Chapter Five

Recalling 'Therapeutic Exiles': Who Speaks for Women and Children?

Recalling 'Therapeutic Exiles': Who Speaks for Women and Children?

Mrs Helen Ochuko Kwanashie
Professor of Pharmacology
Department of Pharmacology and Therapeutics
Faculty of Pharmaceutical Sciences
Ahmadu Bello University, Zaria
Kaduna State, Nigeria

Wednesday, 30th April, 2014



Mrs Helen Ochuko Kwanashie
Professor of Pharmacology

Dedication

To My Father and My Mother
Gray Augustine Akpobi, and
Jane Eseoghene Akpobi:
Who being used of God
Tirelessly bore me up.
In recalling exiles
They did much more than speak
For this woman, their child.

Acknowledgements

By way of acknowledgements, I had attempted a list of all who had played any positive role in my academic pursuit and career development, and was amazed that at the time I decided to abandon the list (which included institutions, teachers, supervisors, colleagues, students, family, friends, individuals and groups, etc), it had run into several pages! Though not in print here, each one of them is highly appreciated. *Still, I must mention some.*

First and foremost, I wish to thank the Vice-chancellor and other principal officers of ABU, Chairman and members of the University Organised Lectures Committee, Ahmadu Bello University Press, Public Affairs Directorate; and all others who have contributed in one way or the other to the actualization of this lecture. Secondly, my heartfelt appreciation goes to each and every one of you who make up this audience; for your kind attention. I must admit that in today's *still largely men's world*, it requires large doses of patience and tolerance to sit through, and listen to one hour of mainstreaming women and children's issues into pharmacology teaching, research, community service and their applications - for which reason, I thank you *most profusely!*

I am immensely grateful to my supervisors at various levels:

- BSc - Prof Godwin Emerole and Prof Michael Fafunso
- MSc - Prof Godwin Emerole, Prof (Mrs) M. Ira Thabrew and Prof B.O. Osinusi
- PhD - Prof Charles Wambebe, Prof Gabriel Osuide and Prof Christopher Ikediobi
- Postdoc - Prof Brian Burchell.

Prof Emerole's enthusiasm for biochemistry was infectious, resulting in my developing a sustained preference for science, over and above medicine. Prof Wambebe was instrumental to my conversion from biochemistry to pharmacology, of which finally, I am very glad!

It is also my honour to pay respect to my fathers and mothers in pharmacology (in addition to Prof Osuide), in the persons of:

- Prof Lateef Salako

- Prof Abdul Fattah Biola Mabadeje
- Prof David Okpako
- Prof Hope Obianwu
- Prof (Mrs) Lotte Lege-Oguntoye, and
- Prof (Mrs) Janet Makinde.

The greater part of the contributions I have made on the subject of pharmacology (especially as presented in this lecture), was the outcome of active collaboration with my teachers, colleagues and students; and with the highly valued technical support of other (non-academic) colleagues. Many of them are actually reflected in the cited publications we co-authored; all are hereby acknowledged particularly the following:

- Dr Janet Ejiofor who did some of the artemether and siculine studies,
- Dr Temidayo Olurishe and Dr Sherifat Anafi who investigated the co-administration of antimalarial and antiretroviral drugs.

Special thanks are due to my husband, Prof Mike Kwanashie, our children (plus their spouses) and our adorable grandchildren. The *enabling space* Mike gave me to achieve was phenomenal, and I owe much of my personal success to that. I first met him in 1972, and although it's 40 odd years since then, Mike's still very much *my guy!*

I am most pleased and highly honoured to pay a special tribute to two very loving and highly supportive persons; in appreciation of their faith in me, and the seed they planted and nurtured in my life. This inaugural lecture is dedicated to them. I cannot think of anyone more deserving of the honour than these two, my parents: *Late* Mr Gray Augustine Akpobi (1926-2008) and *Late* Mrs Jane Eseoghene Akpobi (nee Oguma, 1937-1979). I dedicate this lecture to them because in addition to several other inputs into my life; together, they recalled me from a multifarious exile! The choice of cimetidine (the antiulcer drug, Tagamet®) as the drug subject of my PhD research, is itself, a tribute to my father who suffered severely from duodenal ulcer before the discovery of cimetidine, other H_2 receptor antagonists (and newer antiulcer drugs), as well as the definite implication of *Helicobacter pylori* in the aetiology of peptic ulcer disease. (I should add that he benefitted

greatly from using cimetidine). Similarly, my life-long interest in women issues may be attributable in part, to the times and experiences of my mother. It is an extremely deep sense of personal loss, pain and regret I feel, that neither of them is here today to witness my inaugural lecture presentation.

Last to be acknowledged herewith, but certainly not the least, my deepest, most profound gratitude of all goes to the triune God - Father, Son and Holy Spirit, who more than everyone else, worked with me... Indeed, like Isaiah 26:12 proclaimed, God has established peace for me all round, *and all that I have accomplished, He has done for me!*

While the pharmacological basis of this inaugural lecture had previously been expounded upon, the theme was inspired primarily, by some texts taken from The Holy Bible. The first two of these texts (one from each of the Testaments) make the point that God, the creator of the entire universe and all that is in it (including human beings), intended for men and women to be equal partners (albeit with different roles). I quote these key texts as follows:

> So God created man in his own image, in the image of God he created him; male and female he created them... He created them male and female and blessed them. And when they were created, he called them 'man.'
>
> *- Genesis 1:27,5:2, NIV.*

> *Submit to one another out of reverence for Christ.* Wives, submit to your husbands as to the Lord. For the husband is the head of the wife as Christ is the head of the church, his body, of which he is the Savior. Now as the church submits to Christ, so also wives should submit to their husbands in everything. Husbands, love your wives, just as Christ loved the church and gave himself up for her to make her holy, cleansing her by the washing with water through the word, and to present her to himself as a radiant church, without stain or wrinkle or any other blemish, but holy and blameless.
>
> *- Ephesians 5:21-27, NIV. (italicised emphasis, mine).*

The third inspirational text reports on God's constant desire to recall exiled persons, as exemplified by King David's dealings

relating to his recalcitrant son, Absalom - a figure of God's dealings with us. The text, and my exposition on it, read:

> The King's heart longs for us in exile (separated on account of wrong doing) … Who does not take away life; but devises ways so that a banished person may not remain estranged from Him.
> - *2 Samuel 13:39-14:1,14b. (paraphrased by me).*

And the King so loved
He gave *Him*:
Whose blood speaks
Far more eloquently
Than that of Abel…
And as many as would believe
Shall be eternally
Recalled from exile!
- © HelenOK, 2010.

Mr Vice-chancellor Sir, Ladies and Gentlemen, once again, I thank you for your attention. God bless!

Summary

This inaugural lecture is presented in four integrated parts (equivalent to chapters), with Part I being an introduction that sets the stage. Part II highlights the plight of women of child-bearing age, pregnant women, women in labour, breastfeeding mothers, and children below the age of 12, as *therapeutic exiles* since they are theoretically banished from using most drugs due to paucity of laboratory and clinical data (rather than damaging data). Nonetheless, since their disease conditions are treated with these same drugs, women and children are automatically the targets of *therapeutic smuggling*, which worsens their sorry state in exile. It is shown that the outcome of therapeutic smuggling is that women and children are frequently uninformed participants in unplanned, uncontrolled, usually unreported experimental drug usage! The lecturer posits that the needs and rights of women and children to effective and safe drugs are no less than those of the rest of the population, and that the time is overdue for recalling women and children from therapeutic exile through research and documentation, as a prelude to ending the dangerous practice of therapeutic smuggling. Part III outlines some modest contributions made by the lecturer (together with her colleagues and students) over thirty odd years of research (mostly in Ahmadu Bello University), towards recalling women and children from therapeutic exile. In these her ethically-sensitive research, the interfacing interests are disease conditions that are prevalent in the tropics and developing world, and to which women and / or children are particularly susceptible directly and indirectly - such as malaria, HIV/AIDS and sickle cell disorder. These *in vitro* and *in vivo* research are mainly into drug effects in animals, but include also, some non-animal based research - such as tissue culture and 'human studies' which have more direct clinical applications. The lecturer also reports routine mainstreaming of these philosophies, principles and practices into her teaching, student supervision-cum-guidance, professional discourse and community service. In Part IV, using several examples to buttress the point, the lecturer hypothesizes that therapeutic exiling and smuggling are just extensions of the gender discrimination against females in other spheres of life, and the somewhat lesser

discrimination against children. Noting that the millennium development goals are not just about human development in general, but more about women and children (the girl-child in particular), the lecturer believes that the need to recall them from exile has become a universal, and perhaps even legal project. Triangulating the three main parts, she puts forward a clarion wake-up call for all to actively engage in the proposed recalling of therapeutic exiles by challenging them with some identified roles for biomedical researchers and others alike. Thus, drawing on the outcome of her research efforts and experiences some of which are highlighted in this lecture, and in the light of her future goals, the lecturer champions the cause of *recalling women and children from therapeutic and indeed other exiles*, in one small voice.

Chapter One

Introduction

1.1 Protocol

The Vice-chancellor, Prof Abdullahi Mustapha - also Member, Faculty of Pharmaceutical Sciences
The Deputy Vice-chancellor (Administration), Prof Ibrahim N. Sada
The Deputy Vice-chancellor (Academic), Prof Ali Adamu
The Acting Registrar, Mal Ahmed Abdullahi Kundila
The Bursar, Mal Ibrahim Shehu Usman
The Acting University Librarian, Dr Kosoko O. Momoh
Dean, School of Postgraduate Studies, Prof Joshua Adebayo
Prof B.B.M. Dewu - Chairman, University Organised Lectures Committee; and other Members of the Committee
Prof Mike Kwanashie (Vice-chancellor, Veritas University, Abuja)
Prof Ibrahim Abdu-Aguye (Professor of Pharmacology), and other Professors of ABU extraction
Prof Godwin Emerole (Retired Professor from University of Ibadan), and other Professors from elsewhere
Dr Umar Usman Pateh - Dean, Faculty of Pharmaceutical Sciences; and other Deans and Directors
Dr Abdulkadir Umar Zezi - Head, Department of Pharmacology and Therapeutics; and other Heads of Departments
Members, University Senate
Distinguished Colleagues
Highly Esteemed Students
Invited Guests
Ladies and Gentlemen:

1.2 Preamble

I wish to begin this lecture by making reference to the vision statement of this great university - Ahmadu Bello University (ABU), Zaria, Kaduna State, Nigeria; hereby rendered.

> Ahmadu Bello University shall be a world-class university comparable to any other, engaged in imparting contemporary knowledge, using high quality facilities and multi-disciplinary

> approaches, to *men and women* of all races, as well as generating new ideas and intellectual practices relevant to the needs of its immediate community, Nigeria and the world at large.
>
> *- ABU's Vision from 2012 to date (italicised emphasis, mine).*

As an aspirational description of what ABU will like to accomplish, it may be viewed as an improvement on the vision at the university's inception in some respects, such as: being of *world-class standard*, imparting *contemporary knowledge*, intended use of *high quality facilities* and *multi-disciplinary approaches*. That notwithstanding, the original vision statement remains one of my favourite quotes, and is hereby rendered.

> The cardinal principle upon which our University is founded is to impart knowledge and learning to *men and women* of all races without any distinction on the grounds of race, religious or political beliefs.
>
> *- Sir Ahmadu Bello[60], in Our Charter, 23rd November 1963 (italicised emphasis, mine).*

These keywords namely: *men and women* are by no means restricted to our vision here in ABU; similar sentiments having been expressed in the vision statements of many other universities from within Nigeria (e.g. Benson Idahosa University), in Africa (e.g. University of Swaziland in South Africa) and outside the continent (e.g. Tufts University in the United States). Indeed, some universities and other establishments (e.g. Tufts University and the United Nations in some of its renditions), speak of *women and men* rather than of *men and women*.

Ladies and Gentlemen, against this background, I must proceed with the fact that like the current vision statement (and many others from all over the world), ABU's honourable first chancellor, deliberately spoke of *men and women* in one and the same breath, conveying the belief that men and women are to be joint and equal beneficiaries of the lofty ideas in his proclamation - so akin to the thesis I am about to propound! Because we share

---

[60] Sir Ahmadu Bello, (KBE, MHA), Sardauna of Sokoto and Premier of defunct Northern Region of Nigeria, after whom the University was named, was First Chancellor of ABU.

these same ideals, I dare say that were Sir Ahmadu Bello to be alive today, and a professor of pharmacology in this blessed university, perhaps, he could be the one delivering this inaugural lecture; which for me, increases the privilege and pride I feel, to be engaged in this very exercise.

This is the first inaugural lecture from ABU's Department of Pharmacology and Therapeutics (erstwhile Department of Pharmacology and Clinical Pharmacy until 2009). It is the third in the Faculty of Pharmaceutical Sciences, which as Department of Pharmacy and Pharmacology, came into being in 1968[61]. The earlier two inaugural lectures from the Faculty were given by Late Prof Musa Shok of the Department of Pharmacognosy and Drug Development (and once our Deputy Vice-chancellor), in 1999; and Prof Josiah Onaolapo of the Department of Pharmaceutics and Pharmaceutical Microbiology in 2008.

1.3 Anecdote about a 'Mummy-General'

Permit me, Ladies and Gentlemen, to narrate a small and personal anecdote about a 'Mummy-General': Today, many (particularly students), in the Faculty of Pharmaceutical Sciences where I had been teaching since 1982, refer to, and address me as 'Mummy', rather than the more professional 'Prof(essor)' or even more formal 'Madam'. I suppose reference to me as 'Mummy', has to do in part, with biological age; and partly with 'service longevity' - having taught many lecturers (some of whom are professors themselves), in this same Faculty[62]. But things were not always so; and yes, I did have a less desirable nickname.

Towards the end of the last decade of the last millennium, much to my chagrin, I stumbled upon the fact that students in the Faculty had nicknamed me 'General'. My distress should be understandable because at the time of this chance finding, within the context of the social, economic and political history of our country,

---

[61] This was under the headship of Prof Gabriel Osuide; with first student admissions in 1970, these graduating with BSc Pharmacy in 1973. Transition from Department to Faculty (again under the headship of Prof Osuide as founding dean), occurred in 1982 which has since then, trained students to be awarded Bachelor of Pharmacy (BPharm) degrees by the University.

[62] Other old students of mine are professors outside the Faculty and outside this University.

in addition to various other reasons, no regular person wanted to be associated with the military, let alone its top echelon - symbols, jokes and nicknames inclusive! Not even the explanation that I had genuinely earned the nickname which had its origin in the fast, no-nonsense, firm (even tough), organized, strategic and precise nature of my character and dealings with students and staff, in and outside of the classroom, was much comfort. Nor were the assurances that the nickname had been given, used and meant to be a *compliment* to me! I do not know for how long the nickname had been in existence before I became aware of it; and I must confess that as at today, I do not know if it is still applied to me. All of these notwithstanding, my ultimate response to this nickname, was to draw on a general principle I tend to apply in my life, which is: to graciously, positively and wholeheartedly accept and work with(in) situations and circumstances that I cannot change, regardless of my initial feelings. On several occasions, I had even gone beyond this acceptance level, to celebrate such circumstances - a situation example being my transformation from angling for the pursuit of a seemingly exotic medical training-cum-profession into what I have come to embrace and hail as the truly exciting world of experimental science! It is on this note, Ladies and Gentlemen, going by the verdicts of highly important stakeholders in my career (being my students), that I see myself as a *Pharmacology 'Mummy-General'*, who is privileged to share some thoughts with you today regarding women and children as therapeutic exiles to whom most drugs are first denied, then smuggled; and in so doing, attempt to champion the worthy cause of challenging many to redress their plight. Accordingly, I have titled my lecture: *Recalling 'Therapeutic Exiles': Who Speaks for Women and Children?*

1.4 Pharmacology, Pharmacy and Therapeutics

Considering that this audience is made up of individuals from highly diverse backgrounds stretching from the pure or liberal arts through pharmacology and other biomedical sciences, to nuclear energy and politics, etc, in order for us all to start off on the same page, I feel it is expedient for me to explain what Pharmacology is (and what it is not), since this is the first inaugural lecture from Pharmacology, and the discipline is frequently confused with allied disciplines, especially Pharmacy.

The Department of Pharmacology and Therapeutics here in ABU, is situated in the Faculty of Pharmaceutical Sciences[63] which is made up of four additional departments, namely:

- Department of Pharmacognosy and Drug Development
- Department of Pharmaceutics and Pharmaceutical Microbiology
- Department of Pharmaceutical and Medicinal Chemistry
- Department of Clinical Pharmacy and Pharmacy Practice.

This set up is similar to what obtains outside ABU - elsewhere in Nigeria, and in several institutions abroad. Although there are various MSc and PhD programmes available in the Faculty, at undergraduate level, only one degree, namely: BPharm[64], is currently offered and awarded. Holders of BPharm degrees are eligible to be registered/licensed as pharmacists to practice pharmacy which is a profession concerned with the safe and effective use of medicinal substances, appropriately sometimes termed: *pharmaceuticals*. Table 1 provides the meaning of pharmacology, its beginnings and aims, and the meaning of therapeutics - both essential concepts to understanding this lecture.

[63] The Department of Pharmacology and Therapeutics is also a clinical science department in the Faculty of Medicine where Pharmacology is required for training of medical and nursing students, as well as for accreditations by the National University Commission, Medical & Dental Council of Nigeria and Nursing & Midwifery Council of Nigeria.

[64] The BPharm degree may have a Doctor of Pharmacy (Pharm D) degree added to it, or replacing it, in future.

Table 1: Pharmacology, Pharmacologists and Therapeutics

Terminology / Concept	**Meaning**
Pharmacology, its Beginnings and Pharmacologists	Derived from the Greek words *pharmakon* meaning 'drug' and *logia* meaning 'study', Pharmacology (one of several science subjects taught to medical, pharmacy, nursing, veterinary and allied students), may be defined as the study of drugs, their sources, nature and properties, as well as all aspects of their interaction(s) with living organisms. Before the 19th century, pharmacology focused on natural substances, mainly plants (modern day Pharmacognosy), but has since developed into a biomedical science that apply the principles of scientific experimentation to therapeutic contexts. It replaced the old *Materia Medica* which had described drugs and their effects without bothering on mechanisms of action. The subject can be sub-divided into Basic Pharmacology and Clinical Pharmacology. Thus by background, pharmacologists could be scientists (of which the lecturer is one), medical doctors, pharmacists and veterinarians, etc.
Aims of Pharmacology	Pharmacology has two prinicipal aims: • to understand the interaction of life with its chemical surroundings in terms of cause and effect; and • to promote health by, and prevent toxicity from, chemicals by means of such understanding. Pharmacology shares its goal / aims with its sister disciplines - Physiology and Pathology - which studies life under normal and abnormal conditions respectively.
Therapeutic	Derived from the word 'therapy', therapeutic refers to the treatment of disease conditions.

