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MEDICATION ERRORS AND DRUG TRAGEDIES: CASEBOOK OF A NIGERIAN CLINICAL PHARMACOLOGIST/NEPHROLOGIST

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MEDICATION ERRORS AND DRUG TRAGEDIES: CASEBOOK OF A NIGERIAN CLINICAL PHARMACOLOGIST/NEPHROLOGIST

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SUMMARY

A drug is any chemical substance, synthetic or natural, extracted from plant or animal tissue and of known or unknown composition, which is used to diagnose, prevent, ameliorate or cure a disease. When used judiciously drugs can improve the quality of life. However when used irrationally drugs can cause more harm than good. The drug management of any patient is an exercise in Experimental Pharmacology. Clinical Pharmacology is the field of medicine which deals with the safe and effective use of drugs. Rational drug use involves the use of the right drug in the right dose and dosage form at the right interval for the right duration of time. Rational prescription implies that the therapist encourages compliance by doing the above with due consideration of cost and ensuring that the patient knows why, how, and when to use both prescription and non-prescription drugs.

At present there is a large amount of irrational drug use in Nigeria. This results in an unacceptable frequency of iatrogenic disease. A substantial number of cases of endstage renal disease seen in our hospital is a result of injudicious use of herbal and orthodox modern drugs. Polypharmacy is frequent and when adverse reactions occur it is difficult to pinpoint the offending causative drug. Moreover patients do not comply with all the prescribed drugs; the tendency is for them to buy only the cheapest drugs or use only those which appeal to their fancies. Often these are not the ones appropriate for their disease. The end result is that the disease progresses from acute phase to a chronic state and where infectious agents are responsible for the disease, resistant organisms may emerge.

Where non-communicable diseases such as hypertension and diabetes are the causes of the ill health, complications such as stroke, heart failure, kidney failure, gangrene and blindness may occur. These are much more expensive to treat than the original diseases. The use of counterfeit drugs sold by unqualified and unscrupulous exploiters to the public (who for economic reasons prefer cheaper drugs) has led to severe adverse reactions. By feeding back the results of drug utilisation surveys and by teaching students and young interns Pharmacotherapy Course they can be sensitised to the need to prescribe drugs rationally. Government can help to improve the drug availability and drug use situation in the country by enforcing the drug laws, and promoting clinical pharmacology and clinical pharmacy by

awarding scholarships to graduates who wish to specialise in these disciplines. Government can also help by reducing the import duties on drugs and equipment for manufacturing drugs as well as those for drug quality assurance.

Objectives

- **To trace the history of medicine, pharmacology and toxicology**
- **To introduce the new disciplines of Clinical Pharmacology and pharmacoepidemiology**
- **To focus on rational drug use**
- **To highlight the consequences of irrational drug use**
- **To give examples of medication errors and drug disasters**
- **To suggest measures for reducing medication errors and drug disasters by**
  - **a) proper education of medical students and interns in pharmacotherapy**
  - **b) enforcing drug regulations**
  - **c) ensuring that all practising doctors and pharmacists attend scientific conferences and refresher courses annually and attain minimum credit hours before practising licenses are renewed**
  - **d) ensuring that pharmacists are always present at licensed drug stores**

