understand that the University Staff Development Programme will be executed under his administration to train all categories of staff in the best laboratories and schools in the world wherever such existed emphasizing that his position was informed solely by the search for excellence. After due consideration, my colleague and I consented and proceeded to London bearing in mind that the University was to bear the full cost of our tuition and maintenance as opposed to the full scholarship offered us in the US. One must salute the foresight of the man who contributed immensely to the development of academic excellence in the university system in

Nigeria particularly in making it possible for people like me to stand before you today and inaugurate the first chair of Pharmaceutical Chemistry in this great University. May his sweet soul continue to rest in perfect peace (Amen).

C. TOXICOKINETICS OF ASPIRIN

Toxicokinetics, a branch of Pharmacokinetics, is the study of the absorption, distribution and elimination of drugs in the overdose situation. It is known that following the ingestion of a large dose of some drugs each of the processes aforementioned may be altered. An awareness of the toxicokinetics of specific drugs may assist in the choice of intervention by the physician. My encounter with this area of research in drug misuse occurred in 1981 when I received the Commonwealth Academic Fellowship award which I spent at the School of Pharmacy and Pharmacology, University of Bath in U.K. It happened that this was a period when Britain was experiencing a new dimension of drug misuse involving over-the-counter drugs like common analgesics. These medicines such as aspirin and paracetamol were taken in very high doses with the intent of committing suicide but sometimes through accidental ingestion, for example, by children. Aspirin is a very versatile drug indicated in pain, fever and inflammatory conditions and more recently in the secondary prevention of myocardial infarction and stroke. Its wide availability is responsible for its misuse either accidentally or intentionally often resulting in overdose which can cause hyperventilation, tinnitus and deafness to mention but a few. Overdose with aspirin have also proven to be fatal. The classical treatment for severe salicylate poisoning is forced alkaline diuresis, a method usually considered by physicians as cumbersome and severe for the patient. Our work, carried out in collaboration with Dr. Peter Bennett, a notable Consultant Physician to the Royal United Hospital in Bath and Reader in Pharmacology at the University of Bath, centred on the development of an alternative mode of intervention to be based on the knowledge of the toxicokinetics of the drug. Aspirin, when administered to man, is converted by hydrolysis to salicylic acid which is further metabolised. One of the important metabolic routes thereafter for salicylic acid is a conjugation reaction with glycine (an amino acid) resulting in the formation of salicyluric acid. It has been asserted by previous workers that this process becomes saturated in aspirin overdose probably due to the depletion of the glycine pool in the body. The consequence of the

saturation of the process is an accumulation of high salicylate concentration in the body manifesting in the adverse effects mentioned above (or death). We, therefore, investigated the effect of exogenously administered glycine as a possible antidote in salicylate poisoning. The hypothesis here is that if the body is supplied with glycine there is no reason why it cannot utilize it for the metabolic conversion of salicylic acid to salicyluric acid which will be excreted rapidly in urine. Essentially, we would be using the glycine as a pharmacodynamic agent to assist the body mechanism in its detoxification process. Our subjects for the trials were volunteers drawn from the patients of Dr. Bennett admitted to the Clinical Pharmacology Unit of the Royal United Hospital in Bath. We had to develop a new liquid chromatographic method which was used in measuring aspirin, salicylic acid and its metabolites in the urine collected from the patients. The results of our study showed that the administration of glycine in the first few hours following ingestion of aspirin in large doses may prove beneficial to patients presenting with salicylate poisoning. This is because it enabled the body to rapidly clear aspirin from the human system since it reversed the saturation step in the metabolic process aforementioned (Patel *et al.* 1990 a,b, Ogunbona 1986). The success of this new intervention technique became so overwhelming that it was becoming increasingly difficult for us (at that time) to recruit volunteers to use as control *i.e.* those to be given other methods of intervention or no treatment at all. More importantly, the impact of my research visit to Bath, at that point in time, served to change my focus to the area of Clinical Pharmacokinetics involving more collaboration with consultants in our environment in order to solve drug-related clinical problems.