Thus, pharmacology forms the basis for therapeutics, and it explains how the subject matter of this lecture *Recalling 'Therapeutic Exiles': Who Speaks for Women and Children?* deals with potential / actual uses and consequences of drugs, and the significance of the effects they produce, when administered in pregnancy, during delivery or breastfeeding, as well as in early childhood; regardless of the disease conditions of use.

I should add that by my background, I am neither a *pharmacist* pharmacologist, a *medical doctor* pharmacologist nor a *veterinarian* pharmacologist, etc; but rather, that I am a *biochemical* pharmacologist!

1.5 Aim and Objectives

The overall aim of this lecture is to demonstrate that the seemingly rhetorical question *Recalling 'Therapeutic Exiles': Who Speaks for Women and Children?* is a timely and answerable one in practical terms. To achieve this aim, four specific objectives will be addressed, as follows:

i. To set the stage for the discourse via an introduction.

ii. To define *therapeutic exiles* and *therapeutic smuggling* and explain their significance.

iii. To highlight some of the lecturer's contributions over a period of thirty odd years, in recalling therapeutic exiles and redressing this sorry situation of women and children.

iv. To conclude that therapeutic exiling is an extension of the more pervasive gender (and sometimes child) discrimination in society, and that everyone has a role to play in recalling therapeutic and other exiles.

Chapter Two

Therapeutic Exiles and Therapeutic Smuggling[65]

2.1 'Therapeutic Exiles'

2.1.1 Who Are Therapeutic Exiles?

The perinatal period which refers to that period of life just before, during and shortly after birth (Stern, 1975), is very often neglected in studies involving drug use because of possible adverse effects especially to the baby at this critical stage of its development. Obviously, such caution is needful and well meant. Nevertheless, the restraint is carried too far, with the result that in virtually all aspects of drug investigations, the perinatal period is nearly always excluded (Shirkey, 1968a, 1999 and Wilson, 1975). Consequently, pregnant women, women in labour, breastfeeding women and young children are often excluded from many useful drugs, since usually little or no data is available on either the pharmacodynamics or pharmacokinetics of such drugs when given to these subjects. It was in recognition of the limited availability of drugs for children, that Shirkey (1968a) coined the expression "*therapeutic or pharmaceutical orphans*".

In view of the prevalent exclusion of perinatal subjects in general from useful drugs, the term '*therapeutic exiles*', coined by the lecturer and used for the first time in her PhD dissertation (Kwanashie, 1990), may aptly be employed to describe pregnant, obstetric and breastfeeding patients in addition to Shirkey's paediatric 'orphans'.

---

[65] Most of this Chapter is culled from Chapter One of the lecturer's PhD dissertation (Kwanashie, 1990). It is informative that in the nearly 25 years since then, therapeutic exiling and therapeutic smuggling has not changed significantly.

2.1.2 Background to the Exiling Process

Therapeutic exiling dates from the late 1930s (Shirkey, 1968a). However, the most significant landmark in that history, is the celebrated limb and other congenital malformations that accompanied the use of thalidomide in the late 1950s and early 1960s (Lenz, 1962). The thalidomide incidence underscored the point that the placenta is not an absolute barrier (Flowers, 1959 and Howe *et. al., 1*981) and maternally administered drugs may have detrimental effects on the foetus particularly if administered at the critical stages of organogenesis. This obviously dictates that drugs be cautiously used in all women of child bearing age who are sexually active, which has since formed the basis for the banishment of a large proportion of women from many drugs.

Furthermore, when barbiturates were administered to the mother during labour, the newborn's respiration was depressed indicating that the drug was transported via the placenta to the baby before birth (Villee, 1965). Clearly, cautious use of drugs during labour is advocated, a restraint that has been overtly exaggerated leading to the obstetric patient being therapeutically exiled.

Besides transplacental routes, maternally administered drugs may reach the newborn via breast milk (Anderson, 1977 and Wilson *et. al., 1*980). The excretion of drugs in milk means of course that the breastfed infant is of necessity exposed to drugs taken in by the mother. It is for this reason that breastfeeding women are also frequently exiled.

It is known that drug effects in adult and the young are sometimes different (Atlas *et. al.*, 1977, and Szorady *et. al., 1*987). For example, many hepatic microsomal isozymes and renal excretion mechanisms of the newborn are not fully developed until the age of two or much more. Consequently, the very young child is usually more susceptible to drug effects than the adult. It is therefore necessary to exercise restraint in the use of drugs in infants. In practice however, such restraint has led also to the exiling of children from the therapeutic domain.

2.2 'Therapeutic Smuggling'

2.2.1 Disclaimer Notices and Therapeutic Smuggling

What amounts to disclaimer notices are very often inserted in drug packages or manufacturers' prescribing information sheets. Some of the frequently encountered warnings read thus:

Not to be used in pregnancy
Avoid use while breastfeeding
Its use in children has not been evaluated.

It should be noted that this does not apply to orthodox drugs alone, especially as there is a growing interest in herbal remedies and other dietary supplements which stemmed from the shortcomings of conventional medicines, the beneficial effects reportedly derived from the traditional medicines, and society's erroneous view of herbal medicines as being always safe just because they are 'natural'. Indeed, the Paxherbal bitters – a herbal health tonic from Ewu, Edo State, carried the following disclaimer and caution.

These claims have not been evaluated by NAFDAC.

The safety of use of Pax Bitters during pregnancy has not been evaluated. Physicians' advice is required before use during the first trimester of pregnancy.

The situation is similar for other complementary and alternative medicines regardless of their country of origin, as was observed for Kasapreko (Alomo bitters from Accra, Ghana) and EDMARK Shake Off (Phytofiber from Malaysia). In accordance with the tenets of the disclaimer notices, perinatal subjects would be excluded from most drugs. The reality of the situation however is that these subjects, that is, pregnant or lactating women and young children are not immune to diseases for which drug therapy is required. In practice, they do in fact need and receive drugs prescribed, or by self medication in spite of whatever body of words are inserted in leaflets by manufacturers (Wilson, 1975). Such practices amount to smuggling of materials (in this case drugs) to

those in exile! *And smuggling is always a dangerous exercise, perhaps more so, on this arena.*

Even a cursory look at the rather fashionable disclaimer notices reveal that the warnings exiling women and children are seldom absolute in their phrasing. The disclaimers often present the physician or potential drug user with one or two clauses such as:

> The physicians should weigh risks against benefits.
>
> The physician should use his judgement.

The onus of decision is therefore left with the physician or patient who is often unaware of the exact risks he is told to weigh. In fact, usually, neither the manufacturers nor other independent researchers know exactly what these risks are, the reasons being the lack of data concerning drug effects in the perinatal period. The situation is therefore such that there is often nothing actually on the "risk pan" of the balance against which to weigh drug benefits. Generally, what the physicians or patient usually know are possible benefits, to the exiled patient, based of course on data collected from subjects outside this category. It is understandable therefore, that where he is encouraged to use his judgment or weigh unknown risks against known benefits, the physician is likely to go along with the therapy in spite of the disclaimers and their clauses (Shirkey, 1968a and Wilson, 1975). It had been shown that where disclaimers were due to lack of data rather than damaging data, physicians considered them mere opinions or legally motivated-statements and ignored them (Wilson, 1975). As a result, the child bearing woman and her baby are frequently uninformed participants in unplanned, uncontrolled, usually unreported experimental drug usage[66]. This situation of drug smuggling or *therapeutic smuggling* to *therapeutic exiles* is more precarious and fraught with danger when compared to that in which planned, controlled and published studies are preliminarily carried out in animals, before being cautiously and appropriately extended to humans.

---

[66] The controversial clinical trial of Pfizer's new (at the time), untested and unproven antibiotic, Trovalfloxacin (Trovan) against *Meningococcal meningitis* in paediatric patients Kano, Nigeria, is a case in point.

In the biomedical literature, there is mammoth evidence for this dearth of information from the premises of both drugs and diseases. For example, analysis of the available information for over 500 commonly used drugs carried out by the lecturer in the 1990s, had shown that for half to two thirds, there was little or no information regarding their use during pregnancy and breastfeeding (Kwanashie, 1999). Treatment of malaria (a disease of high morbidity and mortality in many parts of the world), with old and new drugs, against sensitive and multi-drug resistant forms of the causative *Plasmodia* parasite, also portrays the limited availability of safe and effective medicines for the highly vulnerable populations of women and children; as is the situation for most other disease conditions including HIV/AIDS. More recently, we showed that 94.09% of 59 generics/brands of antimalarials had no information regarding their safe use in women and children (Kwanashie *et. al.*, 2011). Non-availability of information in women was of the following magnitudes: pregnancy (91.93%) and lactation (88.54%). In contrast, adequate prescribing information for use in children, was available for 80% of the antimalarials studied. However, even when information was available, the antimalarials may still not be used in lactation (11.46%), pregnancy (7.42%) and children (0.56%) as a result of cautions due to lack of data, rather than damaging data. Thus, the gross inadequacy of information available for rational prescribing and dispensing of antimalarials in women and children remains unchanged.

2.3 The Foetus: A Patient in His Own Right

So far, this issue of drug use in the perinatal period has been examined solely from the point of view of toxicity. However the use of drugs in the perinatal period need not be seen only in terms of adverse effects to child and/or mother. While it is easy to appreciate direct advantages of drug therapy to mothers and children, benefits to foetus may not be so obvious. Yet successful diagnosis and management of erythroblastosis foetalis by transfusions *in utero* (Liley, 1963) had infact propelled the foetus into a legitimate exalted status as a patient in his own right. It is now known that maternally administered drugs may cause beneficial, and not always detrimental effects in the foetus. For example, antibiotic treatment of maternal

syphilis in pregnancy, resulted in the cure of foetal infection which was of even greater consequence than the maternal disease itself (Yaffe and Stern, 1976). Secondly, administration of phenobarbitone to the mother for two weeks prior to delivery had been used to treat foetuses sensitized with haemolytic disease by causing foetal microsomal enzyme induction and subsequent metabolism of the excessive bilirubin (Yaffe and Stern, 1976). Other intrauterine foetal diseases have been demonstrated e.g. acid peptic disease (Lee and Wells, 1923) which may respond equally well to drug therapy *in utero*. Studies on drug use in the perinatal period may therefore unearth therapeutic advantages to the unborn as well as the born child and his mother.

2.4 Recalling 'Therapeutic Exiles'

2.4.1 Animal Studies

While appreciating the ethical grounds for restraints in pharmacological research in the perinatal period in humans, there is no reason why such studies should not be carried out in animals. Of course, there will be problems of species differences and extrapolation of data obtained from such studies to man. However, such difficulties would not be exclusive to studies on effects of drugs in the perinatal period. Indeed they apply equally well in other periods of life. And if in spite of such difficulties, reasonable extrapolations are made, there is no reason why the same should not be possible in the perinatal period. It is pertinent at this juncture to remark that the thalidomide disaster which provided a major impetus for the exiling of perinatal subjects, could have been averted if pre-market animal studies had been extensive since such studies later conducted, showed the same limb defects in animals as observed in man (Bignami *et. al., 1962*). Emphasis therefore must be placed on extensive and multidisciplinary studies, in several species of animals besides the rodents, and including wherever possible non-human primates such as the monkey since the latter generally provide more relevant data to man than lower species of animals (Wong, 1972 and Dvorchick *et. al.*, 1974). Following such extensive animal studies, positive aspects can then be followed up in man. It is unlikely that the risk factor in such cases, will be any greater than in studies involving other periods of life.

2.4.2 Human Studies

In fact, some experiments may actually be carried out on human tissues which will not prove detrimental to mother and child. For example, *in vitro* isolated transplacental perfusion techniques may be employed to study placental transport and metabolism of drugs and so provide relevant information concerning drug effects *in utero* (Dancis, 1974). Secondly, isolated human uterine myometrial strips (obtainable as trimmings during Caesarean sections or hysterectomies), may be used in *in vitro* research to provide valuable data regarding the effects of drugs on uterine contractility and relaxation; with appropriate clinical significance/application in abortion and labour. Thirdly, drug excretion in breast milk can be easily studied in a mother whose baby is being artificially fed for other reasons. These are some examples of safe yet valuable studies that can be carried out in human subjects during the perinatal period. Although such studies are being carried out, they are neither comprehensive nor extensive and much can be achieved if they are made more routine. More conclusive human studies may in fact be contemplated and executed following positively indicated results from such preliminary studies. The current practice of smuggling drugs to perinatal subjects in exile, as previously asserted, is perhaps more dangerous than the human studies so recommended. Recently in 2013, the UK National Centre for Replacement, Refinement and Reduction of Animals in Research (NC3Rs) and the Medicines and Healthcare products Regulatory Authority (MHRA) convened an expert working group on the use of human tissue in testing the safety of potential new medicines, with an initial focus on safety pharmacology studies.

Evaluation of human epidemiological data will definitely also provide additional understanding about drug effects in the perinatal period. A major problem with this however, is that under-reporting is usually high, especially as some of the drug usage is 'illegal'. Needless-to-say, prospective epidemiologic studies must involve drugs which not only would have passed severe animal studies, but which are also essential drugs with regards to the disease conditions and particular patient groups.

2.4.3 *In Vitro* Studies

The continuing debate about animal rights and their use for experimental purposes has led to the development and use of cell lines and tissue culture techniques, to the extent that these have even more direct applications to humans.

2.4.4 Perinatal and Paediatric Pharmacology: Who Will Test the Drugs?

The current practice of evaluating drugs using only *male adult* animals and humans need to be reviewed. Their female counterparts and the young ones need attention too! Perinatal subjects need not remain *'therapeutic exiles'* to whom most drugs are first denied, then *'smuggled'*. Their needs and rights to effective yet safe drugs are no less than those of the rest of the population. This latter situation requiring extra caution where humans are involved, though formidable should not be intimidating. Drug toxicities in the newborn for example, that once seemed formidable such as those due to chloramphenicol, can now be avoided only because they are better understood.

In answering his own question, *Pediatric pharmacology: Who will test the drugs?*, Wilson (1972) identified roles for the scientist as well as the paediatric pharmacologist. Indeed as far back as nearly a half century ago, it had been recognized that 'therapeutic orphans is everybody's business' (Shirkey, 1968b, 1970, 2006). Sadly, other than a few desperate questions (Shirkey, 1970, Wilson, 1972 and Gazarian, 2003), not much has changed since Shirkey first blew the whistle on therapeutic orphans in 1968 (Collier, 1999, Stephenson, 2001 and Gazarian, 2003); although some positive changes are more recently being seen (Feng, 2012). Does this pose special challenges to the female biomedical scientist engaged in fundamental experimental pharmacology as well as allied professional women? Should it be the purview of their male counterparts as well? While a modest amount of additional information may not cause the disclaimer notices to be completely removed due to the ever-present liability stances, it will certainly lead to a re-wording of the clauses. At any rate, users of drugs in the perinatal period will certainly be

better informed, which ought to enhance rational use of drugs in the overall interest of women and children.

2.5 Art Exhibition

I have translated the aforementioned situation of women and children into an artwork which was displayed at the 3rd Exhibition of KINESIS Women Art and Science[67]. The theme of the exhibition which held in Abuja, from 26th November to 2nd December, 2001 was *Matter*[68]; and my exhibited poster makes the point that recalling women and children from therapeutic exiles is the crux of the *matter!*

The artwork shows a boat conveying a variety of drugs in diverse dosage forms (tablets, capsules, syrups and injectables) from the mainland (basically a man's world, including therapeutically) to women and children in their 'lonely island' where they had been banished from these drugs - Figure 1. Persons featured in the mainland represent the clinician who is implicated in the smuggling, and the scientist who together with the clinician can provide the requisite research data for rational drug use in women and children, making therapeutic smuggling unnecessary, and thereby recalling women and children from therapeutic exile. The expanded statement for the artwork is summarised in a short poem beneath the miniature version of the artwork, reproduced in this lecture.

In the original exhibited artwork, the words of the poem were strewn along, and across the body of water[69].

---

[67] KINESIS is an association of women (led by Dr Adele Garkida of the Dept of Industrial Design), who research the interaction between art and science in their daily lives, and portray this in the form of art. KINESIS is affiliated to CATALYST, a similar organization based in the U.K.

[68] The themes of previous KINESIS exhibitions were: *Essence* (Kaduna, 1999) and *Essence* 2 (Zaria, 2000). A 4th exhibition was tagged *Molecular Construction* (Zaria, 2003), chosen to commemorate the 50th anniversary of the discovery of the genetic code, DNA; and for which this lecturer had written a poem celebrating women as hardworking goods producers, services providers and care givers - see Chapter Four.

[69] This artwork was assembled by the lecturer, a member of KINESIS, using a combination of several computer packages: Microsoft Word, Windows Draw and Instant Artist. Most of the components were imported directly from the clip art works in these packages (then

In light of the above, and in answer to this lecture's poser: *Recalling 'Therapeutic Exiles': Who Speaks for Women and Children?*, I have earnestly sought to be a voice for them throughout my career by making studies on effects of drugs in the perinatal period and in the very young, a priority area of my research. I shall now proceed to summarise what modest contributions I have been able to make in this regard through my research, teaching and community service.

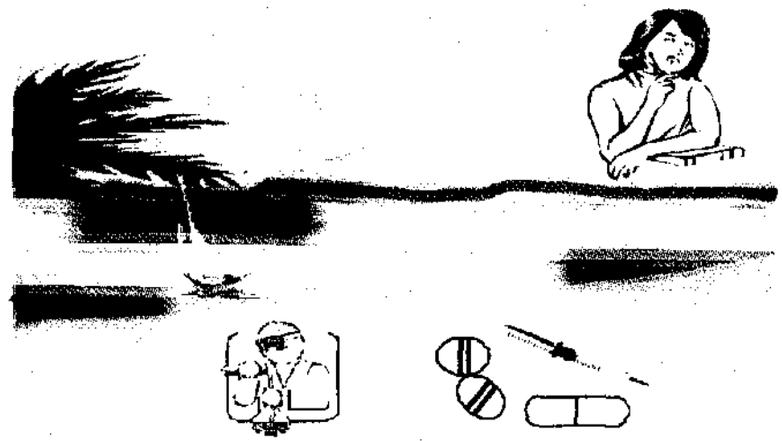


Figure 1: Therapeutic Exiles and Therapeutic Smuggling

Women and young children:
Therapeutic exiles
To whom most drugs are *first* denied
Then smuggled.
Who speaks for women
And children?
That is the crux of the matter!
- ©HelenOK, 2001

---

manipulated); but a few (tablets and capsule) were created *de-novo* by the lecturer. Despite constraints imposed by the imported clip art pieces, the work itself is without respect to race, sex, and the like.

» HelenOK, derived from Helen Ochuko Kwanashie is the pen name of the lecturer in the literary arts. Kwanashie is keen on developing interphases between science and art with poetry and computer graphics as her principal modes of expression - See also Chapter Four.