Introduction

Health is a state of complete physical and mental well-being and not merely the absence of disease or infirmity. Hence the Latin saying "*Mens sana in corpore sano*" meaning "A sound mind in a sound body". From time immemorial man has always had recourse to drugs to keep him in a fit physical and mental state. Those beverages - coffee, tea, caffeine-containing soft drinks - which we consume daily are stimulant drugs which have become socially acceptable through the ages. Indeed, Sir William Osler said in 1891 that "A desire to take medicine is, perhaps, the great feature which distinguishes man from other animals"[1]. Every patient who consults a doctor hopes to receive at least one drug at the end of such consultation . In the past most drugs were crude extracts of natural products and could be consumed in galenic quantities without unpleasant side effects apart from the bitter alkaloid taste. However, with the drug explosion of the twentieth century there are now powerful synthetic drugs that are potent not only for good but also for unwanted adverse reactions. An adverse drug reaction is any unwanted noxious reaction to a drug that is unintended by the doctor. The progressive improvement in physician's diagnostic skills does not seem to be matched by improvement in therapeutic decisions. Indeed therapeutic decisions are often guided by personal impression, tradition, sentiment, or uncritical acceptance of advertisement claims[2]. Relative inattention to the therapeutic decision process is not new. Aristotle (384-322 B.C.) once wrote "*Even in medicine, though it is easy to know what honey, wine and hellebore, cautery and surgery are, to know how and to whom and when to apply them so as to effect a cure is no less an undertaking than to be a physician*". In 1903 Wilcox stated that "the day has come when something more is demanded of the practitioner or physician-consultant than a diagnosis; the what (i.e. diagnosis) may be the easiest determined; the how much, the when and in what form and under what precautions must be fully stated"[3]. To administer drugs optimally knowledge is needed of the absorption, distribution and elimination (metabolism and excretion) - collectively termed pharmacokinetics of the drug. The application of pharmacokinetic principles to the therapeutic management of the patient is called clinical pharmacokinetics. The consequences of drug administration can be subdivided into **a pharmacokinetic phase** that relates dose, frequency and route of administration to drug concentration-time relationships in the

body and **a pharmacodynamic phase** that relates drug concentration at site of action to the magnitude of response produced. Depending on the drug concentration therapy may be ineffective if the concentration is too low or there may be unacceptable toxicity if the concentration is too high. Optimal dosage regimen is defined as one that maintains the plasma concentration of the drug within a therapeutic window[4] that produces the desired effect without toxicity.

History of Medicine and Drug Use

In the Holy Qur'an Chapter 16 v 68-69 we read "And thy Lord taught the bee to build its cells in hills, on trees, and men's habitations; then to eat of all the produce of the earth and find with skill the spacious paths of its Lord: there issues from within their bodies a drink of varying colours (i.e. honey) wherein is healing for men: verily in this is a sign for those who give thought"[5]. Abdallah bin Mas'ud reported the Holy Prophet Muhammad (PBOH) as saying "Make use of the two remedies: honey and the Qur'an[6]". When the Prophet was bitten by a scorpion when he was praying one night he said "God curse the scorpion! It does not leave alone one who is praying or a prophet or anyone else." He then called for salt and water, and putting it in a vessel he began to pour it over his finger where it had stung him and wiped it seeking refuge in God by reciting the Muawwidhatan in the Qur'an[7]. The Prophet also said "God has not created a disease without creating a cure for it"[8]. Abu Sa'id Al-Khudri said that a man came to the Prophet and told him his brother's bowels were loose, the Prophet said "Let him drink honey". The man came a second time and said "I gave him honey but it has made his bowels more loose". The Prophet repeated "Let him drink honey". The man did so again without improvement and when after the fourth episode he came back and was told to give him honey to drink he said "I have done so but it has only increased the looseness". The Prophet said "God has spoken the truth but your brother's bowels have lied. Let him drink honey". So the man made his brother drink honey a fifth time and he was cured[9,10]. From the above accounts it will be seen that man has been fighting disease with medicinal substances for a long time, that there should be feedback communication between the patient and the therapist and that persistence with right treatment will achieve cure eventually.

As far back as 2700 B.C. the Chinese Canon of Medicine, the Nei Ching, discussed malaria-like symptoms and the relationship between fevers and enlarged spleens. Cuneiform tablets excavated from Assurbanapli's royal library in Nineveh (what is now Iraq) in the 6th century B.C. mentioned deadly malaria-like fevers that afflicted the populace of Mesopotamia. The writings of Homer, Aristotle, Plato, Socrates, Horace, Tacitus, Carus, Varro, Chaucer, Pepys, and Shakespeare all mentioned fevers that were undoubtedly related to malaria[11].

One of the significant events that led to the development of pharmacology as a separate medical discipline was the contribution of Paracelsus (1493-1541). Before his time the purpose of chemistry was to search for the philosopher's stone, a fictional charm which could confer perpetual youth and convert the baser metals into gold. But it was Paracelsus who said "The purpose of chemistry is not to make gold but to study the fundamental sciences and turn them against disease". "Not gold but medicine is the purpose of chemistry" he declared[12].