D. PHARMACOKINETICS OF ANTIMALARIA DRUGS

It is known that over 40% of the world population live in malaria-endemic regions with the mortality rate due to the parasitic infection put at about 1.2 million annually. Malaria still remains one of the major causes of mortality and morbidity in Nigeria particularly among children. There are many drugs in use for the prophylaxis and cure of this debilitating disease which is the major source of loss of many man hours in the country. It is instructive to observe that with health education at various levels, Nigerians have stopped wasting resources on prophylaxis for the general populace since it has been well established that such a practice lacks any merit. Prophylaxis against malaria is now recommended for special risk groups namely the pregnant women,

sickle-cell patients and non-immune residents. While pyrimethamine and proguanil are usually the drugs of choice in the semi-immune who require prophylaxis, it is often recommended that the non-immune visitors begin a weekly course of chloroquine a week before travelling to the malaria zone particularly if the area(s) being visited have prevalence of chloroquine-sensitive *Plasmodium*. When the area being visited has chloroquine-resistant *Plasmodium* strain, a weekly dose of 250 mg mefloquine is recommended for the non-immune residents. The chemotherapy of malaria in the endemic regions of the world has been a subject for debate at several conferences with the frightening rapid spread of chloroquine-resistant *falciparum* malaria. However, it has always been agreed that given due consideration to the safety, affordability, availability and efficacy of chloroquine, the drug should continue to be used as the first line drug in malaria infection where the sensitive strain of the notorious *falciparum* is prevalent. The combination of pyrimethamine with a sulphonamide (common brands: Fansidar® & Metakelfin®), mefloquine, halofantrine, amodiaquine and quinine are the second line drugs available in the country today.

In the last one and half decades, we began studies on the metabolic and pharmacokinetic aspects of antimalarials in man. This research has been carried out in collaboration with my colleagues within and outside our Faculty, the University and the country. It is on record that several graduate students have worked with me to earn their master's and doctorate degrees of this University on the project. Indeed, the first two Ph.Ds in Pharmaceutical Chemistry to be awarded in Nigeria were produced in this University (Great Ife), under my supervision, on this project. A third one is in the making.

In the course of our investigation into the pharmacokinetics and metabolism of the antimalaria drugs, we have had to develop new methods for the identification and determination of these compounds in their pharmaceutical preparations but most importantly in biological fluids. The antimalarials we studied included: pyrimethamine, proguanil, chloroquine, amodiaquine and the cinchona alkaloid, quinine.

a) *Pyrimethamine*

We examined, in great depth, the disposition of pyrimethamine (the common Sunday-Sunday medicine, marketed as Daraprim®) in man monitoring the levels in biological fluids for weeks after a single dose.

We could not isolate a single metabolite of the drug in man. Dr. Bolaji received his M.Phil. degree of the University after synthesizing and characterising all the possible metabolites of pyrimethamine and faithfully demonstrating that none of them could be found in man (Ogunbona & Bolaji 1980). I believe that today he is benefitting from his honest approach to pharmaceutical research since in those days and up till today we avoid sensationalism and artifacts which may only make local heroes of scientists. In essence, we try never to sacrifice honesty in our everyday life, including research, on the altar of the number game. It is pertinent to note that up till date, given all the state-of-the-art technology now available to us in biopharmaceutical analysis, no single metabolite of the drug has been isolated and characterised in man.