Chapter Three

Recalling 'Therapeutic Exiles': Contributions by Lecturer

3.1 Presentation and Evaluation of Contributions

The approach I have chosen to utilize in summarising my contributions to recalling therapeutic exiles through research, teaching and community service, is ordered as follows.

i. Chronologically from my BSc to Post-doctoral research projects (Table 2)
ii. Other research carried out outside my education and training, especially those on antimalarial drugs, antiretroviral drugs, sickle cell disorder, etc, and including those of supervised students' research projects
iii. Contributions through teaching and community service.

Avoiding technicalities wherever possible, briefs on the objectives and key findings in each case will be presented. However, some details of representative research will be provided (e.g. research on cimetidine on isolated uterus, tissue culture and sickle cell disorder).

How do we evaluate a research, teaching and community service output to arrive at the conclusion that it has made a contribution to recalling women and children from therapeutic exile? The answer to the above pertinent question is that the output must meet one or more of the following criteria based on the definition / aims of pharmacology as previously described:

- lead to a better understanding of the physiology (normal situation) and/or pathology (abnormal situation) of the condition under investigation
- promote health
- prevent toxicity
- describe what the drug (medicine/chemical) does to the body, i.e. effects produced by the drug

- describe how the body responds to the drug (medicine/chemical), i.e. responses produced by the body
- make for rational drug use in women and children.

3.2 BSc Research on Food, The Ultimate Medicine

My first attempt to speak for women and children, and so contribute to recalling them from exile was in both of my BSc research projects, one of which dealt with detection of carcinogenic polycyclic aromatic hydrocarbons (PAHs) in Nigerian smoked fish, and which had possible toxicological consequences for women who usually carry out the food smoking (Akpobi, 1979a). The other project dealt with aspects of nutritional changes that take place when maize is processed to the popular Nigerian weaning food called *ogi*[71] (Akpobi, 1979b). After all, there are several facets for food-drug interactions, and food may easily be considered, the ultimate drug - dealing with toxins, inflammation, damaged tissue, suppressed immunity - to mention but a few (http://www.highstrangeness.tv/show_news.php?n=6027; Wolcott and Fahey, 2002; Bell, *et. al., 2014*)! Doesn't the absorption of both take place at the same primary site, being the first part of the small intestine? Don't the same factors such as physicochemical properties of the substance, nature of the biomembrane interphase, pH of the medium, small intestine residence time, etc, also govern the absorption of both? Aren't both food and drug subject to other similar pharmacokinetic processes of distribution via the blood, biotransformation in the liver, and excretion by the kidney? Etc, etc?

Indeed many foodstuffs, condiments and spices have long been recognised as medicinal e.g. pawpaw, garlic, ginger, bitter kola, bitter leaf and different forms of peppers, serving as complementary and alternative medicine (CAM). However, in recent decades, there has been a tremendous upsurge in the use of CAM, a good number of which are no more than food supplements, containing basically vitamins and minerals. Kwanashie (2011) had

[71] The fermented corn starch popularly cooked for a breakfast porridge, and largely employed in weaning children, termed *ogi* in Yorubaland where this work was carried out, is known as *akamu* in Ibo, and *kamu* in Hausa.

sounded a note of safety and quality concerns about the proliferation in West African of *very expensive* CAM products from outside the sub-region (mostly Asia), the vast majority of which are not subject to regulation. Unregulated radio, television, print and word-of-mouth advertisements of unsubstantiated benefits of these products is rampart despite the fact that most carry disclaimers, and this pose dangers to the unsuspecting, uninformed and gullible public. It should be noted that it is women who mostly use these products.

Table 2: Highlights of Some Research Contributions by Kwanashie in Recalling 'Therapeutic Exiles'

Career Stage	Research Institution	Department	Perinatal Period Covered	Research Project / Publications	References
BSc	Ibadan	Biochemistry	Childhood	Changes in the β-Carotene, Vitamin A and Sugar Content During the Preparation of '*Ogi*' from Maize Varieties	Akpobi (1979b)
BSc	Ibadan	Biochemistry	Women...	Detection of Polycyclic Aromatic Hydrocarbons in Nigerian Smoked Fish	Akpobi (1979a)
MSc	Ibadan	Biochemistry	Women... Pregnancy	Drug Metabolising Capacity of Placental Tissues From Nigerian Women at Late Gestation	Kwanashie (1981, 1987, 1988)
PhD	ABU	Pharmacology...	Women... Pregnancy	Effects of Cimetidine on Female Fertility and Pregnancy Outcome in the Mouse and Rat	Wambebe *et. al.* (1990)
PhD	ABU	Pharmacology...	Labour	Action of Cimetidine on the Rat Uterus Preparation	Kwanashie *et. al.* (1987)
PhD	ABU	Pharmacology...	Breastfeeding	Effects of Maternally Administered Cimetidine During Lactation on the Development of Drug Metabolising Enzymes in Mouse Pups	Kwanashie *et. al.* (1989)
				Dose-related and Other Effects of Maternal Cimetidine Pretreatment During Lactation on Drug metabolism in Mouse Dams and Pups	Osuide *et. al.* (1990)
PhD	ABU	Pharmacology...	Childhood	Effects of Cimetidine on Drug Metabolism in Rat Pups	Ikediobi *et. al.* (1991)
Post-doc	Dundee, UK	Biochemical Medicine	Women	Interactions Between Ethinyloestradiol and Food Additives via Glucuronidation Using Human Cloned Stably Expressed UGTs	Kwanashie (1994, 2008)

3.2.1 Changes in the β-Carotene, Vitamin A and Sugar Content During the Preparation of 'Ogi' from Maize Varieties (Akpobi, 1979b)[72]

In Nigeria, maize grain (*Zea mays*) is often fermented, milled and sieved to yield *ogi* – the corn starch popularly cooked for a breakfast porridge, and largely employed in weaning children. The objective here, was to track changes in β-carotene, Vitamin A and diverse sugar levels during the local processing of different maize varieties into *ogi*. β-carotene and vitamin A were found to be higher for whole maize grain than for *ogi*, average values being 25.17 µg β-carotene/100 g whole maize; 16.00 µg β-carotene/100 g *ogi*; 13.75 µg vitamin A/100 g whole maize and 7.50 µg/100 g *ogi*. Losses were attributed to the milling and sieving processes, as well as the *ogi* wash water (supernatant) and the chaff, being discarded during the processing.

The sugars identified were glucose, fructose, sucrose, maltose, mannitol, raffinose, xylose and rhamnose. The total sugar content was found to decrease during processing of *ogi* from maize. The sucrose, glucose, fructose and mannitol of *ogi* was less than that of maize grain. The maltose, ramnose and xylose of *ogi* was more than in maize. On the whole, fermented corn was richest in simple sugars, its glucose and fructose being more than in whole grain even; which is in line with other studies that have shown fermentation to increase the nutritional attributes of foods, particularly of the micro-nutrients, vitamins.

From this work, a significant contribution to recalling therapeutic exiles lies in improved nutrition for children in particular. Since the study showed that the processing technique resulted in some losses, it was recommended that the sieving process after fermentation be omitted. Food-drug interactions are important in malnutrition, the latter of which are more likely to occur in women and children. This is particularly so in protein-energy-

[72] This, like the other BSc project on smoked fish (Akpobi, 1979a), was jointly carried out by the lecturer along with Bunmi, Ekenobi and Jeremiah with individualized reports, under the supervision of Prof Michael Fafunso.

malnutrition, where available albumin for plasma protein binding of drugs are reduced, as are liver microsomal inactivating enzymes, resulting in exaggerated drug effects and toxicity. Adequate vitamin intake (including of vitamin A), has additionally been associated with drug action; and fortification programmes have been vigorously pursued internationally by the World Health Organization (WHO) and locally by agencies such as National Agency for Food and Drug Administration and Control (NAFDAC). Appropriate adaptation and utilization of knowledge gained from the project work reported above, would be natural forms of fortification, which should be preferred. Recommendations on how to maximize the nutritional value of *ogi* made in the said project report (including suggested recipes) are a further step in recalling therapeutic exiles.

3.2.2 Detection of Polycyclic Aromatic Hydrocarbons in Nigerian Smoked Fish (Akpobi, 1979a)[73]

In this project which also dealt with food, the significance to recalling therapeutic exiles is in Toxicology - that specialized aspect of Pharmacology that deals with the adverse effects of agents some of which are contaminants of our foods (and environment), including the prevention and amelioration of such adverse effects. Nigerian smoked fish obtained from local markets were examined to see if any PAH was present. Solvent extraction produced an oil concentrate which contained PAHs found to be present in all smoked fish species utilized for this study. The principal PAHs so detected were: anthracenes, benzpyrenes and other unidentified PAHs. Methods of fish preservation other than smoking were discussed.

The smoking of fish and other foods is usually a task for women folk in many communities. This exposes them to intake of PAHs, many of which are mutagenic and carcinogenic to the lungs, liver and other organs. Furthermore, we shall see a possible association with the ability of the placenta to metabolise drugs as my MSc research (described next) would show.

---

[73] This, like the other BSc project on Ogi (Akpobi, 1979b), was jointly carried out by the lecturer along with Buami, Ekemobi and Jeremiah with individualized reports, under the supervision of Prof Godwin Emerole.

3.2.3 Contributions of the Food Studies to Recalling Therapeutic Exiles

The *ogi* study will lead to enhanced nutrition for all, children in particular. The smoked fish project is a pointer to possible exposure of women to carcinogenic PAHs as an occupational or routine home-environment hazard. Both should translate to better health promotion.

3.3 MSc Research on Drug Metabolism by the Human Placenta

My MSc research project was on drug metabolizing capacities of placentae taken from Nigerian women following caesarean deliveries. Levels and activities of a spectrum of drug metabolizing enzymes were determined and compared to those of rat liver, the latter being the reference standard in drug metabolism studies. Three distinct aspects of this work are described below.

3.3.1 Drug Metabolising Capacity of Placental Tissues From Nigerian Women at Late Gestation (Kwanashie, 1981 and 1987)

Late gestation placental tissues obtained from Nigerian women showed a definite but lower capacity to metabolise drugs when compared to rat liver. N-demethylation of aminopyrine, O-demethylation of p-nitroanisole and hydroxylation of 3,4 benzopyrene (3,4-BP) were demonstrated. NADPH cytochrome P-450 reductase activity was also observed in both tissues. Reduced glutathione and gluthation reductase assays revealed a potential for gluthatione conjugating system. However, aniline hydroxylase activity (AH) present in rat hepatic microsomes, was absent in placental microsomes. Hydroxylation of 3,4 BP which had elsewhere been observed only in the placentae of cigarette-smoking mothers, was observed in the placentae of Nigerian women, who though were non-smokers, were chronically exposed to other sources of PAHs. Such exposure could be from smoking of foods (e.g. fish as seen in the BSc project), cooking with firewood or other fuel sources that generate smoke. Consumption of smoked foods is also associated with intake of PAHs and their ill-effects.

3.3.2 Subcellular Localization of Drug Metabolising Enzymes in the Human Placenta at Term (Kwanashie, 1987)

While most drug metabolism takes place in the smooth endoplasmic reticulum of liver cells, the intracellular site for drug metabolism may differ particularly for organs other than the liver. The localization of intracellular sites for drug metabolism is important for a truly biochemical understanding of the role played by the organs concerned in the metabolism of drugs and other xenobiotics in normal and disease states. The objective of this study was to locate the primary site of key drug metabolizing reactions undertaken by the human placenta - an organ whose role in the inactivation and activation of foreign compounds was not and is still not appreciated fully.

Nuclei, mitochondrial, microsomal and cytosolic sub-cellular fractions were obtained by standard procedures of homogenization and ultra-centrifugation from human placenta at term. Each of these fractions was used as enzyme source in the assay of aryl hydrocarbon hydroxylase (AHH), p-nitroanisole O-demethylase (p-NAO-D), glutathione reductase (GR) and NADPH cytochrome C reductase. Both cellular fractionation and enzyme assays were carried out at 0-4^{O}C. The relative specific activity for each subcellular fraction vis-à-vis percent of total protein was the criterion used to determine the primary, secondary and other sites of activity of each enzyme studied.

All four fractions showed varied levels and activities of each of the enzymes studied. AHH (a bioactivation oxidative enzyme) and p-NAO-D (a typical oxidative enzyme), were mostly located in the microsomal fraction as is typical of most enzymes responsible for drug oxidations. GR was mostly located in the cytosol and microsomes, again typifying most conjugation systems. However, NADPH cytochrome C reductase activity was found more in mitochondrial and nuclei fractions than in the microsomes. Thus, this routinely employed marker enzyme for microsomes may not be employed as such for placental microsomes.

In conclusion, sub-cellular localization of these drug metabolizing enzymes in the human placenta was similar to what obtains in the liver, except with respect to the cytochrome P_{450}-dependent NADPH cytochrome C reductase.

3.3.3 A Rapid Precipitation Method for Microsomes Isolation From Human Placental and Rat Liver Homogenates

(Kwanashie, 1988)

The most commonly used technique of total differential centrifugation for isolation of smooth endoplasmic reticulum (microsomes) was time consuming and not always feasible beyond the post-mitochondrial 10,000 g supernatant, especially for laboratories in resource-poor settings where high speed ultracentrifuges may not be available. This study was undertaken to develop a rapid precipitation method for isolating microsomes by evaluating two precipitation methods.

To 15 ml aliquots of microsomal fractions obtained from rat liver and human placental tissues, were added 0.25 ml, 0.50 ml, 1.00 ml and 2.00 ml of 0.2 M sodium acetate buffer (pH 4.0); and 0.6 ml of 250 mM magnesium chloride plus 0.3 ml of 200 mM calcium chloride. Buffer was added to make the homogenate volume 20 ml. Whereas it was possible to precipitate microsomes from rat liver employing both the sodium acetate and the magnesium chloride/calcium chloride methods, the latter failed for placental tissues. Of the variant sodium acetate procedures, use of 0.50 ml buffer was found to be optimal in terms of pH (final being 5.4), microsomal yield, microsomal protein and enzyme assays. Adoption of this protocol removes pH adjustment delays of the basic sodium acetate method, thus providing a suitable means of isolating microsomes with the dispatch required in materno-foetal enzyme studies.

3.3.4 Contributions of the Placenta Studies to Recalling Therapeutic Exiles

These studies on placental metabolism of drugs emphasized the role placenta could play in detoxification of drugs and other foreign compounds, thereby protecting the foetus. The studies also exposed possibilities of toxicity to both mother and child as a result of placental metabolism of drugs. In particular, placental AHH was believed to be inducible by PAHs present in cigarette smoke, and is ordinarily absent in non-smokers. Measurable AHH activity therefore in the placentae from these subjects who were non-smokers, was suggestive that perhaps they were exposed to other

sources of PAHs in the environment such as smoked foods and firewood smoke. Such knowledge would normally precede prevention of toxicity. The enhanced methodologies described from my work made such studies easier to conduct, providing much needed information about drug effects when administered during pregnancy (and even during labour).

3.4 PhD Research on the Effects of Cimetidine in the Perinatal Period of the Mouse and Rat

Cimetidine (Tagamet®, Smith, Kline and French[74]) was developed from a logical manipulation of the structure of histamine and became the first drug ever to reach more than $1 billion a year in sales, thus making it the first blockbuster drug (Whitney, 2006). It acts by competitive inhibition of histamine at H_2-receptors in the parietal cell of the gastric mucosa. The drug is well absorbed from the gastrointestinal tract (GIT), partly metabolized in the liver to mainly the sulphoxide and excreted mostly unchanged in the urine. Cimetidine is also excreted into bile and breast milk. Side effects though many, are generally minor, infrequent and / or reversible. Four mechanisms underlying cimetidine-drug interactions were known, the most important being inhibition of drug metabolism. Compared to other anti-ulcer drugs in use in the 1980s, cimetidine was superior although its use and safety in the perinatal period was poorly researched and documented. Cimetidine is slowly transported across the placenta but was reportedly lacking in teratogenic effects. When administered in pregnancy, the drug was associated with adverse effects on the sexual development and behavior of the male offspring. In obstetric anaesthesia, cimetidine played a formidable role in prophylaxis against acid aspiration pneumonitis and was superior to the older approaches including diverse intubations, application of cricoids pressure, antacids and anticholinergics. The drug was also used in children in acid peptic diseases and related conditions. Despite these actual and potential uses of the drug, the efficacy-safety profile of cimetidine in the perinatal period was not clearly established. The objective of my PhD research was to study some of the controversial, unclear and unresearched aspects using laboratory animals.

---

[74] Through a series of amalgamations with other pharmaceutical companies, Smith, Kline and French later became GlaxoSmithKline.

3.4.1 Effects of Cimetidine on Female Fertility and Pregnancy Outcome in Mouse and Rat (Wambebe *et. al.*, 1990)

Cimetidine, 100 mg/kg administered i.p. daily for 2 weeks to female adult mice did not influence their mating power or fertility, the pregnancy rate being unaltered. When administered i.p. daily to mice and rat during the 1st, 2nd and 3rd trimester (50 mg/kg), and throughout pregnancy (both 50 and 100 mg/kg), cimetidine was found not to affect the general outcome of pregnancy. A number of parameters investigated, namely: abortion, gestation period, congenital physical deformities, litter size and viability, neonatal deaths, lactation, weaning and attainment of puberty, were not affected by prenatal administration of cimetidine. However, cimetidine 100 mg/kg i.p. daily throughout pregnancy resulted in weight loss in dams and even in the indirectly exposed pups, the latter effect being carried into adulthood.

3.4.2 Effects of Cimetidine and Its Interaction With Oxytocin on the Isolated Rat and Rabbit Uteri (reported partly in: Kwanashie *et. al.*, 1987, 1990 and 1992)

No major qualitative species differences were observed either in the intrinsic activity, or in the responsiveness to oxytocin and cimetidine, of three sensitive-types of rat and rabbit uteri namely, quiescent, non-quiescent and pregnant. Cimetidine (100-1,000 μg/ ml) like oxytocin (10-100 ηg/ml), exhibited concentration-dependent spasmogenic actions; with cimetidine found to be less potent by $1.6\text{-}3.7X10^{-4}$ - Figures 2 and 3. However, cimetidine-induced contractions were typically charcaterised by multiple, gradually increasing peaks preceded by concentration-related latent periods. In contrast, contractions due to oxytocin were more immediate and characterized by single peaks on the non-pregnant uterus. The effects were synergistic when both cimetidine and oxytocin were used simultaneously on the non-perfused and perfused uteri, a potentiation that was concentration-dependently related to cimetidine (Figure 4).

These effects of cimetidine were observed at concentrations that were 10^3 times higher than those likely to be encountered clinically. The administration of cimetidine to decrease acid secretion in obstetrics may therefore not interfere with the normal progress of labour. The differences between the actions oxytocin and cimetidine may derive from different mechanisms. Receptor characterization experiments showed that whereas oxytocin acted on oxytocic receptors, cimetidine's action on the uterus may not

involve receptors, but rather a combination of calcium ion modulation and the synthesis-cum-release of prostaglandins.