South American Indians used cinchona bark as a traditional remedy for fevers. In 1630 the Peruvian Cinchona Bark extract was used to treat the wife of the Spanish Viceroy of Peru who had malaria fever. In 1639 Jesuit priests brought some of the bark to Europe where it eventually became the treatment of choice for fevers. It was not until 1820 that Bienaime Caventou and Pierre Joseph Pelletier, two French chemists, isolated quinine from the Cinchona bark[13,14]. In 1760 Louis Cadet, apothecary to the French Army, made cacodyl oxide $(CH_3)_2AsÄOÄ(CH_3)_2As$ by heating together potassium acetate and arsenious oxide the first time that an arsenic atom was attached to a carbon atom. This was the forerunner of the organic arsenical - arsphenamine - which 2 centuries later Paul Ehrlich synthesised for use in treating syphilis.

In 1785 the English physician William Withering published his monograph on the use of digitalis titled "An Account of the Purple Foxglove and its Medicinal Use"[15]. In 1807 the German Serturner isolated the alkaloid morphine from opium (poppy) plant; this was a forerunner of the rapid discoveries to follow in this field. Shortly after it there followed the isolation of strychnine, caffeine, emetine, atropine and quinine. Francois Magendie the *first pharmacologist* (1783-1855) studied the pharmacological actions of these drugs.

One of the most significant events in the history of mankind was the synthesis of urea by Wohler in 1828. This he did by evaporation of an aqueous solution of ammonium cyanate NH_4 OCN ® $CO(NH_2)_2$ By so doing he had made urea without a kidney, and synthesised an organic compound in the laboratory without the intervention of nature - the mysterious vital force.

In the middle of the seventeenth century Christopher Wren and Robert Boyle at Oxford University showed that a quill inserted into the vein of a dog provided a means of injecting drugs directly into its blood stream. Alexander Wood utilised this finding to develop a hypodermic needle in Edinburgh in 1853. Needless to say that the hypodermic needle has been a device of revolutionary importance in the field of therapeutics.

Pharmacology as a Science

Pharmacology emanated from a background of mystery and magic, folklore and empiricism. Since the organic chemist was rapidly making available new synthetic medicinal products it was necessary to test them as well as natural products of medicinal interest. It was also necessary to bridge the gap between the manufacturer and the prescriber. In 1900 John Abel and his associates in Johns Hopkins Medical School separated adrenaline from the adrenal medulla as a benzoyl derivative. In 1902 Takamine crystallised adrenaline as burr-like crystals. Its synthesis was accomplished by Stoltz a few years later. Thus, the credit of having isolated the first hormone belongs to John Abel and the science of pharmacology[16,17]. In 1905 Reid Hunt working in Abel's laboratory isolated acetylcholine from the adrenal medulla. Suffice it to say that this is an important substance in the body of all animals including man - being the transmitter at all ganglia, parasympathetic peripheral nerve endings and skeletal neuromuscular junctions.

The standardisation of drugs

One of the outstanding contributions of pharmacology to medical practice is that of drug standardisation. The safety, efficacy and dependability of dosage are contingent on this. Standardisation can be performed either chemically or biologically. In fact hormone drugs like insulin and pituitary extracts are mainly standardised by bioassay.

Anti-infective drugs

Paul Ehrlich in 1912 synthesised arsphenamine for the treatment of syphilis. He suggested the search for a drug that would sterilise blood of streptococci or staphylococci and named such a drug a "*Magna Therapia Sterilisans*". In 1920 mercurochrome was synthesised but although active as a local antiseptic it was too toxic for systemic use. In 1927 hexylresorcinol was synthesised as a non-metallo organic compound of low toxicity and high bactericidal potency. It was useless in systemic infections because its germicidal activity was not exhibited in blood. In 1935 Domagk showed that the dyes Prontosil and Neoprontosil were effective in the treatment of streptococcal septicaemia. They were excreted in urine partially as sulphanilamide which was the precursor of sulphonamides. In 1928 Alexander Fleming accidentally discovered penicillin from a mould (*Penicillium notatum*) which contaminated his bacterial culture plate. In 1941 Lord Florey and Professor Chain first used penicillin to treat a patient thus heralding the era of antibiotics. Streptomycin (1943), chloramphenicol (1948) and tetracycline (1952) soon followed penicillin. Today there are numerous antibiotics to treat various infections.