b) *Proguanil*

In our work on proguanil, a new liquid chromatographic method was developed enabling the measurement of nanogram levels of the drug and the known metabolites, cycloguanil and *p*-chlorophenyl biguanide, in human biological fluids. This project was done in collaboration with Dr. Ogungbamila. Earlier in the work carried out with Olowu, we had shown that the disposition of proguanil in man is influenced by the age of the individual. In fact, our results revealed that with an increase in age up to forty years there was a gradual and significant increase ($p < 0.05$) in the percentage of an oral dose of proguanil excreted unchanged in human urine (Ogunbona & Olowu 1986). Recently, we have demonstrated that proguanil is passively secreted into human saliva (Onyeji *et al.* 1989). The results of the study carried out with Dr. Onyeji showed that there was a good correlation ($r = 0.82$) between the saliva and plasma concentration of the drug. The significance of the findings here is that saliva level measurement can be substituted for blood level determination in therapeutic drug monitoring as well as in the computation of pharmacokinetic parameters of proguanil.

c) *Amodiaquine*

Although amodiaquine is no longer recommended for use in any official compendia, it is a fact that it is still being prescribed by our physicians here in Nigeria. We investigated its pharmacokinetics in Nigerians, healthy and those presenting with parasitemia. Our results showed that N-dealkylation to monodesethylamodiaquine is a significant route in the metabolism of the drug in man. More importantly, our findings (Fabayo

& Ogunbona 1991, Fabayo *et al.* 1992) on the various aspects of the fate of this drug in man has served to confirm how changes in the side chain of a drug molecule can tremendously alter the pharmacokinetic behaviour of the drug when administered. The difference between chloroquine and amodiaquine is in the structures of the side chain on the 4-aminoquinoline moiety. The results of the study carried out with Dr. (Mrs.) Fabayo revealed that amodiaquine is not just another 4-aminoquinoline drug that can be assumed to have similar basic pharmacokinetic profiles like chloroquine. Indeed, it has completely different disposition kinetics in man with expected toxicological implications, thus underscoring a note of caution on the use of amodiaquine in malaria chemotherapy. In fact, it is no longer recommended for use in Britain and many other parts of the developed world because of high incidence of agranulocytosis associated with the drug. This serious toxic effect, which is missing with chloroquine therapy, has proved to be quite fatal in some cases. It was reported that, in a period of one year (ending March 1986) of close monitoring of patients presenting with this adverse effect following amodiaquine therapy in Britain, U.S.A. and Switzerland, seven of the twenty-three reported cases proved fatal (Martindale 1993). The results of our pharmacokinetic study on the drug (using Nigerian subjects with or without parasitemia) do not support the prescription practice and wide use of amodiaquine in Nigeria. It is relevant to note that the drug is not included in the Essential Drugs List in Nigeria. It is hoped that Pharmacists will continue to advise both physicians and patients on the need to stop the use of this drug until clinical research conducted here in Nigeria proves that our people are not predisposed to agranulocytosis following amodiaquine ingestion with the risk of this fatal side-effect worldwide now put at between 1 in 1,000 and 1 in 5,000.

d) Quinine

Recently, it has been asserted by the Malaria and Vector Control Unit of the Federal Ministry of Health that chloroquine - resistant strains of *Plasmodium falciparum* has become widespread in the country particularly in the South-Eastern zone leading to increased morbidity and mortality from malaria infection in that area (Ekanem 1985). Quinine is a drug of choice in the management of patients presenting with chloroquine - resistant malaria as well as severe and complicated malaria. The re-introduction of this cinchona alkaloid into malaria chemotherapy should be guided by an understanding of its