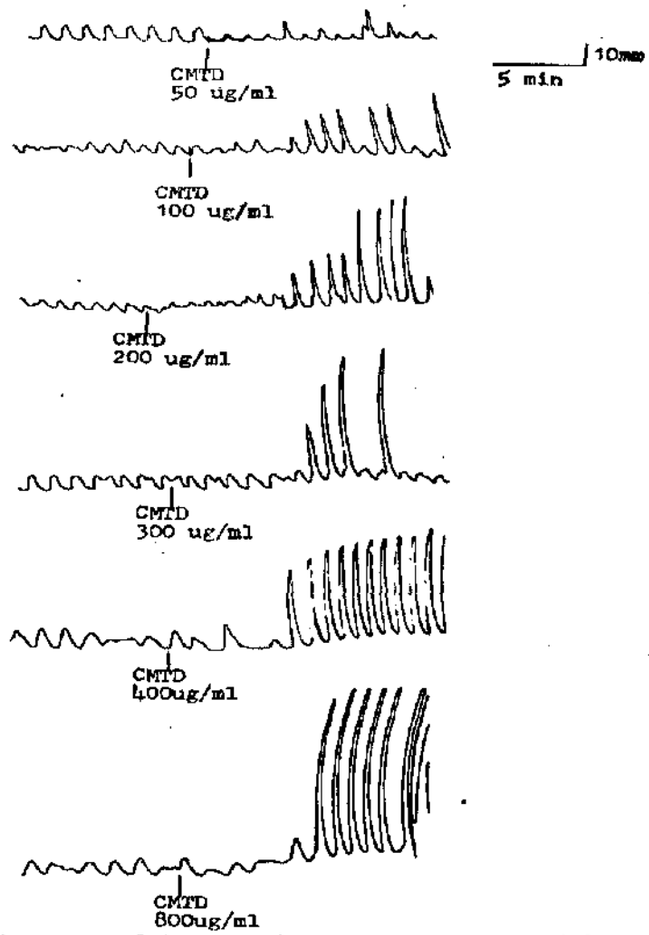


Figure 2: Responses of the non-quiescent rat uterus to graded concentrations of cimetidine over 15 minutes.

Note that amplitude and rate of contraction increased while the latent period decreased as cimetidine (CMTD) concentration increased.
Microdynamometer sensitivity was 1/10.

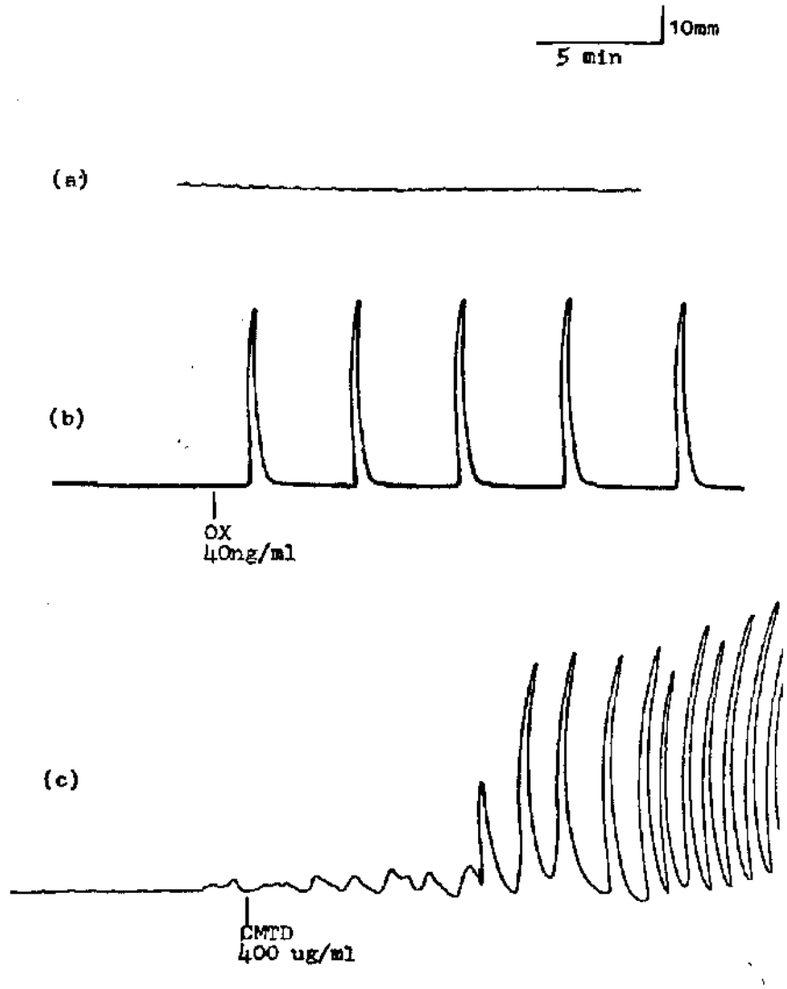


Figure 3: Effect of oxytocin and cimetidine on the frequency of contraction of the quiescent rat uterus.

The rate of contraction due to cimetidine (CMTD) 400 µg/ml was 3-fold that of oxytocin (OX) 40 ηg/ml.
Microdynamometer sensitivity was 1/10.

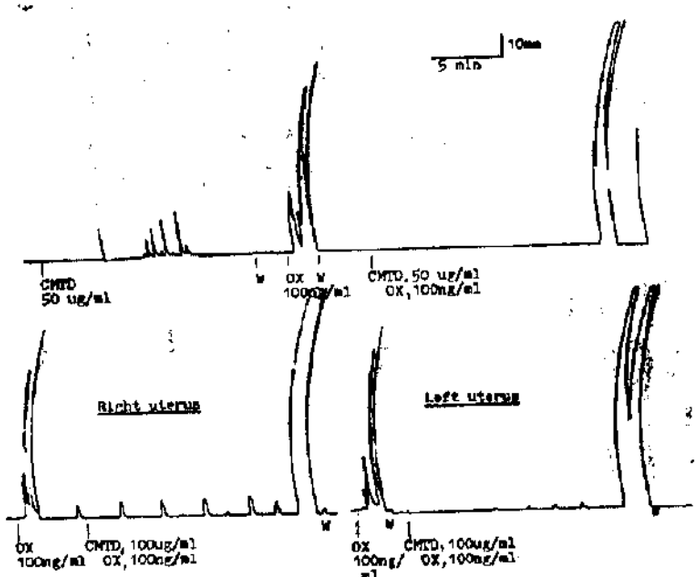


Figure 4: Interaction between oxytocin and cimetidine on the non-perfused rabbit uterus

Cimetidine (CMTD) 50 and 100 μg/ml dose-dependently potentiated the amplitude of contraction to oxytocin (OX) 100 ηg/ml. Microdynamometer sensitivity was 4/10.

3.4.3 Matters Arising From the Cimetidine-Uteri Experiments and Future Research Goal

Two issues arising from the cimetidine-uteri experiments are worthy of mention. First, my efforts to use human uterine myometrial strips to confirm or otherwise, the above effects observed with rat and rabbit uteri, did not materialize because I did not receive the requisite ethical approval from the teaching hospital, despite frequent enquiries on my part. Incidentally, I was not refused either, and perhaps now is an appropriate time to call on ethical committees to review such research proposals with greater dispatch. The post-surgery uterine strips I needed for the research plus the *in vitro* perfusion of the placenta (contained in the same proposal), would not have been detrimental to the women from

whom they would have been derived, since there are discardable tissues. Secondly, my work showed *agonist* effects of cimetidine on uterine and intestinal smooth muscle (latter not presented in this lecture). Well known as an antagonist at histamine H_2 receptors, this agonist property I observed remains worthy of further investigation. Histamine H_3 and H_4 receptors have been described since my studies, that are unrelated to the spasmogenic actions of cimetidine I had seen with uterine and intestinal smooth muscles. Could this be due to cimetidine acting on yet another histamine receptor? Could it be a non-histamine receptor? Could the action be non-receptor related? Or could the mechanisms I had postulated at the time be sorely responsible? These and other unanswered questions warrant my further investigations, and indeed the attention of other researchers.

While cimetidine may no longer be the anti-ulcer 'magic bullet' it was in the 1980s due to availability of better H_2 receptor antagonists such as ranitidine, discovery/development of better anti-acid drugs such as omeprazole, introduction of antibiotics into treatment of peptic ulcer disease, etc, etc, experience has shown that not abandoning old (and even 'cursed') drugs is scientific and therapeutic wisdom! For, despite its teratogenicity and axonal neuropathy, thalidomide has found new uses in treating leprosy, graft-versus-host-disease (GVHD) plus other severe and disabling conditions where standard anti-inflammatory or immunosuppressive agents have failed (Medscape, 2000). Other new uses for thalidomide include treatment of multiple myeloma and other types of cancers when combined with dexamethasone (Jones, 2008). Thus, cimetidine may yet be an evolving biomedical saga waiting to be unearthed[75].

[75] *Sir James Whyte Black (1924-2010) was a Scottish doctor and* pharmacologist who was awarded the 1988 Nobel Prize in Medicine for work leading to discovery of histamine H_2 receptor, the development of cimetidine as an H_2 receptor antagonist; as well as that of propranolol, the non-selective β-adrenergic blocker.

3.4.4 Effects of Maternally Administered Cimetidine During Lactation on Drug Metabolim in Mouse Dams and Pups

(reported in: Kwanashie *et. al.*, 1989 and Osuide *et. al.*, 1990)

Maternally administered cimetidine inhibited drug metabolizing enzymes in both dams and pups. The inhibition of drug metabolism in adult dams which received cimetidine directly was lower than that observed in pups which could only have received a small fraction of the administered dose through the milk. In 2-weeks old pups, at a maternal cimetidine pretreatment dose of 50 mg/kg/day, APN-D activity was reduced by 58.4% in male and 62.1% in female test pups compared to the controls. In the same manner, pentobarbitone sleeping time (PBST) was prolonged by 28.7% in male and 65.9% in female test pups. Using PBST determinations as an inversely related index of drug metabolizing capacity, maternal cimetidine pretreatment with 50 mg/kg/day for 6 weeks, resulted in quantitative as against qualitative inhibitory effects on the development of drug metabolizing enzymes in pups from age 2 to 10 weeks. AMN-D, AH and PBST determinations in both dams and pups following maternal pretreatment with 15, 25 and 50 mg/kg/day cimetidine showed inhibitions that were dose-dependent. Of the three indices investigated, AH was the least influenced by cimetidine pretreatment. In general, the inhibition of drug metabolism was more pronounced in the female.

In summary, maternally administered cimetidine during lactation inhibited the levels of drug metabolizing enzymes in mouse pups much more than it did in the dams which received the drug. These effects varied with the dose, sex and substrate. Obviously, the already poor ability of newborn mice to metabolise drugs was further jeopardized by maternal administration of cimetidine.

3.4.5 Effects of Cimetidine on Drug Metabolim in Rat Pups

(Ikediobi *et. al.*, 1991)

The effects of cimetidine on drug metabolism were also studied in male and female rat pups and compared to similar effects in adult rats. As in adult rats, cimetidine 50 mg/kg/day i.p. for 7 days in the 2^{nd}, 3^{rd}, 4^{th} or 5^{th} weeks of life resulted in prolonged PBST (equivalent to diminished pentobarbitone hydroxylase

activities), particularly when administered during the 3rd week. These effects of cimetidine were reversible since they continued only up to 2 weeks in males and 4 weeks in females, but by the 6th week were no longer observed. Pretreatment with cimetidine 15, 25 and 50 mg/kg/day i.p. for 7 days, resulted in a dose-dependent inhibition of APN-D and AH as well as a prolongation of PBST in both pups and adults, AH being the least affected. In general, female pups were more adversely affected than male pups and adults.

3.4.6 Contributions of the Cimetidine Studies to Recalling Therapeutic Exiles

These aforementioned studies which deal with potential use of cimetidine in women of child-bearing age, during pregnancy, labour and breastfeeding as well as in the very young should make its use in the perinatal period more rational. The therapeutic and toxicological implications are manifold. Although these studies were carried out in animals, rodent models that can be extrapolated to man were used (e.g. rat uterus). Thus, the use of cimetidine during pregnancy and labour appear to be safe. However, the use of cimetidine during breastfeeding and in the young requires caution due to its ability to inhibit drug metabolism with ample potential for drug-drug interactions.

It is pertinent to draw attention to the fact that by 2012, GlaxoSmithKline had sold Tagamet® (cimetidine) along with 16 other brands to Prestige Brands, and the drug is now available as an over-the-counter medicine for heartburn in many countries. Yet its safety profile in the perinatal period in actual clinical situations remains largely unknown!

3.5 Post-Doctoral Research on the Metabolism of the Oral Contraceptive, Ethinyloestradiol

Part of my contributions to perinatal pharmacology relates to women of child-bearing age, sometimes put at 15-45 years. For women who are sexually active within this population, drug use in general, could easily translate to drug use in pregnancy, with possible negative implications.

Whereas other studies in the female described so far, involved drugs taken by the male as well, the use of traditional oral contraceptive drugs are exclusive to women[76]. Our studies with ethinyloestradiol, using tissue culture techniques, showed possibilities of interactions with food, cosmetic and pharmaceutical additives via drug metabolism, specifically glucuronidation (Kwanashie, 1994 and 2008; Kwanashie and Burchell, 1994)[77]. Inhibition of the glucuronidation of ethinyloestradiol by antioxidants like octyl gallate, propyl gallate, and colouring agents like erythrosine B, tartrazine, may lead to increased blood levels of the contraceptive and toxicities, including the genesis of certain types of cancer.

3.5.1 Interactions Between Ethinyloestradiol and Food, Cosmetic and Pharmaceutical Additives Via Glucuronidation (Kwanashie, 1994)

Isolated human Uridine di-phoshate Glucuronosyl Transferase (UGT) cDNAs had been stably expressed in HepG-2 or HuH-7 liver cell lines (HP1, HP2, HP3), and in Hek293 kidney cell line (HP4) using V79 Chinese hamster fibroblast cells, with expression of the transport proteins being assessed by immunoblotting (Wooster *et. al.*, 1991).

Using these V79 cells transfected with UGT HP1, HP3 and HP4, as well as rat liver microsomes (RLM), the glucuronidation of several drugs being a battery of endobiotics and xenobiotics (against 1-naphthol as standard), were examined through *in-vitro* incubation with ^{14}C-UDPGA. This was followed by thin layer chromatography (TLC), leading to separations of any glucuronides formed as described by Visser *et. al.* (1993). The major criteria for drug selection were frequent use in the clinical setting and proven or possible glucuronidation; and so included NSAIDs, H_2-receptor antagonists, ethinyloestradiol and food/cosmetic/pharmaceutical additives. That V79HP3 has similar affinities towards the semi-

---

[76] Male oral contraceptives are currently being developed.

[77] These studies were conducted under the supervision of Prof Brian Burchell at the Department of Biochemical Medicine, Ninewells Hospital and Medical School, University of Dundee, Dundee, Scotland; with support from The Wellcome Trust, UK

synthetic oestrogen-ethinyloestradiol and some food additives led to their further investigation. No glucuronides were detected for chloroquine, cimetidine, colchicine, paracetamol, probenicid, ranitidine, thyroxin and tri-iodothyronine. Since many of these drugs are known to undergo glucuronidation, their non-detection may be due to involvement of UGTs other than those listed above; or to limitation of the assay procedure. Glucuronide formation was nonetheless demonstrated with ethinyloestradiol (V79HP3, V79HP4 and RLM), the food additive, octyl gallate (V79HP3, V79HP4 and RLM) as well as propofol (V79HP4 and RLM) - see Table 3. From this, interaction between ethinyloestradiol and octyl gallate via transfected (HP3) V79 cells was an obvious possibility and was therefore explored further.

3.5.2 Interaction Studies Between Ethinyloestradiol and Food Additives (Kwanashie, 2008)

Ethinyloestradiol is the most commonly used oetrogen in combined oral contraceptive preparations, and as such, the potential for its interaction with commonly used food additives is real, which could result in therapeutic and / or toxicological consequences. Octyl gallate is an anti-oxidant which is widely used in the food, cosmetic and pharmaceutical industries. This study was undertaken to investigate possible interactions between ethinyloestradiol and octyl gallate, as well as other food additives.

A radioactive assay technique using ^{3}H-ethinyloestradiol was employed and optimized for substrate concentration (200 µM), incubation time (30 minutes), pH (7.5) and amount of protein (0.15 mg). Interaction studies were carried out between ethinyloestradiol, octyl gallate, propyl gallate (both anti-oxidants) and gallic acid (from which they are derived). Further interaction studies were carried out between ethinyloestradiol and other commonly-used food additives / constituents; namely: vanillin, saccharin, vitamin C, vitamin E, protocatechuic acid, catechin, benzoic acid, p-hydroxy benzoic acid, 4-chlorobenzoic acid, 2,5-dihydroxybenzoic acid, tartrazine, erythrosine B and tannic acid. The concentrations of each of the food additives was 50 µM relative to 100 µM for the oestrogen. Octyl gallate (10-50 µM) was shown to inhibit the glucuronidation of ethinyloestradiol (100 µM) in a concentration-dependent manner (Table 4).

Table 3: Drugs Glucuronidated by One or More Transfected V79 Cells or Lubrol-activated Fed Rat Liver Microsomes

Drug	V79HP1	V79HP2	V79HP3	Lub-FRLM
1-Napthol	26.98	1.06	1.20	20.77
Propofol	0	Nd	7.63	1.06
Ethinyloestradiol	0	0.48	0.10	Nd
Octyl gallate	Nd	2.61	17.5	Nd
Bilirubin*	0.008	0.139	0.008	0.770

V79HP = Human cloned stably expressed UGTs in
V79 Chinese hamster fibroblast cells
Lub- = Lubrol-activated; FRLM = Fed Rat Liver Microsomes
Glucuronidation estimated by Uridine di-phoshate Glucuronosyl Transferase (UGT) in nmol/min/mg
*Spectrophotometric assay method; others by TLC
Nd = Not done / or determined with poorly-active cell homogenate

Table 4: Concentration-dependent Inhibition of Ethinyloestradiol Uridine di-phosphate Glucuronol Transferase by Some Food Additives

Concn (μM)	Gallic acid	Propyl gallate	Octyl gallate	Erythro-sine B	Tartra-zine	Tannic acid
0	100	100	100	100	100	100
10	95.90	94.08	80.20	17.68	107.96	72.80
30	98.71	87.69	63.09	15.48	104.68	46.40
50	97.67	72.89	60.28	10.21	78.96	21.01

*Control = 100%
Incubation concentration: ethinyloestradiol = 100 μM,
others = 50 μM.

Its close relative, propyl gallate, a less favoured anti-oxidant, also showed concentration-dependent inhibition of the glucuronidation of ethinyloestradiol. Whereas octyl gallate was the more potent of the two as inhibitors, gallic acid had no effect on the glucuronidation of ethinyloestradiol, indicating a Structure Activity Relationship (SAR).