During the World War II dimercaprol, the British anti-Lewisite (BAL) was used as a specific antidote in arsenical war gas and other heavy metal poisoning. During the years immediately following the World War II vitamin B_{12} was introduced for the treatment of pernicious anaemia and cortisone was introduced for the treatment of arthritis and connective tissue diseases. Another advance in the field of drug therapy is the use of reserpine and chlorpromazine for the treatment of the mentally ill and of the former in hypertension. Lately many new drugs have been introduced for the treatment of diverse diseases like tuberculosis, leprosy, epilepsy, diabetes, hypertension, peptic ulcers, leukaemias and cancers. Noteworthy is the introduction of genetically engineered human insulin for the treatment of diabetes. This general review provides a background of the science of pharmacology. It shows that it touches almost every phase of medical endeavour. This is not surprising since most if not all patients who consult a doctor hope to receive some drugs or a prescription for drugs at the end of the consultation.

Herbal and Traditional Therapy

From time immemorial man has used animal parts, roots leaves and barks for treating diseases. The Holy Prophet Muhammad (PBOH) recommended honey as well as cummins seeds and he also said that kohl which contained antimony cleared the eyes. Squill was known as a medicine to the ancient Egyptians. The Romans used it as a diuretic, heart tonic, emetic and rat poison. The dried skin of the toad has been used for centuries as a drug by the Chinese[18]. In Nigeria today herbal and traditional medicines are still used a lot. Attempts have been made to encourage herbal and traditional medicine practitioners to document their successes and failures as well as to try and find out the active ingredients of the concoctions which have been proven to effect cures for certain diseases. The establishment of the WHO Collaborating Centre for Traditional Medicine in the Department of Pharmacology of the College of Medicine of the University of Lagos is one of the steps taken to attain this goal. Unfortunately, funds are lacking to support the centre's activities which include monthly meetings with the traditional practitioners, and documentation of cases brought to the centre by them. The centre needs medically qualified research fellows, postgraduate pharmacology students and equipment.

Plants yield large numbers of constituents which are used for treating diseases. Menthol from peppermint is a secondary alcohol and ephedrine from *Ephedra sinica or E. equisetina* is an alkaloid. Often the chemical composition of the herbal preparations used is not known; it therefore becomes necessary to classify these substances from the point of view of their use as medicinal agents. A knowledge of this classification is important when herbal drugs are used. The following classes are recognised

1. Alkaloids
2. Glycosides
3. Oils----- a) Fixed Oils b) Volatile Oils
4. Resins
5. Gums
6. Tannins
7. Antibiotics

1. Alkaloids are basic substances containing nitrogen. They are amines and are generally white crystalline substances with bitter taste. They are probably waste products of plant metabolism and their poisonous nature may serve to protect them from being

used as food by animals. Examples are quinine, atropine, caffeine, pilocarpine and morphine. Certain alkaloids which do not contain oxygen in their molecule are liquid. Nicotine from tobacco is one such. Adrenaline is an alkaloid of animal origin. Some alkaloids are violent poisons e.g. strychnine and nicotine will cause death in very small quantities. Death is devoid of anatomical lesion in the body being due mainly to excessive stimulation or depression of one or more physiological systems in the body.

2. Glycosides are reasonably large molecules which may or may not contain nitrogen being a combination of a sugar with an aglycone or genin.The most well known are cardiac glycosides (digoxin, digitoxin, ouabain) from digitalis plants; others are salicin from willow bark and rutin from buckwheat.

3. Oils are either fixed or volatile. Fixed oils are mainly the glycerides of palmitic, oleic and stearic acids. Many of them are edible oils of high caloric value like palm, olive and cotton seed oils. Others like castor oil (purgative) and cod liver oil (vitamin A source) have specific pharmacological actions. Volatile oils usually contain terpene or its polymer derivative which serves as a diluent or solvent for other active oils present in the plant source. Oil of peppermint contains 50% terpene and 50% menthol; oil of spearmint contains 50% carvone, a ketone while oil of clove contains 82% eugenol, a phenol. Volatile oils are mildly bacteriostatic, hence their use in mouth washes. Some are carminative, i.e. they relax the cardia of the stomach and permit expulsion of gas. In high dilution they stimulate the gastric mucosa to release gastric juice. Oil of wintergreen which contains methyl salicylate is used as local application for muscle pain and arthralgias. Solutions of peppermint and spearmint oils in water (0.1%) are used as solvents and flavours in liquid medicines.