pharmacokinetics so as to minimize, if not completely eliminate, the undesirable toxic effects of the drug which led to its withdrawal from widespread use against the disease. The need to gather pharmacokinetic data in volunteers and patients became necessary in order to ensure, among other things, that the dosage regimen for the drug is based on sound scientific knowledge. There have been some reports in literature on the pharmacokinetics of the drug in Thai volunteers and patients. It was thought necessary to gather such data in Nigeria since there could be differences in the fate of drugs between the two races. We worked in close collaboration, in this regard, with Professor Salako and his vibrant research group in the Clinical Pharmacology Unit of the University College Hospital, Ibadan. We developed a liquid chromatographic method for analysing the drug in various biological fluids (Babalola *et al.* 1993). Using this method, we have investigated the fate of quinine in healthy Nigerian volunteers and in patients presenting with malaria. The results of our study on this drug revealed that there were differences in the fate of the drug in Nigerians compared to the Thais suggesting the possibility of inter-ethnic variation in the disposition of quinine in man. It was also demonstrated that saliva level determination could provide a non-invasive method of monitoring quinine levels in man in order to ensure compliance and prevent toxicity. Our findings also revealed that quinine pharmacokinetics was linear over the dose range of 250 - 1,000 mg thus making it possible to predict the effect(s) of increased dosage of the drug in man (within this range).

e) Chloroquine

Our Pharmacokinetics Research Group in Ife became quite famous since the 80s because of our contribution to the disposition kinetics of chloroquine, a drug which has retained its position as the first line drug in the chemotherapy of malaria in Nigeria given its unique properties earlier mentioned. We developed a simple, accurate, specific, reproducible and sensitive liquid chromatographic method for the analysis of the drug and its major metabolite, monodesethylchloroquine (CQM), in various biological fluids *viz.* plasma, saliva, urine and breast milk. This method has been found suitable for determining nanogram levels of the two compounds in biological fluids (Ogunbona *et al.* 1986a). There was no interference from other drugs which are usually co-administered with chloroquine(CQ). The method has found use in our laboratory and other laboratories all over the world not only in

pharmacokinetic studies of the drug but also in quality assurance tests for CQ products - capsules, syrup and tablets.

i) Antimalaria-Associated Pruritus

Armed with this method, we have investigated the pharmacokinetic aspects of chloroquine associated pruritus in due consideration of our finding from an epidemiological survey carried out in 1979 in the University community (here in Ife) that the incidence of the pruritus seemed to be on the increase compared to what had been reported in literature by Ekpechi and Okoro in 1964 and Olatunde in 1977. Ten years later Ajayi and others using the same University community here in Ife reported that 74% of the total respondents (1,100) to their survey reacted with pruritus to antimalaria therapy. 64% of the itchers reacted to chloroquine, 30% to amodiaquine and 2.5% to pyrimethamine/sulphadoxine (Ajayi *et al.* 1989). Antimalaria - associated pruritus is a well known side effect of chloroquine with the incidence claimed to be higher in blacks than in the Caucasians (Lindquist 1972). There is no doubt that it has been one of the main factors responsible for non-compliance in malaria therapy involving the use of chloroquine. This is well illustrated by the finding of Mnyika & Kihamia (1991) in a study conducted on patients in Dar es Salaam, Tanzania which showed that 91% of habitual itchers said that this side-effect had deterred them from using chloroquine for treatment of malaria. The consequence of the lack of compliance in such endemic regions may be inadequate chemosuppression and this may contribute to the emergence and spread of multidrug resistant strains of the malaria parasite. In our pharmacokinetic investigation using habitual itchers and non-itchers, it was our hope that we could find distinct differences in the disposition kinetics between the two groups of Nigerians. However, there was no significant difference found in the various pharmacokinetic parameters of the drug computed from the blood level data in the two groups of volunteers. It was only in the metabolism of the drug, as determined from urine level data of the drug and its major metabolite (desethylchloroquine), that some differences began to emerge indicating that habitual itchers appear to be poor metabolisers of the drug. This finding has been corroborated by the work of Ademowo (1994) at the University College Hospital, Ibadan when he showed that some genetic factors are involved in the pruritic reaction to chloroquine. All researchers in malaria chemotherapy in the country have recognised the need to elucidate the aetiology of this side effect with a view to evolving

an effective therapeutic management beside the discontinuation of the chloroquine therapy. There is no doubt that an inter-disciplinary approach will be required to reach our goal in this regard.