Propyl and octyl gallate were subsequently shown to be weak (20-39%) and moderate (40-59%) inhibitors respectively, indicating that the longer the side chain, the more potent the ester was, as an inhibitor - see Table 5. Vanillin, saccharin, vitamin C, vitamin E, protocatechuic acid, catechin, benzoic acid and its derivatives - p-hydroxybenzoic acid, 4-chlorobenzoic acid and 2,5-dihydroxybenzoic acid (a.k.a. gentisic acid) had little (<20% inhibition) or no effect on the glucuronidation of ethinyloestradiol. On the other hand, tested colouring agents were found to be inhibitors of the glucuronidation of ethinyloestradiol. While tartrazine was found to be a weak inhibitor (20-39%), erythrosine B and tannic acid were shown to be strong inhibitors (60-79%). Thus, the potency of the indicated food additives as inhibitors of ethinyloestradiol glucuronidation, in decreasing order was as follows: erythrosine B > tannic acid > octyl gallate > propyl gallate > tartrazine. As with the gallic acid esters, concentration-dependent inhibitions were also shown to be the case for erythrosine B and tannic acid (Table 6).

Table 5: Inhibition of Ethinyloestradiol Uridine di-phosphate Glucuronol Transferase by Some Food Additives

Group	Drug	Percent UGT Left*	Verdict
Gallic Acid and their Esters	Gallic acid	97.67	No effect
	Propyl gallate	72.89	Weak inhibition
	Octyl gallate	60.28	Moderate inhibition
Vitamins	Vitamin C	100.42	No effect
	Vitamin E	97.84	No effect
Benzoic Acid and their Derivatives	Benzoic acid	99.11	No effect
	p-hydroxy benzoic acid	105.17	No effect
	4-chloro benzoic acid	99.76	No effect
	2,5-dihydroxy benzoic acid	101.60	No effect
Colouring Agents	Erythrosine B	10.21	Very strong inhibition
	Tartrazine	78.96	Weak inhibition

Sweetening / Flavouring Agents, etc	Tannic acid+	21.01	Strong inhibition
	Saccharin	104.54	No effect
	Vanilin	92.66	No effect
	Catechin	100.20	No effect
	Protocatechuic acid	99.32	No effect

*Control = 100%; + = Natural occurring plant component
Incubation concentration: ethinyloestradiol = 100 μM,
others = 100 μM

Researcher's Scale for Designation of Potency of Inhibition (% Ethinyloestradiol left-Verdict): >85 No effect, 81-85 Very weak, 61-80 Weak, 41-60 Moderate, 21-40 Strong, <21 Very strong

Table 6: Concentration-dependent Inhibition of Ethinyloestradiol Uridine di-phosphate Glucuronol Transferase by Erythrosine B

Erythrosine B Concn (μM)	Per cent UGT Left*
0.1	94.75
0.2	90.08
0.5	78.64
2.0	40.77
5.0	24.42
10.0	17.68
30.0	15.48
50.0	10.21

*Control = 100%
Incubation concentration: ethinyloestradiol = 100 μM

Although not carried out due to time constraint, these interactions could have been confirmed *in-vivo* by addition of the oestrogen and food additive(s) simultaneously to whole cells in tissue culture medium, in order to assess competition of the two substrates for the enzyme (HP3). Analysis of the glucuronide formation would then have been by high performance liquid chromatography (HPLC) with the use of β-glucuronidase as well as radioactive assays (Ebner *et. al.*, 1993).

3.5.3 Contributions of the Ethinyloestradiol Studies to Recalling Therapeutic Exiles

The significance of the ethinyloestradiol studies was that inhibition of the glucuronidation of oestrogen by food additives (and co-administered drugs metabolized reasonably by V79HP3 cells as well as by rat liver), may lead to increased blood levels and toxicities of the oestrogen, including the genesis of certain types of cancer. Based on my data described above, prediction of ethinyloestradiol interaction with other food additives can reasonably be made. Thus, clinicians who prescribe ethinyloestradiol and even the women themselves who take this oral contraceptive should be mindful of the additives in the foods and medicines they take concurrently.

3.6 Contributions Relating to Malaria, HIV/AIDS and Sickle Cell Disorder, Etc

The contributions described in this section represent research conducted outside my education and training, and include those of students supervised by me, highlights of which are summarised in Tables 7 and 8. Malaria as a disease is no respecter of age and sex although pregnant women and children (especially those below the age of 5) are particularly susceptible. Thus, research involving the disease itself and/or antimalarial drugs are directly relevant to the perinatal period. Similarly, HIV/AIDS is more common in females, and hence research in this area is of primary benefit to women. Furthermore, as will be argued later, sickle cell disorder is primarily, a disease of children. Some details about the old antimalarial drug, quinine, which is still in use in severe, complicated and cerebral malaria, especially in East Africa (Kwanashie and Kwanashie, 2011), and is used in folkloric medicine for illegal abortions is reported in 3.6.1. Our surveys confirmed that the specific most sold antimalarial drugs in the Zaria area was artemether-lumenfantrine followed by artesunate-amodiaquine (Kwanashie *et. al.*, 2011); the two artemisine derivatives (artemether and artesunate) having earlier been investigated by our team, administered alone, and together with antiretroviral drugs.

Table 7: Other Research Contributions by Kwanashie in Recalling 'Therapeutic Exiles': Malaria and HIV/AIDS

Disease / Other Conditions	Perinatal Period Covered	Additional Information	Research Project / Publications	References
MALARIA	Women... / Pregnancy	Old antimalarial drug, still in use for complicated / cerebral malaria	Pharmacological Evidence for Cautious Use of Quinine in Late Pregnancy and its Frequent Failure as an Abortifacient	Kwanashie *et. al.* (2002)
	Women... / Pregnancy	Newer antimalarial drug (artemether)	Some Pregnancy-related Effects of Artemether in Laboratory Animals	Ejiofor *et. al.* (2006)
	Women... / Pregnancy	Newer antimalarial drug (artemether)	Effect of Artemether on Mid-Gestation Period of Pregnancy in Rats	Ejiofor *et. al.* (2007a)
	Women... / Pregnancy	Newer antimalarial drug (artesunate)	Preliminary Studies on the Effects of Artesunate on Rat Uterine Smooth Muscle	Ayanwuyi *et. al.* (2009)
MALARIA & HIV/AIDS	All	Artesunate-Lamivudine co-administration	Effects of Lamivudine-Artesunate Coadministration on Some Pharmacological and Biological Parameters in Healthy and Disease State Laboratory Rodents	Olurishe (2010), Etc
	All	Artemether-Nevirapine co-administration	Exploratory Studies on the Effect of Co-administration of Artemether and Nevirapine in Normal and Diseased Rodents	Anafi (2014), Etc

Table 8: Other Research Contributions by Kwanashie in Recalling 'Therapeutic Exiles': Sickle Cell Disorder and Postpartum Haemorrhage

Disease / Other Conditions	Perinatal Period Covered	Additional Information	Research Project / Publications	References
SICKLE CELL DISORDER	Children mainly	The disorder	Incidence and Prevalence of Sickle Cell Anaemia in Northern Nigeria	Kwanashie *et. al.* (1998a)
	Children mainly	The disorder	Pharmacological and Non-Drug Management of Sickle Cell Anaemia at ABUTH, Zaria, Nigeria	Kwanashie *et. al.* (1998)
	Children mainly	Siculine syrup	Pharmacological Studies on Siculine - I: Antisickling and Analgesic Activities	Ejiofor *et. al.* (2007b)
	Children mainly	Siculine syrup	Phytochemical, Antimicrobial and Pharmacological Studies on 'Siculine' - A Herbal Remedy for Sickle Cell Anaemia	Ejiofor *et. al.* (2008)
	Children mainly	Siculine syrup	Pharmacological Studies on Siculine Syrup II: Effects on Various Smooth Muscles	Kwanashie *et. al.* (1998c)
			Pharmacological Studies on Siculine Syrup. II: Effects on Smooth, Skeletal and Cardiovascular Muscle Preparations	Kwanashie *et. al.* (2009)
POSTPARTUM HAEMORRHAGE	**Women in labour**	Misoprostol	A Randomised Clinical Trial Comparing the Effects of Oxytocin Injection and Oral Misoprostol Tablets in the Prevention of Postpartum Haemorrhage in Maiduguri Nigeria	Uthman *et. al.* (2011)

While Ejiofor *et. al.* (2006 and 2007a) had shown that artemether did not adversely affect the outcome of pregnancy in *in vivo* experiments in rats, Ayanwuyi *et. al.* (2009) reported that artesunate produced concentration-dependent contractions of the isolated rat uterus (*in vitro*) just like oxytocin though less potent, suggesting that its administration during pregnancy and/or labour, may affect the outcomes. The effects of these first line antimalarial drugs on pregnancy from various angles definitely need further investigations. Hence, another MSc student of mine (Mrs Maryam Usman) has just completed her laboratory work investigating the effects of old and new antimalarials on the oestrous cycle and uterine contractility in rats.

The research on antiretroviral drugs were undertaken as PhD research by students I had supervised, and these focussed on interactions with antimalarial drugs using laboratory animals (3.6.2). Dr Temidayo Olurishe had looked at the effects of lamivudine-artesunate coadministration on some pharmacological and biological parameters in healthy and disease state laboratory rodents (Olurishe, 2010), from which he has published extensively (e.g. Olurishe *et. al.*, 2011a,b, 2012a,b and 2013). Dr (Mrs) Sherifat Anafi more recently concluded exploratory studies on the effect of co-administration of artemether and nevirapine in normal and diseased rodents (Anafi, 2014), and is in the process of publishing her findings (Anafi *et. al.*, 2013a,b). Mrs Fatima Abdurahman had also just concluded a pharmacoeconomic analysis of HIV/AIDS management involving both adult and paediatric patients in Kano (Abdurahman, 2014).

Studies on sickle cell disorder itself and on siculine syrup, a herbal remedy purported to be useful in its treatment (most of which were conducted by myself, and by Dr Janet Ejiofor for her MSc Pharmacology project), are reported in 3.6.3. In 3.6.4, the use of misoprostol in managing postpartum haemorrhage investigated by Dr Sadiq Uthman for his PhD, evaluation of drug use and medication errors in paediatric patients investigated by Dr Basheer Chedi (also for his PhD), and other contributions relevant to the discourse, are summarized. Publications arising from all of these studies are described in those sub-sections.

I have included briefs about some of these students' contributions in my presentation because the research projects were

initiated and supervised by me with the purpose of providing relevant data towards recalling women and children from therapeutic exile. By thus grooming the students to make perinatal-cum-paediatric pharmacology their life-long research priority also, one has the hope and expectation of achieving a multiplier effect. Additionally, all their publications referred to, were co-authored by me (see reference list).

3.6.1 Pharmacological Evidence for Cautious Use of Quinine in Late Pregnancy and its Frequent Failure as an Abortifacient (Kwanashie *et. al.*, 2002)

Quinine, the principal alkaloid from *Cinchona* bark is an antimalarial agent that can be life-saving in multi-drug resistant, complicated or cerebral malaria. Its use in pregnancy however, is fraught with uncertainties since quinine is believed to be an abortifacient in high doses; and a teratogen. The objective of this study was to determine the pharmacological action of quinine on the isolated rat uterus, a model that can be meaningfully extrapolated to man. Non-pregnant and pregnant uterine preparations were set up in organ baths filled in either non-perfused or oxytocin-perfused manner, with De-Jalon solution at $37^{O}C$ and challenged with quinine and/or oxytocin. Amplitudes and rates of contractions were recorded using a microdynamometer. The results showed that unlike oxytocin (20-320 ηg/ml) which contracted the uterus concentration-dependently, quinine (120 μg/ml-1.2 mg/ml) had no agonist effect on the non-pregnant uterus. Furthermore, it was shown that quinine blocked the rhythmic contractions of the pregnant uterus, even mimicking relaxation. Quinine (480 μg/ml) also decreased the amplitude of 160 ηg/ml oxytocin-induced contractions in the non-perfused uterus to 84% and 78%. In 10 ηg/ml oxytocin-perfused uterus, the effect was shown to be concentration-dependent since amplitudes were decreased to 89% and 43% following pretreatment with 120 and 240 μg/ml quinine respectively. Corresponding decreases of contraction rates, also in the perfused uterus, were to 71% and 26%. These results negate the widely held view that quinine has oxytocic action. The results also suggest that when used in late pregnancy, quinine could inhibit the action of endogenous oxytocin and may therefore interfere with the initiation of labour at

term. In addition, the data explains, at least in part, the frequent failure of quinine when employed as an abortifacient.

3.6.2 Effects of Antimalarial-Antiretroviral Co-administration (reported in Olurishe, 2010, Olurishe *et. al.*, 2011a,b, 2012a,b & 2013 and Anafi, 2013a,b & 2014)

In summary, Olurishe showed that artesunate possessed analgesic properties, and that piroxicam-mediated analgesia was significantly reduced when co-administered with the antimalarial (Olurishe *et. al.*, 2011a). Concurrent lamivudine-artesunate administration resulted in histopathological changes in rat liver and kidney (Olurishe *et. al.*, 2011b, 2012a and 2013). Olurishe (2012b) also showed that glucose tolerance was altered when lamivudine was administered with artesunate, a possible advantage since hypoglycaemia is often a complication of malaria. Anafi *et. al.* (2013a) had reported antimalarial effect for the antiretroviral drug, nevirapine. Additionally, nevirapine was shown to abolish the analgesic effect of artemether in malaria-infected mice (Anafi *et. al.* 2013b). Idemyor (2007) had likened the interactin of HIV and malaria to two elephants colliding; which these drug interactions and co-toxicities seemed to corroborate. However, it should be noted that all the drug interactions were not necessarily bad (e.g. Olurishe *et. al.*, 2012b).

3.6.3 Studies on Sickle Cell Disorder and Siculine Syrup (*Kwanashie et. al., 1998a,b, 1999 and Ejiofor et. al., 2007b,* 2008)

My interest in sickle cell anaemia derives partly from its being basically (including in Nigeria), a disease of childhood. Although the sickle cell trait and disease is common in Nigeria, the prevalence, incidence and other basic data relating to its occurrence and management were largely unknown in the northern parts of the country. That was prior to our examination of data available over five years from two weekly sickle cell clinics run by the ABU teaching hospital (ABUTH) Zaria. Of the 6,466 patients sent for haemoglobin genotyping from 1993 to 1997, 63% had normal haemoglobin, 24% were carriers of the sickle cell trait/gene while 13% had the full-blown disorder. While 'labels' are discouraged for ethico-social reasons, this last group may be termed 'sicklers' for

ease of reference in this presentation. The predominant genotype among the sicklers was Hb-SS+F (69.7%), followed by Hb-SS (24.0%); 6.2% and 0.1% of the sicklers being Hb-SC and Hb-SC+F genotypes respectively. No sex difference was found regarding the occurrence of sicklers in the study population. However, the vast majority of the sicklers were infants aged one year or below (40.3%) and two years (29.5%). While it may be argued that the relatively high morbidity and mortality associated with the condition, prevents many of those affected from growing into adolescence and adulthood, the present data may have been skewed upwards having been derived from a hospital diagnostic laboratory. That notwithstanding, these data were similar to reports from the south of Nigeria (Fleming, 1982).

In a related study (based primarily on patients' folders and discussions with doctors and other staff), we sought additional basic data relating to sickle cell anaemia in Nigeria (Kwanashie *et. al.*, 1998b). Age and weight correlations showed a generally retarded growth in children with full blown sickle cell disorder, compared to other children, which difference was seen by the 6th month of age, and could be as high as 18%. The hand-foot syndrome, fever, cough and hepatosplenomegaly (especially hepatomegaly) were the most common signs and symptoms of sickle cell anaemia encountered. Laboratory investigations showed extremely low PCV (average being 24.89%) and haemoglobin (average being 7.64 g/dl) compared to 37-54% and 11-17 g/dl in the normal population.

We were also interested in the drug and non-drug management of sickle cell anaemia in Nigeria and whether or not, this was supported with a sound pharmacological basis (Kwanashie *et. al.*, 1998b). Routine drug therapy encompassed pricipally, malaria prophylaxis with proguanil (100%) and the use of folic acid as haematinic (97%). Other frequently used drugs were chloroquine (42%) for the treatment of malaria; several antibiotics (54%) and paracetamol (25%). Since malaria is the single most important trigger of crises in these patients who also needed exogenous folate for the requied haematopoeisis; there was sound rationale for the pharmacological management of sickle cell anaemia patients, in and out of crises situations, at ABUTH Zaria. Non-drug management measures such as advice on good nutrition, general health care and genetic counselling were routinely given. Transfusion of blood and

blood products was largely avoided primarily to prevent possible infection with hepatitis and HIV. Patients were mostly asked to see their doctors every three months, although appointments scheduling could be as frequent as one week. These non-drug management approaches were also adjudged to be in accordance with good medical practice.

Having provided some background data, my interest was directed at the screening of some of the natural products believed to be useful in Nigeria's folkoloric managemnet of sickle cell anaemia. One of such products, 'Siculine Syrup', which is a composite plant extracts purported to be useful in the prevention and treatment of sickle cell pain crisis, became the subject of one of my MSc student's research and my other independent research. Dr Janet Ejiofor found that siculine (0.625-5.000%) concentration-dependently inhibited sodium metabisulphite-induced sickling in both Hb-AS and Hb-SS red blood cells; but had no effect on already sickled RBCs of either genotype. Furthermore, inhibition of sickling was more pronounced in the Hb-SS genotype than in Hb-AS, with 2.5% siculine giving the optimum inhibition of sickling in both genotypes. Siculine (10 and 100 mg/kg) also exhibited a dose-dependent analgesic effect in BALB/c mice, which effect was lower than that of dipyrone. These antisickling and analgesic effects were statistically significant (P=0.05-0.001) when compared to saline controls; and were probably the pharmacological basis for the extract's purpoted usefulness in sickle cell pain crisis. The data (Ejiofor *et. al.*, 2007b) suggests that while siculine may have a place in the *prevention* of sickle cell crisis, as a result of its ability to inhibit sickling, it may not be so useful in the *treatment* of an established crisis, since it had no effect on the reversal of already sickled RBCs.

Further experiments were carried out to determine the effects if any, of siculine on various muscle preparations (Kwanashie *et. al.*, 1998c and 2009). Siculine (0.2-1.0 μg/ml) like acetylcholine (40-400 ηg/ml) contracted the isolated rat uterus preparation concentration-dependently. Similar effects were observed with the guinea pig ileum and rabbit jejunum (0.4-2.0 μg/ml). In contrast to these effects, contractions due to direct and indirect stimulations of the rat phrenic nerve/diaphragm preparation were relaxed by siculine (0.4-0.8 mg/ml), as did d-tubocurarine (0.8 μg/ml). Again, these

effects were concentration-dependent; and may have possible therapeutic and/or toxicological effects.

Phytochemical screening, antimicrobial and other studies were also carried out on siculine (Ejiofor *et. al.*, 2008). Siculine was shown to contain cardiac glycosides, flavonoids, terpenes and sterols; but not alkaloids, saponins, anthraquinones, tannins, phlobatanins, starch or free reducing sugars. The extract also exhibited antimicrobial activity against *S. aureus* but not against *P. aeruginosa* and *E. coli*. Food intake was not affected by siculine administration which increased water intake in both male and female Wistar rats and resulted in diuretic effect especially in the female.

As part of an on-going exercise to map out the pharmacological profile of siculine, the cardiovascular effects using the isolated guinea pig atria, perfused rabbit heart and cat blood pressure set-ups, were investigated (Kwanashie *et. al.*, 1998c, 1999 and 2009). Siculine, concentration-dependently decreased both the rate and force of contraction of the guinea-pig atria (0.05-5.00 ml) and rabbit heart (0.2-0.8 ml). Siculine (0.1-3.2 ml) also resulted in fall in cat blood pressure in a concentration-dependent manner. These effects were similar to those of, and potentiated by acetylcholine while they were opposite to, and antagonised by epinephrine. The mechanism(s) of these actions of siculine, the possibilities of hypotensive side effects when used in sickle cell crisis, as well as its potential as an antihypertensive agent, remained to be investigated. Because the exact composition of siculine remained unknown to us (despite great efforts); its potential as an antisickling agent and as an antihypertensive, etc, could not be investigated further.

This somewhat abrupt ending to the siculine story is typical of many such pharmacological investigations into ethnomedicines. These can only progress into drug development when key challenges such as protection of indigenous knowledge and intellectual property rights have been adequately addressed. Such challenges and prospects have been well identified/reviewed (e.g. by Busia and Kasilo, 2010; Kwanashie, 2011 and Kwanashie *et. al.* 2012), and are merely awaiting action.

3.6.4 Postpartum Haemorrhage and Other Contributions

Dr Sadiq Uthman, a PhD graduate supervised by me conducted a comparative study of the efficacy of intravenous oxytocin and oral misoprostol tablet in the prevention of postpartum haemorrhage in Maiduguri, Nigeria (Uthman, 2011). As we are still in the process of publishing the findings, I will simply summarise the conclusion in one sentence, thus: Although the two medication approaches were safe and could be interchanged, 600 μg oral misoprostol tablet resulted in better prevention of postpartum haemorrhage than 10 IU intravenous oxytocin (Uthman *et. al.*, 2011). Despite the fact that ethical issues regarding possible misuse of misoprostol for criminal abortions if made widely available, is still being debated, the potential for saving lives, and meeting millennium development goal No. 5 is obvious. Similarly, Dr B.A.Z. Chedi had evaluated drug use and medication errors in paediatric patients in Kano State (Chedi, 2012) - findings of which will make for rational drug use in children. Again, our findings are not yet fully in the public domain, and hence cannot be shared at this forum.

Then, there is the issue of malnutrition, to which children and women are particularly vulnerable. From her MSc research project, the very first postgraduate student supervised by me (Dr Hafsat Shittu), we had reported that the combined effects of malnutrition (specifically protein-energy malnutrition) and cimetidine on hepatic drug oxidation is synergistic inhibition to the greater detriment of female and young rats (Shittu *et. al.*, 1994a,b). Similar studies on the effect of nevirapine on combined malnutrition and immunosuppression in Wistar rats have just been concluded by Mrs Hauwa Faruk, another MSc student of mine, who is awaiting external examination.

Other studies carried out by my group testing out natural products on uterine contractility have potential for informing better drug use during pregnancy and labour. These include medicinal plants like *Khaya senegalensis* (Olurishie *et. al.*, 2006) and minerals like the food additive, natron (aka *kanwa*, Alawa *et. al.*, 2010). In addition, I should mention also a number of other research and reports that may not directly be restricted to women, but by their very nature, may find special applications in females - e.g. measurements of toxic formaldehyde levels in cosmetics (Ugye *et.*

al., 2011), pharmacological and non-pharmacological management of obesity (Kwanashie, 2000a) and significance/implications of drug abuse by women (Kwanashie, 2000b).

3.6.5 Contributions of the Malaria, HIV/AIDS, Sickle Cell Disorder and Postpartum Haemorrhage Studies to Recalling Therapeutic Exiles

These various studies on malaria, HIV/AIDS, sickle cell disorder, postpartum haemorrhage and medication errors in children, highlighted above are directly poised to recalling women and children from therapeutic exile (having met several of the criteria outlined in 3.1), and hence need no further elaboration.

3.7 Contributions Through Teaching and Community Service

The contributions outlined here may relate to recalling women and children from exiles other than therapeutic exiles. However, given the WHO's extended definition of health to include 'mental and social well-being', these like those in Chapter Four do qualify for inclusion in this discourse!

3.7.1 300 Level Lecture on Drug Treatment of Anaemia

Forum: Undergraduate pharmacology class

Duration: Two hours contact time annually

Approximate Reach: Over 100 female students every year

Perinatal Period: Women and children across the perinatal period

Contribution: Female students are encouraged to ensure that they and their children eat sufficient highly nutritious foods rich in (protein), vitamins (like folic acid) and minerals (like iron) required for production of red blood cells such as green leafy vegetables, plantain, meats, liver. This they can and should do during food preparation in the kitchen, if it is culturally unacceptable for them to eat the best and enough portions of such foods as meat at the dining table. Students are also requested to pass the message on.

3.7.2 Community Service to the Blind and Visually Challenged

Forum: Hope for the Blind

Duration: Two hours a week at intervals between 1992 and 1997

Approximate Reach: Difficult to estimate, but could be hundreds of blind or visually challenged students

Perinatal Period: Children mostly

Contribution: I was reading textbooks into audio media in a recording studio. These were then reproduced and distributed to secondary school students who were blind or visually challenged across the nation.

3.7.3 Community Service to Improve Teaching

Forum: Eduwatch Workshop for Teachers in Yaba, Lagos

Duration: 2 days (17^{th}-18^{th} February 2010)

Approximate Reach: About 40 school teachers

Perinatal Period: Women directly, children indirectly

Contribution: I was co-organiser and co-facilitator of a workshop on *Developing and Strengthening Reading and Writing Skills Across the Curriculum.*

3.7.4 Community Service to Professional Society

Forum: West African Society for Pharmacology , (WASP) programmes at Exco and general assembly levels
Duration: Approximately quarterly, from 2011 to 2013

Approximate Reach: Varies, potential beneficiaries are in tens (and is continuing)

Perinatal Period: Women and children

Contribution: As president, with the cooperation of WASP Exco, I initiated and promoted provision of crèche facilities and nannies at WASP programmes, paid for, by the society. This was borne out of the belief I held and propagated that no woman should stay away from attending a conference or other academic programme, just because she's a woman. Many women benefitted and attended WASP meetings and workshops with their young children as a result of this policy/programme, earning the lecturer the nickname - 'Grandma Prof'!

3.7.5 Community Service to Gender-based Association

Forum: ABU Chapter of National Association of Women Academics (NAWACS-ABU)

Duration: Continually from 1999 to 2002

Approximate Reach: Over 100 women academics
Perinatal Period: Women

Contribution: As president and working with NAWACS-ABU Exco and other members, I initiated and promoted the career advancement programme, code-named *At Least One!* This became a greeting and response amongst members, and is intended to remind each woman academic to aim, in the course of every session, to:

- present *at least one* seminar
- attend *at least one* conference, to which she should contribute *at least one* paper
- publish *at least one* article in a reputable peer-reviewed journal in their discipline
- be part of *at least one* research grant in some capacity/level such as proposal writing, grant administration or retirement, etc.

Although, it is difficult to assess the overall benefits of the *At Least One!* programme, women academics in ABU themselves attest frequently to having been gingered by it.

In addition, trainings were organised for NAWACS-ABU members on proposal writing, paper presentation and paper

publication to give the women the requisite skills they needed for the *'At Least One!'* programme to work. The setting up of a post-workshop monitoring group (PWMG) in which senior members assisted 1 to 3 junior ones (each within their disciplines), became the beginning of a semi-formal mentorship scheme. This scheme I believe, contributed in some way to the advancement of the careers of women academics in Ahmadu Bello University and to their job satisfaction in the years since.

From two female professors at the initiation of the *At Least One!* programme, now there are tens of female professors in the university (over a period of 15 years). It is possible that this programme and the training workshop alluded to above, contributed to the accelerated career advancement among these women academics.

3.7.6 Community Service to the University

Forum: ABU Gender Studies Group, Etc

Duration: From 2002 to 2006

Approximate Reach: Difficult to estimate
Perinatal Period: Female students and Women

Contribution: As part of a group of six comprising of Prof (Mrs) Doris Bozimo, Dr Clara Ejembi, Prof (Mrs) Juliana Okpapi, Prof (Mrs) Felicia Adeyanju and Prof Emmanuel Gyong (the only male member of the group), we undertook a situation analysis of gender equity in ABU as at 2003 (Bozimo *et. al.*, 2003). This work contributed to the university securing the Carnegie Corporation of New York grant which included bursary awards to female postgraduate students as part strategy to bridge gender inequality. A follow-up to this showed some measure of progress in ABU's attempt at gender equity (Kwanashie *et. al.*, 2004; Kwanashie and Aliyu, 2006).

3.8 Reference to Other Contributions

There are many other contributions which I have made towards rational drug use in women and children, and towards their

general emancipation, that space and time does not permit me to present at this lecture. What I have done at this forum is to show sample contributions from my research mainly, but also from my teaching and community service that directly and indirectly work towards recalling women and children from exile. In the next and final chapter, through a clarion call for action, I hope to demonstrate that there's room for everyone to be pro active in recalling women and children from all sorts of exiles (therapeutic and otherwise), to the benefit of everyone and society.

Chapter Four

A Clarion Call For All

4.1 The MDGs, Women, Children and the Perinatal Period

This chapter emphasises other forms of exiles to which women and children are subjected, including but not restricted to the following: restricted access to education, not being given their rightful place in society, being frequently overworked, not being appreciated for their worth and work, bearing the brunt of wars/conflicts/famine, etc. I believe that given WHO (1948) inclusive definition of 'Health' rendered below (and which has not been amended since 1948), all of the above may be regarded as 'therapeutic exiling' by extension[78].

> Health is a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity.
> - *World Health Organisation, 7th April 1948.*

The millennium development goals (MDGs) appear to be a reasonably good place to start this final part of the discourse in which it is argued that recalling women from therapeutic exiles is, to use Shirkey's words 'everybody's business' (Shirkey, 1968b, 1970 and 2006). Three of the keywords in the lecture content thus far, namely: 'malaria', 'HIV/AIDS' and the 'perinatal period' are linked together by the MDGs. The MDGs were established in 2001 by the United Nations (UN). The overall aim was to create a framework for implementation of the Millennium Declaration which had been adopted the year before, by 189 countries (including Nigeria), with the specific objectives of reducing poverty globally, and creating a climate for sustainable development. The Millennium Declaration states:

---

[78] Not included in this discourse (though equally important) are unequal pay for women doing same jobs as men in some parts of the world, restricted female participation in politics, leadership and inheritance, domestic violence, human / sex trafficking, etc.

> We will spare no effort to free our fellow *men, women and children* from the abject and dehumanizing conditions of extreme poverty, to which more than a billion of them are currently subjected. We are committed to making the right to development a reality for everyone and to freeing the entire human race from want.
>
> *- UN Millennium Declaration, UN A/Res/55/2, 2000 (italicised emphasis, mine).*

It is noteworthy here too, that men, women and in this instance, children are mentioned in one and the same breath.

There are 8 MDGs altogether, with 18 specific targets and 48 indicators, all of which set a most ambitious agenda for greatly improving the quality of human life by 2015. These goals which have since become the international gold standards for measuring development progress especially as they relate to women and children are shown in Table 9. From the table, it is clear that the MDGs are largely about women and children; the girl-child in particular. Furthermore, of the many diseases plaguing the world, only HIV/AIDS and malaria, are mentioned specifically in the MDGs, diseases to which pregnant women, newborn babies and under-5 children (again, the girl-child in particular), are mostly susceptible. Since by definition, the perinatal period applies to that period of life, just before, during and shortly after birth (Stern, 1975), one may say that the MDGs are largely about the perinatal period. In my own small way, I have been a champion of the MDGs as an extension of my goal to recall therapeutic exiles (e.g. Kwanashie, 2007, 2010, 2012; Kwanashie and Alti-Mu'azu, 2009 and Kwanashie *et. al.*, 2008). Again, it is informative that the official event marking the 2014 International Women's Day reflected on the achievements and challenges encountered worldwide in addressing the needs and priorities of women and girls in implementation of the MDGs, and in the formulation of the post-2015 development agenda.

4.2 Generalised and Pervasive Gender Discrimination

The lecturer hypothesis that therapeutic exiling and therapeutic smuggling is a natural outcome of the gender discrimination so pervasive in society, almost from the very dawn of

age. Despite the absence of scriptural, evolutionary, scientific, and other bases, gender remains a development differential in which women are at a disadvantage (United Nations, 1994a,b,c). *Gender* has long been recognized as a social construct rather than a biological or physiological one. Since 1975 – International Women's Year – the UN began the tradition of recognising March 8 as International Women's Day. Incidentally, the subject of this inaugural lecture is in line with the theme of the 2014 internationalwomensday.com global hub, namely: "Inspiring Change" – which is intended to "celebrate the social, political and economic achievements of women, while focussing world attention on areas requiring further action". The lecturer has satirically exposed these sentiments routinely, in and outside of her professional discourse, of which four examples (with the fourth concerning children) are given below:

i. Discordant Evolution
ii. Of Double Helical Structures...
iii. Working Wife and Mother
iv. What Prize?

Table 9: MDGs and Their Primary Targets

Goal No.	MDG	Primary Target Group			Remarks
		Men	Women	Children	
1	Eradicate extreme hunger and poverty	√	√√	√√ (girls esp.)	Women and children (particularly girls) are *the poorest of the poor.*
2	Achieve universal primary education			√ (girls esp.)	Girl-child is particularly disadvantaged.
3	Promote gender equality and empower women		√	√ (girls)	Gender disparity outcomes affect women and girls on several fronts.
4	Reduce child mortality			√	Female children are less likely to receive healthcare.
5	Improve maternal health		√	√ (girls)	Early marriage / motherhood is detrimental in girls.
6	Combat HIV/AIDS, malaria and other diseases	√	√√	√√	Pregnant women and children < 5 are especially vulnerable.
7	Ensure environmental sustainability	√	√	√	
8	*Develop a global* partnership for development	√	√	√	
	TOTAL SCORE	**4**	**8**	**10 (girls, 14)**	

√ Score, not part of the MDGs are assigned by this lecturer.
Double score (√√) emphasises magnitude of target, making the MDGs (in the opinion of the lecturer), much ado about men, more so about women / children, and much more about the girl-child.

4.2.1 Discordant Evolution

This piece is the combination of a newspaper cartoon and a poem. The *Dayton Daily News* is an American newspaper while the cartoonist, Mike Peters is presumably MALE (although in today's world, one never can be certain!). The poem was written by this lecturer to further drive home Peter's message of an unfair gender disparity against women.

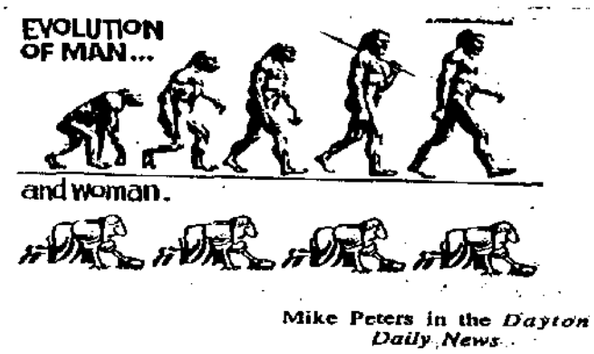


Figure 5: Discordant Evolution

Discordant Evolution

Whether you believe
In it or not
The scientific theory
Of evolution, holds
That *Homo sapiens* was
Once upon a time
Less than even an ape.

From this *lessness*
Man has evolved
To walk tall and upright
To dominate the world
And woman
Who by
The socio-cultural theory
Of evolution, remains'
Less than even an ape.

- © HelenOK, 1992.

4.2.2 of Double Helical Structures...

The second example is a poem (see below) which celebrates women for the work they do, including the so-called menial tasks like drawing water, fetching firewood, etc, that are often unacknowledged, unappreciated and unrewarded.

Of Double Helical Structures, Nobel Prize Winners: Sung and Unsung[79]

Long before '53, James Watson and Francis Crick
Nene held the secret of life in her hands!
Ropes, she herself had constructed
(Not just discovered)
From double strands of rush
Twined to form a helical structure
Each depending on
And strengthening the other.
Ropes, she dutifully employed
Drawing water, bundling firewood, etcetera
In service of mankind
Within her family and community.

Alas! If she had but owned a lab!
And understood base pairs, nucleotide sequences ...
Detailing her knowledge to *Nature* or *Science* or *JBC*[80]
My grandma could have won
The Nobel Prize ...
For she frequently made; and held daily
From childhood through adulthood
A double helical structure
In one; nay, two; nay, several tasks

---

[79] Dedicated to my paternal grandmother, *Nene (this name translates to 'grandmother' in my native Urhobo)*, the poem was originally written as the statement to an artwork meant for KINESIS 4 - an Exhibition of Women Art and Science which held in Zaria, Nigeria, from 1st to 7th December 2003. The theme of the Exhibition was *Molecular Construction*, chosen to commemorate the 50th anniversary of the discovery in 1953, of the genetic code (double helical structure of DNA) by James Watson and Francis Crick, for which they were awarded the Nobel Prize.

[80] *Nature, Science, JBC (Journal of Biological Chemistry)* are top journals for prime publications in science, biochemistry, pharmacology, etc.

As she ministered constantly to the human race.

As the world celebrates
50th year discovery of DNA structure
And the phenomenal advances derived therefrom
Recombinant DNA. Human Genome Project, others ...
Shouldn't we also salute
All who have known other double helical structures
As symbols of sacrificial service?

Though without scientific understanding
Hush. Woman! typified by hardworking *Nene*
Hush. Woman! *you too are a noble prized winner*!

© HelenOK[81], 2003

4.2.3 Working Wife and Mother

The third example (Figure 6) is replication of a drawing of the Fulani Milk Maid, as a salute to all working wives and mothers.

[81] As a pharmacologist with biochemistry background, Kwanashie is naturally fascinated by all that the knowledge of DNA has bestowed on mankind, particularly since the last two decades of the last millennium. As a child, she also had enjoyed making and using handicraft ropes, some of which were strikingly similar to the double helical structure of DNA and which when dry and cut, unravels in much the same manner into single complementary strands ...