ii) Saliva Secretion of Chloroquine

Passage of drugs into the salivary glands is usually by passive mechanism. It has been asserted that while saliva can contribute to drug recycling in the body its volume is too small for it to make any impact on such a process which may lead to prolongation of drug action in man. However, the occurrence of only unbound drug in saliva makes it a useful fluid for estimation of pharmacokinetic data of drugs particularly when a correlation exists between saliva and plasma levels of the drug in question. Use of saliva in pharmacokinetic studies has the advantages of convenience, painlessness and non-invasiveness. Theoretically, the saliva /plasma ratios of basic drugs like chloroquine is given by

$$C_s/C_p = 1 + 10^{(pH_s - pK_a)} / 1 + 10^{(pK_a - pH_p)} \times f_p/f_s$$

where C_s = concentration of drug in saliva
 C_p = concentration of drug in plasma
 pH_p = plasma pH
 pH_s = saliva pH
 f_p = fraction of drug in plasma
 f_s = fraction of drug in saliva

Saliva secretion of drugs has been reported to occur for some drugs including the antimalaria drug, pyrimethamine (Ahmad & Rogers 1981) but no such report was available for chloroquine. Our publication in 1986 on saliva secretion of CQ and CQM in man was, therefore, the first to be reported about the drug in literature (Ogunbona *et al.* 1986b). We showed that pharmacokinetic parameters like elimination half-life and the time of peak concentration (t_{max}) derived from saliva data were similar to same values reported for the drug but derived from plasma data by other workers. The saliva/plasma ratio of the drug was independent of the route of administration. Our findings in the study provide a non-invasive and more convenient method for the therapeutic monitoring of CQ in patients. We also suggested that it was possible to obtain, using saliva data, estimates of some pharmacokinetic parameters of the drug (based on the correlation we found between saliva and plasma levels in the elimination phase and) since it is easier, particularly in our

environment, to recruit volunteers for saliva studies than for blood level trials.

iii) *Chloroquine in Human Breast Milk*

One can assume that any drug administered orally to the mother will be excreted in milk. This means that the infant may be exposed to a wide variety of drugs through breast-feeding. The movement of drugs into the mammary glands is invariably by passive diffusion. Some of the factors which will control the excretion of a drug in breast milk will, therefore, include the pH gradient between plasma (average pH = 7.4) and milk (average pH = 6.8), the pKa of the drug and its lipid solubility. The usual concentration achieved in milk for a majority of drugs has been found insufficient to elicit clinical symptoms in the infants. However, there are some drugs that are excreted in sufficient quantities in breast milk to cause observable and sometimes serious effects in the nursing infant. For example, Patrick *et al.* (1972) have reported that sufficient amounts of diazepam are excreted into milk of the mother to cause sedative effects in nursing infants. Erkola and Kanto (1972) found such high concentrations of the same drug and its metabolite, N-demethyldiazepam, in babies whose mothers received each 10 mg of diazepam three times a day for six days that he suggested that it is not safe for mothers to breast-feed their infants when they are taking diazepam. We, therefore, need information on drugs that are likely to be used by the nursing mothers both from the therapeutic and toxicological points of view. In the case of the antimalarials, such an information was available in literature only for pyrimethamine which was reported in a case study in East Africa by Clyde (1960) to be excreted in such sufficient quantities in breast milk following a weekly dose to the nursing mother to make it possible for prophylaxis to be achieved in her infant.

Our investigation into CQ excretion in breast milk was carried out in collaboration with Dr. Torimiro, a Consultant Paediatrician in our College of Health Sciences, and involved administration of a single oral dose of chloroquine (10 mg/Kg) to nursing mothers followed by collection of blood and saliva samples from the volunteers as well as urine samples from their neonates (patients of the Consultant) admitted into the neonatal ward of the Obafemi Awolowo University Teaching Hospitals Complex (OAUTHC), Ile-Ife. The results showed that higher concentrations of the drug occurred in breast milk compared to plasma suggesting that the drug behaves as expected for a basic drug. However,

computation of our results revealed that the maximum daily dose of chloroquine that could be excreted in human milk and presented to the nursing infant was about 0.7% of the maternal start dose of 600 mg (Ogunbona *et al.* 1987). Since Berlin (1981) has asserted that an amount of 1 - 2% of the maternal dose of a drug is usually considered safe to the nursing infant we concluded that it is safe for mothers to continue nursing their infants during the course of treatment for malaria with chloroquine. International recognition of our contributions to the fate of chloroquine in man is well illustrated by the copious citation given by the current edition of Martindale: The Extra Pharmacopoeia (the universally acclaimed source of drug information) to our publications on secretion of chloroquine in breast milk and saliva. In fact, in the 29th edition of the Martindale, the only citation on the absorption and fate of chloroquine under the sub-title 'Pregnancy and the Neonate' was our breast milk paper published in the *British Journal of Clinical Pharmacology* in 1987. It is pertinent to note that, in due consideration of our results and those of others published later, the American Academy of Paediatrics has declared that chloroquine is compatible with breast feeding.

iv) *Chloroquine in Pregnancy*

Recently, we have started to address the issue of safety of chloroquine in pregnancy by my three visits to the world recognised centre for this purpose at the University of British Columbia, Vancouver, Canada. These trips have been made possible by a fellowship award received in 1991 from Canadian International Development Agency (CIDA) and administered by the Natural Sciences & Engineering Research Council of Canada (NSERC) coupled with the exemplary and kind assistance and encouragement of my host at the Faculty of Pharmaceutical Sciences, UBC, Professor James Axelson. In the laboratories of Professor Axelson, the chronically instrumented sheep model has been developed to study maternal and foetal pharmacokinetics and pharmacodynamics of drugs in pregnancy. In the study on chloroquine, we used a dose of 10 mg/Kg of the drug for the pregnant ewe. Samples for analysis were collected from maternal artery, foetal artery, amniotic and foetal tracheal fluids. Various physiological and pharmacodynamic parameters like arterial pressures, heart rates, blood pH, haemoglobin content *etc.* were also monitored in both the pregnant sheep and the foetus. Our findings revealed that chloroquine did cross the placental barrier in sheep with no observable alteration in the pharmacodynamics of the pregnant sheep and the foetus. The pharmacokinetic profiles of the drug in maternal blood, amniotic

and tracheal fluids of the ewe and the foetus are similar to what have been reported for other basic drugs which have been investigated in the laboratory (Rurak *et al.* 1991). The results of our study so far with chloroquine suggest that the drug is safe in pregnancy if taken as prescribed. This finding confirms the need to further exploit the usefulness of the drug in malaria chemotherapy.

E. BIOAVAILABILITY OF DRUGS

Bioavailability of a drug is the rate and extent at which the drug reaches the general or systemic circulation from the site of administration of a drug product. Therefore, bioavailability is concerned with how rapidly (or slowly) and how much of the drug appears in the blood after a specific dose, which will, in turn, determine the response(s) to the drug. It is, therefore, an important pharmacokinetic parameter particularly for orally administered drugs. Bioavailability is usually determined by measurement of the peak plasma concentration (C_{max}), the time to attain such peak concentration (t_{max}) and area under the concentration-time curve (AUC). AUC is a quantification of the extent of drug absorption while both C_{max} & t_{max} measure the rate of transfer from the site of administration. Bioavailability studies can be employed in drug product development, drug and food interaction evaluation and drug quality assurance. It is employed in the latter to establish equivalence of drug preparations from different sources. It is now apparent that the mere fact that two drug preparations contain the same amount of active ingredient(s) does not assure that they will perform equally after administration. In fact, there are three levels of equivalence *viz.* pharmaceutical (chemical), biological and clinical. It becomes obvious that establishment of bioequivalence should form the basis of substitution of one brand of a drug by another brand or generic. This is because the consequence of inequivalence may be therapeutic failure in terms of lack of efficacy or toxicity. For example, we demonstrated in our bioavailability study on ampicillin in 1985 that substandard ampicillin capsules were in circulation in Nigeria (Ogunbona & Akanni 1985). Any patient who was unfortunate to be given the substandard ampicillin capsules at that time might not be cured of his infection even if laboratory tests showed that the causative microorganisms were quite sensitive to the drug. A change to another antibiotic by the physician with successful outcome in the patient may then be blamed on a false result from the laboratory. In several presentations to my colleague Pharmacists (at seminars, symposia *etc.*) I have always stressed the need