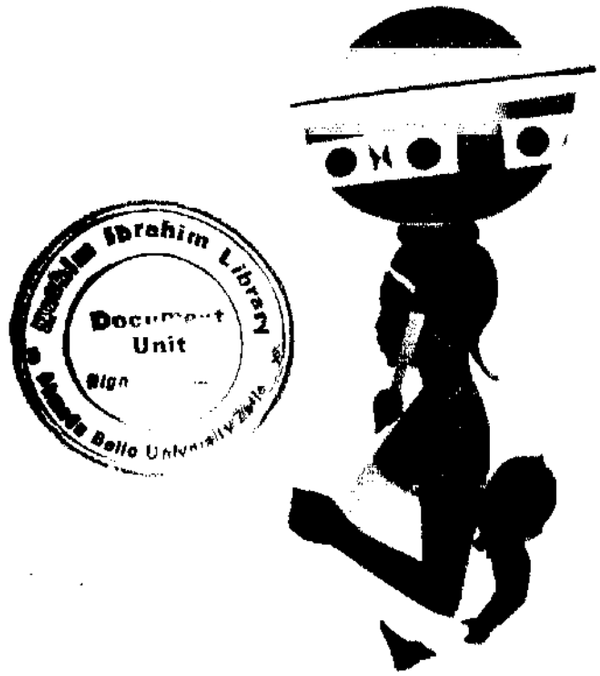

Ibrahim Library
Document Unit
Sign
Bello University

Figure 6: Fulani Woman at Work with Her Child
(**Source:** Baraka Press, Kaduna, Nigeria)

The Fulanis are nomadic cattle rearers and constitute a major ethnic group in Nigeria (and across parts of West Africa). Their womenfolk are rugged; effortlessly bearing the strains of frequent movements while selling fresh milk, yoghurt and other dairy produce (as in the picture above), even as they care for their families and their homes. A Fulani woman like other women in Nigeria and like their counterparts the world over, fulfil multiple roles of being wife, homemaker, mother, worker, food and healthcare provider, as well as being involved in community service. Many fulfil each of these roles to varying degrees, excelling in some areas, but not in others... Still this picture is a tribute to the many women worldwide *working both in the home, and out of it!* It is also to showcase that therapeutic exiles are vital contributors to society, and deserve to be recalled.

4.2.4 What Prize?

In the fourth example (Figure 7), I had written a piece, titled: 'What Prize?' to question the attitude of the winner of the 1994 Pulitzer photo prize, and I present it here to question the attitudes of all of us who walk away from a need such as helping a dying child, or recalling women and children from therapeutic and other exiles.



Figure 7: The 1994 Pulitzer Prize Winning Photo
(Source: One of the weekly newsmagazines in Nigeria)

The comment beneath this photo in the newsmagazine was:

This PHOTO is the "Pulitzer prize" winning photo taken in 1994 during the Sudan famine. The picture depicts a famine-stricken child crawling towards a United Nations food camp, located a kilometer away.
The vulture is waiting for the child to die so that it can eat it. This picture shocked the whole world. No one knows what happened to the child, including the photographer Kevin Carter who left the place as soon as the photograph was taken. Three months later he committed suicide due to depression.

In response to the photo and comment, I had written this piece:

What Prize?

Perhaps, if Kevin Carter had helped that poor child get to the food camp, he may not have gone into depression and committed suicide.

What do you do when confronted with a need or evil? Snap a photo and walk away?

- © HelenOK, 2006.

4.3 Negative Discrimination, Positive Discrimination And Roles For Everyone

Starting from age-long negative discrimination against women, the decade for women (1975-1985) saw an increase in efforts to assess the degree of gender inequity and evolve strategies to redress it. Central to this, was the 1979 Convention on the Elimination of all Forms of Discrimination Against Women (CEDAW) which established wide-ranging and explicit principles of gender equality in the political, social, cultural, legal, economic and civil spheres. As previously argued, this partly informed majority of the MDGs goals, targets and indicators. Part of the redress of gender inequality has had to do with positive discrimination or affirmative action in favour of women, and which the lecturer endorses as a good strategy in the short run (despite its limitations and disadvantages). This has led to some significant changes, socially, biomedically and clinically. Only last year (2013), there was the promulgation that the heir to the British throne is now the first born, regardless of whether the individual is male or female. For animal toxicity testings, females are increasingly becoming the preferred sex to use, simply because they are more susceptible to drug effects than their male counterparts. Even in the clinical setting, some sex differences in drug effects are now being more researched. Recently, for example, Darpo *et. al.* (2014) using a therapeutic dose of sotalol found that the change in QTc interval was steeper in women than in men which possibly explains why women may be more susceptible to drug-induced arrhythmias. Some of the world's renown professional societies practice some form of positive gender discrimination e.g. via the Women in Pharmacology programme of the British Pharmacological Society. Another example is the setting up of Gender Equality in Science grants by the Biochemical Society, and for which even non-members may apply. Thus, one is optimistic that in both social and non-social contexts (e.g. basic and clinical pharmacological research), regarding gender inequality, as the saying goes, the future is bright - the future is orange; including for *therapeutic exiles*.

4.3.1 Roles for the Biomedical Researcher

The potential roles for biomedical researchers and scientists in recalling women and children from therapeutic exile are many and varied. Obviously, this includes research and documentation at both basic and clinical levels as earlier defined (Kwanashie *et. al.*, 1989). While this should not be exclusive to female biomedical researchers, the challenge I think, should appeal specially to *women biomedical scientists and clinicians*. Rebecca Anderson's recently published book, *Nevirapine and the Quest to End Pediatric AIDS* (Anderson, 2013), is an example of one way to fulfil this role. Incidentally, she had worked for 25 years in pharmaceutical research and development prior to her becoming a medical writer. Education and advocacy is one other role, and with all due modesty, this lecturer's constant advocacy to recall therapeutic exiles is one way to fulfil this role. This also was the role of the paediatrician, H.C. Shirkey who from the 1960s and several decades, led the campaign to make provision for therapeutically orphaned children. There are lots more roles... and together, fulfilling those roles speak for women and children.

4.3.2 Roles for Everyone

In a plan of action to meet the HIV prevention needs of Africans living in England, Dodds *et. al.* (2008) emphasised the need to combine knowledge, will and power in order to effect changes. No less is required in recalling women and children from therapeutic and other exiles. "People may understand the importance of a particular behavior (knowledge), and they may want to undertake it (will) but lack the actual capacity (power) to do so." The knowledge and the will are succinctly captured in UN Secretary-General Ban Ki-moon statement to mark this year's International Women's Day with the theme: *Equality for women is progress for all.* He had said:

> "This International Women's Day, we are highlighting the importance of achieving equality for women and girls not simply because it is a matter of fairness and fundamental human rights, but because progress in so many other areas depends on it.
> Countries with more gender equality have better economic growth. Companies with more women leaders perform better. Peace agreements that include women are more durable. Parliaments

> with more women enact more legislation on key social issues such as health, education, anti-discrimination and child support.
> The evidence is clear: equality for women means progress for all.
> This simple truth must be central as we work to accelerate progress towards the Millennium Development Goals by next year's deadline and craft an agenda for the years beyond 2015."
> - *UN Secretary-General, Ban Ki-moon, 8th March 2014.*

I like to think that presently, we have the knowledge... hopefully, we will develop the will... but always the power is in our hearts and our hands, as we keep as frontlet, the following quote.

> Have the end in mind and everyday make sure you are working towards it.
>
> - *Ryan Alus.*

Ladies and gentlemen, let's just do it!

4.3.3 *Institution* of Prizes for Best Female Students in Pharmacology

I wish to use this occasion of the presentation of my inaugural lecture to institute two annual prizes in the Department of Pharmacology and Therapeutics. The prizes are to be awarded to the best graduating female students in Pharmacology amongst:

- Pharmacy (BPharm) graduands, Faculty of Pharmaceutical Sciences, and
- Medical (MBBS) graduands, Faculty of Medicine.

At an appropriate time in future, I hope to institute similar prizes at MSc and PhD levels. The prizes are meant to stimulate female students' interest in pharmacology and encourage them to want to pursue pharmacological research in general, and hopefully, those research that will be particularly beneficial to women and children.

4.4 A Mummy-General's Final Word

At the start of this lecture, I made reference to my being nicknamed 'General', and to being called 'Mummy'. It seems fitting, that I end it on a similar note.

This 'General' wants to believe that for the onerous cause of recalling women and children from therapeutic and other exiles, she has been one small voice in the past, and today. I must add the fact though, that she prefers to be perceived, known and addressed by the more mundane title of 'Teacher', rather than 'General'! As for

being called 'Mummy' rather than 'Prof(essor)', I can find an acceptance and explanation, again in the words of the founding chancellor of our university, Sir Ahmadu Bello, who insisted that ours must be a home-grown university, in the following words:

> *... our character must reflect the needs, the traditions, the social and intellectual heritage of the land in which we live.* Inevitably in a country developing as fast as ours, we must call on outside help. That we have received in generous measure. But in seeking help from outside it is not our intention to copy a standard pattern of University from the United Kingdom, from the Commonwealth, or from the United States of America. *We must develop our own pattern to suit our present background and our needs. Our University must grow out of our own soil. We shall be truly Nigerian institution and not the mirror image of some alien body.*
> - *Sir Ahmadu Bello, in Our Charter, 23rd November 1963. (italicised emphasis, mine).*

Fifty years on, and still so remarkably correct! I interpret this to mean that in Nigeria, students don't necessarily just see their lecturers as professionals, but rather as someone more holistic... to the point of meeting their other (non-academic) positive needs (yes, even primordial ones). I must admit that the idea of being perceived as a 'Mummy-Professor' or even 'Mummy-Teacher' is tonnes more attractive, than being seen as a 'Mummy-General'! As it turns out, I understand that the in-word now is 'educator' rather than 'teacher'... so perhaps, who knows, I may even wind up eventually as a 'Mummy-Educator' (alias Grandma-Prof)!

Mr Vice-chancellor Sir, Ladies and Gentlemen, in my continuing research, documentation and advocacy to recall women and children from therapeutic and other exiles, I rest my case (for now).

References

Abdurahman, F. (2014). Pharmacoeconomic Analysis of HIV/AIDS Management at Murtala Muhammad Specialist Hospital, Kano. Unpublished MSc Thesis, Ahmadu Bello University, Zaria.

Akpobi, H.O. (1979a). Detection of Polycyclic Aromatic Hydrocarbons in Nigerian Smoked Fish (1979a). Unpublished BSc Biochemistry Project Report in Toxicology, University of Ibadan, Ibadan, 73 pp.

Akpobi, H.O. (1979b). Changes in the β-Carotene, Vitamin A and Sugar Content During the Preparation of '*Ogi*' from Maize Varieties (1979b). Unpublished BSc Biochemistry Project Report in Food and Nutrition, University of Ibadan, Ibadan, 116 pp.

Alawa, J.N., **Kwanashie H.O.**, Singh S.P. and Alawa B.I.C. (2010). Effects of Natron (*kanwa*) on Murine Uterine Contractility. *J. Anim. Prod. Res.*, 22(1): 23-26.

Anafi, S.B. (2014). Exploratory Studies on the Effect of Co-administration of Artemether and Nevirapine in Normal and Diseased Rodents. Unpublished PhD Dissertation, Ahmadu Bello University, Zaria.

Anafi, S.B., **Kwanashie, H.O.**, Anuka, J.A., Muktar, H.M. and Agbaji, A.S. (2013a). Antimalarial Effect of Nevirapine in Malaria-Infected Mice Receiving Artemether. Presented at the 37th Regional Scientific Conference of the West African Society for Pharmacology (WASP), 21st-24th October, in Lagos, Nigeria.

Anafi, S.B., **Kwanashie, H.O.**, Anuka, J.A., Muktar, H.M. and Agbaji, A.S. (2013b). Nevirapine Abolishes Analgesic Effect of Artemether in Malaria-infected Mice. Proceedings of the British Pharmacological Society at http://www.pA2online.org/abstracts/Vol11Issue3abst064P.pdf. Retrieved 18th April 2014.

Anderson, P.O. (1977). Drugs and Breastfeeding - A Review. *Drug Inte. Clin. Pharm.*, 11: 208-23.

Anderson, R.J. (2013). *Nevirapine and the Quest to End Pediatric AIDS*. McFarland Publishing.

Anonymous (1982). The Top 200 Prescription Drugs of 1981. *Amer. Druggist.*, 20-5.

Atlas, S.A., Boobis, A.R., Felton, J.S., Thorgeirsson, S.S., and Nebert, D.W. (1977). Oncogenetic Expression of Polycyclic Aromatic Compound-Inducible Monoxygenase Activities and Forms of Cytochrome P-450 in Rabbit. Evidence for Temporal Control and Organ Specificity of Two Genetic Regulatory Systems. *J. Biol. Chem.*, 252: 4712-21.

Ayanwuyi, L.O., **Kwanashie, H.O.** and Hussaini, I.M. (2009). Preliminary Studies on the Effects of Artesunate on Rat Uterine

Smooth Muscle. *Biol. Environ. Sci. J.Trop., (BEST)* 6(4): 35-38.

Bardhan, K.D. (1981). Long-term management of duodenal ulcer - a physician's view. *In:* Baron J.H. (Ed) *Cimetidine in the 80s* - Churchill Livingstone, Edinburgh, Scotland.

Bell, J., Bauer, J., Capra, S. and Pulle, C.R. (2014). Barriers to Nutritional Intake in Patients With Acute Hip Fracture: Time to Treat Malnutrition As a Disease and Food As a Medicine? *Can. J. Physiol. Pharmacol.*, 91(6): 489-495.

Bignami, G., Bovet, D., Bovet - Nitti, F. and Rosnati, V. (1962). Drugs and Congenital Malformations. *Lancet* 11: 1333.

Bozimo, D.O., Ejembi, C.L., **Kwanashie, H.O.**, Adeyanju, F.B., Okpapi, J.U. and Gyong, E. (2003). Situation Analysis of Gender Equity in Ahmadu Bello University. Unpublished Gender Study Group Research Report. 167 pages.

Busia K. and Kasilo O.M.J. (2010). Overview of Traditional Medicine in ECOWAS Member States. *In: The African Health Monitor*, Special issue, 31st August 2010, pp 16-24.

Catz, C.S. and Yaffe, S.J. (1997). Problems in perinatal therapeutics. *In:* Aladjem, S. and Brown, A.K. (*Eds*) *Perinatal Intensive Care.* The C.V. Mosby company, Saint Louis, U.S.A; pp 381-95.

Cayen, N. (1989). World Pharmaceutical Market Review Released by IMS. *International Society for the Study of Xenobiotics (ISSX) Newsletter.* 8: 9-12.

Chedi, B.A.Z. (2012). Evaluation of Drug Use and Medication Errors in Paediatric Patients in Kano State, Northwestern Nigeria. Unpublished PhD Dissertation, Ahmadu Bello University, Zaria.

Collier, J. (1999). Paediatric Prescribing: Using Unlicensed Drugs and Medicines Outside Their Licensed Indications. *Br. J. Clin. Pharmacol.* 48: 5-8.

Dancis, J. (1974). *In:* Dancis, J. and Hwang, J.C. (*Eds*) *Perinatal Pharmacology: Problems and Priorities.* Raven Press, New York, U.S.A., pp 101-8.

Darpo, B., Karnad, D.R., Badilini, F., Florian, J., Garnett, C.E., Kothari, S.I., Panicker, G.K. and Sarapa, N. (2014). Are Women More Susceptible Than Men to Drug-induced QT

Prolongation? Concentration-QTc Modelling in a Phase 1 Study With Oral Rac-sotalol? *Br. J. Clin. Pharmacol.*, 77(3): 522-531.

Dodds, C., Hickson, F. Chinouya, M., Chwaula, J. and Weatherburn, P. (2008). The Knowledge, The Will and The Power. Sigma Research, African HIV Policy Network and National HIV Prevention Programme (NAHIP), pp 28.

Dvorchick, B.H., Sternger, V.G. and Quattropan, S.L. (1974). Fetal Hepatic Drug Metabolism in the Non-human Primate, *Macacu arctoides. Drug Metab, Dispos.*, 2: 539-44.

Ebner, T., Remmel, R.P. and Burchell, B. (1993). *Am. Soc. Pharmacol. Expt. Therap.*, 43: 649-54.

Ejiofor, J.I., **Kwanashie, H.O.** and Anuka, J.A. (2006). Some Pregnancy-related Effects of Artemether in Laboratory Animals. *Pharmacology (Intl. J. Exptl. Clin. Pharmacol.*, 77(4): 166-170.

Ejiofor, J.I., **Kwanashie, H.O.** and Anuka, J.A. (2007a). Effect of Artemether on Mid-Gestation Period of Pregnancy in Rats. *Biol. Environ. Sci. J.Trop. (BEST)*, 4(2): 16-21.

Ejiofor, J.I., **Kwanashie, H.O.** and Abdu-Aguye, I. (2007b). Pharmacological Studies on Siculine Syrup I: Antisickling and Analgesic Activities. . *Biol. Environ. Sci. J.Trop. (BEST)*, 4(2): 176-8.

Ejiofor, J.I., **Kwanashie, H.O.** and Abdu-Aguye, I. (2008). Phytochemical, Antimicrobial and Pharmacological Studies on 'Siculine' - A Herbal Remedy for Sickle Cell Anemia. *J. Pharm. Bioresources*, 5(1): 17-33.

Feng, J. (2012). http://www.oxbridgebiotech.com/review/research-and-policy/a-new-era-of-paediatric-medicine/ (Retrieved 26th April, 2013).

Fleming, A.F. (1982). *Sickle Cell Disease: A Handbook for the General Clinician.* Churchill Livingstone, Edingburgh, UK. 145 pp.

Flowers, C.E. (1959). The Placental Transmission of Barbiturates and Their Pharmacological Action on The Mother and The Infant. *Am J. Obstet. Gynec.*, 78: 730-42.

Gazarian, M. (2003). Why Are Children Still Therapeutic Orphans? *Aust. Presc.*, 26:122-3.

Habbick, B.F., Melrose, A.G. and Grant, J.C. (1968). Duodenal Ulcer in Childhood: A Study of Prediposing Factors. *Archs Dis. Childh.*, 43: 23-7.

Howe, J.P., McGowan, W.A.W., Moore, J., McCaughey, W. and Dundee, J.W. (1981). The Placental Transfer of Cimetidine. *Anaesthesia*, 36: 371-5.

Idemyor, V. (2007). Interaction of HIV and Malaria: When Two Elephants Collide. Seminar presented at Ahmadu Bello University Teaching Hospital (ABUTH), Shika, Zaria.

Ikediobi, C.O., **Kwanashie, H.O.**, Osuide, G. and Wambebe, C. (1991). Effects of Cimetidine on Drug Metabolism in Rat Pups. *Europ. J. Drug Metab. Pharmacokinet.*, 16(1): 1-7.

Jones, C.M. (2008). Thalidomide: New Cancer Uses For An Old Drug. *US Pharm. (Oncology suppl)* 33(7): 3-13.

Kwanashie, H.O. (1981). Drug Metabolising Capacity of Placental Tissues from Nigerian Women at Late Gestation. Unpublished MSc Biochemistry Project Report in Xenobiochemistry, University of Ibadan, Ibadan, 138 pages.