for Pharmacists to ensure that only quality drugs are sold and dispensed from their pharmacies as their contribution to curbing the menace of counterfeit, fake and substandard drugs in Nigeria. I am aware that the Pharmaceutical Society of Nigeria (presently under the able leadership of Professor Ogunlana) has continued to pursue vigorously the sanitization of the drug distribution system in the country as one of the ways of achieving this noble objective.

There have been efforts aimed at evolving fast *in-vitro* methods like dissolution rate test to serve as bioavailability indicator for drug preparations. In our study on diazepam tablets, we showed that dissolution rate test can actually serve as an indicator for the bioavailability of the drug (Ogunbona *et al.* 1985a) because of the good correlation we observed between the results of our *in-vivo* bioavailability study and the *in-vitro* dissolution rate tests on three brands of the drug investigated. We also discovered from our results that a poor quality brand of diazepam tablets was in circulation in the country at that time. This study carried out in collaboration with Professor Olaniyi, a notable author and Fellow of the Pharmaceutical Society of Nigeria, serves to illustrate the usefulness of interaction between Hospital Pharmacists and their academic counterparts because this investigation arose from the expressed curiosity of a Hospital Pharmacist on the quality of one of the brands of diazepam tablets delivered to her hospital.

FOOD AND BIOAVAILABILITY OF DRUGS

Food has been known to be one of the factors which may affect the bioavailability of drug preparations. Food may reduce the amount of drug absorbed or delay the absorption from the gut without affecting the amount absorbed. Furthermore, a dietary component like fat may influence the absorption of drugs particularly when such drugs are poorly water soluble such as digoxin and griseofulvin. Given that the usual times of administration of medicines like three times a day (t.i.d.) or four times a day (q.i.d.) are close to meals, it becomes pertinent to know the effect of taking our drugs with meals or the significance of the instruction and advice by the Pharmacist that certain drugs be taken before or after food. In our study on griseofulvin, a fungal antibiotic, carried out in collaboration with Dr. (Mrs.) Smith, a notable nutritionist, it was illustrated for the first time in literature that increasing fat contents of meals can lead to increasing bioavailability of griseofulvin in man

(Ogunbona *et al.* 1985b). The low fat Nigerian meal employed was *ogi* (pap) and *akara* (fried bean balls), containing 29.3% fat calories while the high fat meal was *dodo* (fried plantain) with corned beef stew, containing 52.4% fat calories. The results of the completely randomized cross-over study, in which overnight fasting and continuous fasting for 4 h after drug intake represented the third leg of the cross-over, revealed an increase of 70% following the ingestion of the low fat meal of *ogi* & *akara* and 120% after the high fat meal of *dodo*.

Another investigation was carried on the interaction of food with nitrofurantoin, a broad spectrum anti-bacterial agent. We showed that a fatty meal of fried plantain (*dodo*) and egg stew significantly increased the extent of absorption ($p < 0.05$) of nitrofurantoin in man (Ogunbona & Oluwatudimu 1986). Our publications on both griseofulvin and nitrofurantoin represent the first time that attempts were being made to examine how our local Nigerian food can influence the bioavailability of drugs. The implication of the findings is that therapeutic efficacy of both drugs may be enhanced in proportion to the fat contents of the meals taken by the patient. It is obvious from our findings, as well as those of other workers, that the nutritional status of the patient may greatly influence the handling of drugs in his body with consequences on the efficacy and toxicity of such drugs. It also stresses the need to undertake further research on how our local foods interact with the medicines that we take.

F CONCLUSION

In the course of my research efforts in the past two and half decades as a Pharmaceutical Chemist, I have had the opportunity to synthesize and characterize a good number of new compounds hitherto unknown in Chemistry. I have also succeeded in developing some new methods for the identification and determination of some drugs. Our contributions in the area of Pharmacokinetics, a phenomenon which describes the movement of drugs into, around and out of the body, has been recognised both at home and abroad. In essence, I have taken on the challenges in three of the areas earlier mentioned as the main areas of research of a reputable Pharmaceutical Chemist (synthesis, pharmaceutical analysis and pharmacokinetics). The impact of the contributions on pharmaceutical research in general and drug therapy, in particular, will be left to posterity to determine. However, it is clear to

me that, for us to continue to benefit maximally from the various innovations in drug therapy, pharmaceutical research must be encouraged in our tertiary institutions in the country. Furthermore, the government and its relevant agencies will have to continue to strive to eliminate the circulation of fake, substandard and adulterated drugs from the country so as to ensure that only good quality drugs reach the consumers. There is the need for the Nigerian populace to show respect for drugs by avoiding the dangerous habits of drug abuse and misuse which can only expose them to the risks and not the benefits of drugs. It is my belief that to derive maximum benefits from drug therapy it is necessary to adhere strictly to the instructions and advice on the use of drugs by the experts *i.e.* the Pharmacists.

Mr Vice-Chancellor, distinguished audience, I thank you all for your patience.

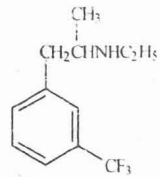
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FIGURE 1: STRUCTURES OF FENFLURAMINE, AND N-HYDROXYFENFLURAMINE



Fenfluramine



N-Hydroxyfenfluramine

FIGURE 2: MAJOR METABOLIC PATHWAY OF ASPIRIN IN MAN

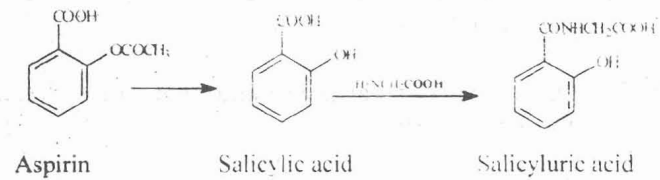
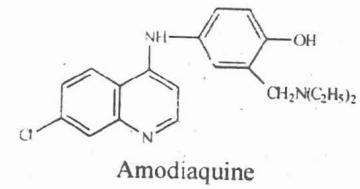
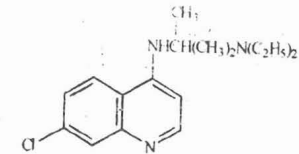


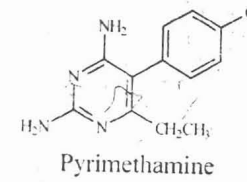
FIGURE 3: STRUCTURES OF SOME ANTIMALARIALS



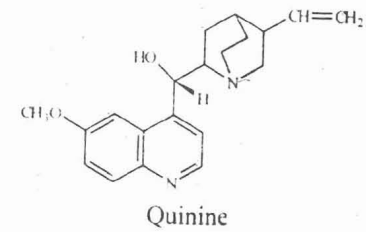
Amodiaquine



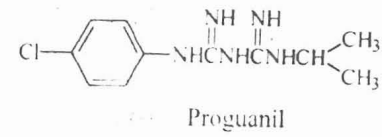
Chloroquine



Pyrimethamine



Quinine



Proguanil

FIGURE 4: METABOLIC DEALKYLATION OF CHLOROQUINE IN MAN