Kwanashie, H.O. (1987). Sub-cellular Localization of Drug Metabolizing Enzymes in the Human Placenta at Term. Presented at the 47th International Congress of the Federation International Pharmaceutique (FIP)/International Pharmaceutical Federation, 30th August - 4th September, in Amsterdam, The Netherlands.

Kwanashie, H.O. (1988). A Rapid Precipitation Method for Microsomes Isolation from Human Placental and Rat Liver Homogenates. Presented at the 4th International Congress of Cell Biology, 14th-19th August, in Montreal, Canada.

Kwanashie, H.O. (1990). Studies on the Effects of Cimetidine in the Perinatal Period of the Mouse and Rat. Unpublished PhD Pharmacology Dissertation in Biochemical Pharmacology, Ahmadu Bello University, Zaria, 301 pages.

Kwanashie, H.O. (1994). Interactions Between Ethinyloestradiol and Food Additives via Glucuronidation Using Human Cloned Stably Expressed UGTs. Unpublished Post-doctoral Research Project Report in Drug Metabolism, University of Dundee, Dundee, Scotland, 48 pages.

Kwanashie, H.O. (1999). Limited Availability of Drugs and Their Usage in Women and Children. Invited lecture, delivered at the

Inauguration of the ABU Chapter of National Association of Women Academics (NAWACS), 30th November, ABU, Zaria.

Kwanashie, H.O. (2000a). Anorectics, Thermogenics and Management of Obesity in Women. Presented at the 2nd International Conference of the National Association of Women Academics (NAWACS), 5th-10th September, at Abuja.

Kwanashie, H.O. (2000b). Significance and Implications of Drug Abuse by Women. Presented at the 2nd International Conference of the National Association of Women Academics (NAWACS), 5th-10th September, at Abuja.

Kwanashie, H.O. (2007). Pharmacologists and the Millennium Development Goals - Before and Beyond 2015. Presented at the 34th Annual Regional Conference of the West African Society for Pharmacology, 10th-14th December, in Zaria, Nigeria.

Kwanashie, H.O. (2008). Interactions Between Ethinyloestradiol and Food Additives Via Glucurondation. Presented at the Gordon Research Conference on Drug Metabolism, 6th-11th July, in Plymouth, New Hampshire, U.S.A.

Kwanashie, H.O. (2010). Towards Attainment of the Millennium Development Goals in Nigeria: Defining Roles for Secondary Schools. Speech Given on 24th July at the Annual Speech and Prize Giving Day, Demonstration Secondary School, Ahmadu Bello University, Zaria.

Kwanashie, H.O. (2011). Promoting Traditional Medicine in the ECOWAS Sub-region: Challenges and Prospects. Keynote address delivered at the West African Health Organisation's (WAHO's) 4th Scientific Congress of Traditional Medicine Practitioners and Conventional Medicine Practitioners, 12th October, in Banjul, The Gambia.

Kwanashie, H.O. (2012). Strategies for Achieving Safe and Effective Medicines in Africa: A Confluence for the MDGs? Invited Plenary Lecture delivered at the 5th All Africa Congress of Pharmacology (ACP2012), on 11th July, in Accra, Ghana.

Kwanashie, H.O. and Aliyu, M.K. (2006). Gender Mainstreaming in Ahmadu Bello University Zaria: A Two-Year Assessment of the Gender Equity Project. Presented at the University of Ibadan (UI) / Working Group on Higher Education (WGHE) of the Association for the Development of Education in Africa

(ADEA) / Association of African Universities (AAU)-Sponsored Training of Trainers Workshop on Gender Mainstreaming in Higher Education in Africa, 24rd-27th September, at Ibadan, Nigeria.

Kwanashie, H.O. and Alti-Mu'azu, M. (2009). Gender-related Challenges in Education in Nigeria: Implications for Girls' Education. 18 pages. (Unpublished manuscript).

Kwanashie, H.O. and Burchell, B. (1994). Drug-drug Interactions During Glucuronidation Using Human Cloned Stably Expressed UGTs. Presented at the 4th Wellcome International Fellows Meeting, 18th January 1994, in London, England.

Kwanashie, O. and **Kwanashie, H.** (2012). Availability and Choice of Antimalarials: III - Comparison Between Two Health Institutions in West and East Africa. Presented at the 5th Ghana Biomedical Convention (GBC) Conference, 30th July-1st August, in Accra, Ghana.

Kwanashie, H.O., Osuide, G., Wambebe, C. and Ikediobi, C.O. (1987). Action of Cimetidine on the Rat Uterus Preparation. Presented at the Xth International Union of Pharmacology (IUPHAR) Congress, 23rd-28th August, in Sydney, New South Wales, Australia.

Kwanashie, H.O., Osuide, G., Wambebe, C. and Ikediobi, C.O. (1989a). Effects of Maternally Administered Cimetidine During Lactation on the Development of Drug Metabolizing Enzymes in Mouse Pups. *Biochem. Pharmacol.*, 38: 204-6.

Kwanashie, H.O., Wambebe, C., Osuide, G. and Ikediobi, C.O. (1989b). The Child as a 'Therapeutic Exile': Defined Roles for the Laboratory Scientist and Pediatrician in Recalling Him. Presented at the 19th International Congress of Paediatrics, 23rd-28th July, in Paris, France.

Kwanashie, H.O., Wambebe, C., Osuide, G. and Ikediobi, C.O. (1990). The Spasmogenic Action of Cimetidine on Uterine and Intestinal Smooth Muscles: Features and Mechanisms. Presented at the International Symposium on New Perspectives in Histamine Research, 6th-8th July, in Noordwijkerhout, The Netherlands.

Kwanashie, H.O., Wambebe, C., Osuide, G. and Ikediobi, C.O. (1992). The Role of Prostaglandin in the Spasmogenic Action of Cimetidine on Smooth Muscles. Presented at the Joint

Congress of the IVth Union of African Societies of Pharmacology (UASPHAR) and the XXIst West African Society for Pharmacology (WASP), 5th-10th October, at University of Lagos, Lagos.

Kwanashie, H.O., Ogala, W., Rafindadi, A.H., Omar, A.S., Omotosho, J.Y. Aboloye, T.O., Sulciman, A., Silvanus, Y., Madu, J., Ejiofor, J.I. and Abdu-Aguye, I. (1998a). Incidence and Prevalence of Sickle Cell Anaemia in Northern Nigeria. *Naunyn-schmiegeberg Arch. Pharmacol.*, 358 Suppl. 2 (1), P57.41, R567.

Kwanashie, H.O., Ejiofor, J.I. and Abdu-Aguye, I. (1998b). Pharmacological and Non-Drug Management of Sickle Cell Anaemia at ABUTH, Zaria, Nigeria. *Naunyn-schmiegeberg Arch. Pharmacol.*, 358 Suppl. 1 (1), P49.42, R483.

Kwanashie, H.O., Ejiofor, J.I. and Abdu-Aguye, I. (1998c). Pharmacological Studies on Siculine Syrup II: Effects on Various Smooth Muscles. *Naunyn-schmiegeberg Arch. Pharmacol.*, 358 Suppl. 2 (1), P37.221, R264.

Kwanashie, H.O., Ejiofor, J.I., Abdu-Aguye, I., Nkweteyim, J.N. and Olanipekun, M.R. (1999). Pharmacological Studies on Siculine Syrup: Cardiovascular Effects in Laboratory Animals. Presented at 26th Annual Regional Conference of the West African Society for Pharmacology, Nsukka.

Kwanashie, H.O., Adamu, H.J. and Alti-Mu'azu, M. (2004). Status of Women at Ahmadu Bello University Zaria in 2004. Presented at the Association of Common Wealth Universities (ACU)/Carnegie Corporation of New York Sponsored West African Regional Training the Trainers Workshop on Women in Management in Higher Education, 3rd-8th October, at Lokoja, Nigeria; Workshop Report, pp 69-76.

Kwanashie, H.O., Kaburuk, B., Olumeyan, M.O. and Rimfa, N.P. (2008). A Mid-term Analysis of Nigeria's Progress Towards Achieving the Health-Related Millennium Development Goals and Proposed Roles for the Pharmacist. Supervised unpublished BPharm project reports, ABU Zaria.

Kwanashie, H.O., Ejiofor, J.I., Abdu-Aguye, I., Nkweteyim, J.N. and Olanipekun, M.R. (2009). Pharmacological Studies on Siculine Syrup. II: Effects on Smooth, Skeletal and

Cardiovascular Muscle Preparations. *Phytotherapy Research*, 23: 236-40.

Kwanashie, H.O., Ejiofor, J.I., Aimola, E.K., Abah, F.S. and Lawal, S.H. (2011a). Availability and Choice of Antimalarials: I - Pharmacy Versus Non-Pharmacy Outlets in Zaria, Nigeria. Presented at the 36th Regional Scientific Conference of the West African Society for Pharmacology (WASP), 12th-16th July, in Kumasi, Ghana.

Kwanashie, H.O., Ejiofor, J.I., Odu, J.E., Hamza, F.A. and Suleiman, H.R. (2011b). Availability and Choice of Antimalarials: IV - Adequacy of Information for Rational Use in Women and Children. Presented at the 36th Regional Scientific Conference of the West African Society for Pharmacology (WASP), 12th-16th July, in Kumasi, Ghana.

Kwanashie, H., Omatiga, J., Busia, K. and Kasilo, O. (2012). Further Situational Analysis of the Development of Traditional Medicine in ECOWAS Member States. Presented at the 5th Ghana Biomedical Convention (GBC) Conference, 30th July-1st August, in Accra, Ghana.

Lee, W.E. and Wells, J.R. (1923). Perforation *In Utero* of a Gastric Ulcer. *Ann Surg.*, 78: 36-41.

Lenz, W. (1962). Thalidomide and Congenital Abnormalities. *Lancet.* 1: 45.

Liley, A.W. (1963). Intrauterine Transfusion of Foetus in Hemolytic Disease. *Br. Med. J.*, 2: 1107-9.

McGowan, W.A.W. (1979). Safety of Cimetidine in Obstetric Patients. *J. R. Soc. Med.*, 72: 902-7.

McPherson, F.J. and Lee, R.M. (1977). Biliary Excretion and Metabolism of ^{14}C-Cimetidine Following Oral Administration To Male and Female Rats. *Experientia*, 33: 1139-40.

Medline Database (1987). Rockville, MD, U.S.A.

Mitchell, S.C., Idle, J.R. and Smith, R.L. (1982). The Metabolism of ^{14}C - Cimetidine in man. *Xenobiotica*, 12: 283-92.

Moore, J., Howe, J.P., Dundee, J.W., Johnston, J.R. and McCaughey, W. (1981). Cimetidine in Anaesthetic Practice *In:* Baron, J.H. (*Ed.*) *Cimetidine in the 80s*, Churchill, Livingstone, Edinburgh, Scotland, pp. 215-20.

Olurishe, T.O., **Kwanashie, H.O.** and Anuka, J.A. (2006). Effect of *Khaya senegalensis* on Uterine Contractility in Rats. *J. Pharm. Bioresources*, 3(1): 30-5.

Olurishe, T.O., **Kwanashie, H.O.**, Anuka, J.A. and Muktar, H.M. (2011a). Lamivudine-Artesunate Co-administration Alters Piroxicam Mediated Analgesia in Mice. *Intl. J. Biomed. Res.*, 2 3): 222-7.

Olurishe, T.O., **Kwanashie, H.O.**, Anuka, J.A., Muktar, H.M. and Bisalla, M. (2011b). Histopathological Effects of Sub-chronic Lamivudine-Artesunate Co-administration on the Liver of Diseased Adult Wistar Rats. *N. Amer. J. Med. Sci.*, 3(7): 325-8.

Olurishe, T.O., **Kwanashie, H.O.**, Anuka, J.A., Muktar, H.M. and Bisalla, M. (2012a). Toxicological Assessment of Lamivudine-Artesunate Treatment on Renal Function, Renal Histology and Some Biomarkers in Parasitised and Immunosuppressed Rodents. *W. Afr. J. Pharmacol. Drug Res., 28*: 28-34.

Olurishe, T.O., **Kwanashie, H.O.**, Anuka, J.A. and Muktar, H.M. (2012b). Lamivudine-artesunate Co-administration Affects Glucose Metabolism in Healthy and Diseased Wistar Rats. *Pakistani J. Pharmaceut. Sci.*, 25(3): 543-7.

Olurishe, T.O., **Kwanashie, H.O.**, Anuka, J.A., Muktar, H.M. and Sambo, J.S. (2013). Renal Impact of Sub-acute Lamivudine-artesunate Treatment in Wistar Rats. *Afr. J. Pharmacol. Therap.*, 2(2): 48-53.

Osuide, G., Wambebe, C., Ikediobi, C.O. and **Kwanashie, H.O.** (1990). Dose-related and other effects of maternal cimetidine pretreatment during lactation on drug metabolism in mouse dams and pups. *Biol. Neonate*, 57(6): 367-74.

Schade, R.R. and Donaldson, R.M. (1981). How Physicians Use Cimetidine. A Survey of Hospitalized Patients and Published Cases. *New Engl. J. Med.*, 304: 1281-4.

Shirkey, H. (1968a). Therapeutic Orphans. *J. Pediat.*, 27: 119-20.

Shirkey, H. (1968b). Therapeutic Orphans-Everybody's Business. *Drug Intellig.*, 2: 323.

Shirkey, H. (1999). Editorial Comment: Therapeutic Orphans. *Pediatrics*, 104: 583-4.

Shirkey, H. (2006). Therapeutic Orphans-Everybody's Business. *Ann. Pharmacother.*, 40(6):1174.

Shirkey, H.C. (1970). Therapeutic Orphans: Who Speaks for Children? *Sth. Med. J., Nashville.*, 63: 1361-3.

Shittu, A., **Kwanashie, H.** and Lege-Oguntoye, L. (1994a). Age and Sex Differences in the Combined Effects of Malnutrition and Cimetidine on Hepatic Drug Oxidation in the Rat. Presented at the Joint (Spring) Meeting of the U.K. Drug Metabolism Group and the 156th British Pharmacological Society, 12th-15th April, in Manchester, England

Shittu, A., **H. Kwanashie** and L. Lege-Oguntoye. (1994b). Synergistic Inhibition of Hepatic Drug Oxidation in the Rat by Malnutrition and Cimetidine. *Can. J. Physiol. Pharmacol.*, 72(1): 320.

Somogyi, A. and Gugler, R. (1979). Cimetidine Excretion into Breast Milk. *Br. J. clin. Pharmacol.*, 7: 627-9.

Stephenson, T. (2001). Medicines for Children-The Last Century and The Next. *Arch. Dis. Child.* 85:177-9.

Stern, L. (1975). Drug therapy in the perinatal period. *In:* Morselli, P. L., Garattini, S. and Sereni, F. (*Eds.*). *Basic and Therapeutic Aspects of Perinatal Pharmacology.* Raven Press, New York, U. S. A., pp. 7-12.

Szorady, I., Santa, A. and Veress, I. (1987). Drug Acetylator Phenotypes in Newborn Infants. *Biochem. Res. Preg.*, 8: 23-4.

Ugye, J.T., Uzairu, A., Idris, S.O. and **Kwanashie, H.O.** (2011). Formaldehyde levels in some cosmetics and other non-food materials found in Gboko township, Benue State, Nigeria. *Intl. Res. J. Pharm. Pharmacol.* (formerly, *Afr. J. Pharm. Pharmacol. Res.*), 1(3): 43-6.

United Nations (1994a). Division for the Advancement of Women. Data contained in the Women's indicators and statistics database (WISTAT).

United Nations (1994b). Women in a Global Changing Economy. 1994 Survey on the Role of Women in Development. United Nations, New York.

United Nations (1994c). Report of the Fourth United Nations International Conference on Population and Development (ICPD). United Nations, New York.

Uthman, G.S. (2011). Comparative Study of Efficacy of Intravenous Oxytocin and Oral Misoprostol Tablet in the Prevention of Postpartum Haemorrhage in Maiduguri, Nigeria. Unpublished PhD Dissertation, Ahmadu Bello University, Zaria.

Uthman, G.S., **Kwanashie, H.O.**, Mairiga, A.G., Gamaniel, K.S., Isa, M.H., Abdu Ibrahim, A., Geidam, A.D. and Nwaosu, C.S. (2011). A Randomised Clinical Trial Comparing the Effects of Oxytocin Injection and Oral Misoprostol Tablets in the

Prevention of Postpartum Haemorrhage in Maiduguri Nigeria. *Intl. Res. J.Pharm.*, 2(3): 76-81.

Villee, C.A. (1965). Placental Transfer of Drugs. *Ann. N.Y. Acad. Sci.*, 123: 237-44.

Visser, T.J., Kaptein, E., Gijzel, A.L., de Herder, W.W., Ebner, T. and Burchell, B. (1993). *FEBS*. 324: 358-60.

Wambebe, C., **Kwanashie, H.O.**, Ikediobi, C.O. and Osuide, G. (1990). Effects of Cimetidine on Female Fertility and Pregnancy Outcome in the Mouse and Rat. *W. Afr. J. Pharmacol. Drug Res.* 9(4): 43-7.

WHO - World Health Organisation (1948). Preamble to the Constitution of the World Health Organization as adopted by the International Health Conference, New York, 19-22 June, 1946; signed on 22 July 1946 by the representatives of 61 States (Official Records of the World Health Organization, no. 2, p. 100) and entered into force on 7 April 1948.

Whitney, J. (2006). Pharmaceutical Sales 101: Me-Too Drugs. (http://www.guernicamag.com/features/111/me_too_drugs/). *Guernica*. Retrieved 31st July 2008.

Wilson, J.T. (1972). Pediatric Pharmacology: Who Will Test the Drugs? *J. Pediat.*, 80: 855-7.

Wilson, J.T. (1975). Pragmatic assessment of medicines available for young children and pregnant or breast-feeding women. *In:* Morselli, P. L., Garattini, S. and Sereni, F. (*Eds.*) *Basic and Therapeutic Aspects of Perinatal Pharmacology*. Raven Press, New York, U.S.A. pp 411-21.

Wilson, J.T., Brown, R.D., Cherek, D.R., Dailey, J.W., Hilman, B.C., Jobe, P.C., Manno, B.R., Manno, J.E., Redetzki, H.M. and Stewart, J.J. (1980). Drug Excretion in Human Breast Milk. *Chris. Pharmacokinet.*, 5: 1-66.

Wolcott, W.L. and Fahey, T. (2002). The Metabolic Typing Diet. Broadway Books.

Wong, K.P. (1972). Bilirubin Glucosyl- and Glucuronyl Transferases. A Comparative Study and the Effects of Drugs. *Biochem. Pharmacol.*, 21: 1485-91.

Wooster, R., Sutherland, L., Ebner, T., Clarke, D., Da Cruz e Silva, O. and Burchell, B. (1991). *Biochem. J.*, 278: 465-469.

Yaffe, S.J. and Stern, L. (1976). *In*: Minkin, B.L. (*Ed.*). *Perinatal Pharmacology and Therapeutics*. Academic Press, New York, U.S.A., pp.335-428.