4. Resins are rosin-like substances found in plants and are usually formed by oxidation or polymerisation of volatile oils. They are insoluble in water but soluble in alcohol and can dissolve in water in the presence of caustic alkali to form resin soaps.

5. Gums are secretory products of plants being polysaccharides which on hydrolysis yield simple sugars. They are dispersible in water to form thick, mucilaginous colloids. They are precipitated from their aqueous dispersions by alcohol. Some are unabsorbed from the gastrointestinal tract and when ingested they add weight to the intestinal contents and act as bulk purgatives. Examples are agar and psyllium seed.

6. Tannins are non-nitrogenous plant constituents with astringent properties on mucous membranes. They are phenolic derivatives and have been used for treating burns and diarrhoea.

7. Antibiotics are substances produced by living cells which are lethal to micro-organisms in high dilution. They are produced by living bacteria, yeasts, moulds and other plants. Penicillin is an organic acid, streptomycin is a complex organic base while chloramphenicol is a simple organic molecule containing chlorine.

History of Toxicology

Toxicology is the study of the adverse effects of drugs and other chemical agents on biologic systems. The earliest man was aware of the toxic effects of animal venoms and poisonous plants and he used the knowledge for hunting, warfare and for getting rid of undesirables within the community. Plant extracts containing cardiac glycosides and hyoscine have been used by natives in various parts of the world as arrow and ordeal poisons for years. Ebers Papyrus (1500 B.C.) of the Egyptian Medicine contained over 800 recipes for treating diseases a good number of which were poisons. They included hemlock (the state poison of the Greeks), aconite, opium, lead, copper, antimony, digitalis and belladonna. Hippocrates (400 B.C.) added a number of poisons and wrote instructions to control absorption of poisons. Aristotle (384-322 B.C.) added to the knowledge of poisons. Theophrastus (370-286 B.C.), a student of Aristotle included numerous references to poisonous plants in his book "*De Historia Plantarum*". Socrates (470-399 B.C.) was executed using a state poison most probably hemlock. Demosthenes (385-322 B.C.) committed suicide with a poison hidden in his pen and Cleopatra (69-30 B.C.) committed suicide by falling on her poisoned asp. Roman women used poisons to kill their husbands until Emperor Sulla issued the *Lex Cornelia* in 82 B.C. Agrippina used arsenic to kill Claudius so that Nero might become Emperor and Nero used arsenic to murder Britannicus, the natural son of Claudius. Dioscorides (A.D. 50), a Greek physician in the palace of Emperor Nero, made the first attempt at classification of poisons into Animals, Plants and Minerals.

Moses ben Maimon (1135-1204 A.D.), the Jewish scholar popularly known as Maimonides wrote a book called "*Poisons and their Antidotes*". Paracelsus (1493-1541) whose real name is Philipus Aureolus Theophrasus Bombastus Von-Hoenheim said

"All substances are poisons; there is none which is not a poison. The right dose distinguishes a poison and a remedy". He formulated many revolutionary views such as "experimentation is essential in the examination of responses to chemicals, distinction between therapeutic and toxic properties, and specificity of chemicals". Mattieu Joseph Bonaventura Orfila 1787-1853, a Spanish physician to Louis XVIII of France and a Professor at the University of Paris singled out toxicology as a discipline and is often cited as the Founder of Toxicology. He devised methods for detecting poisons and suggested that autopsy materials be used for detecting accidental and intentional poisonings. The physiologist Francois Magendie (1783-1855) spent a significant part of his time studying emetine and strychnine. Claude Bernard (1813-1878), a student of Magendie, studied curare. Louis Lewin 1854-1929 studied the toxicology of methyl, ethyl and higher alcohols, chloroform, chronic opiate use and plant hallucinogens. Rudolf Kobert 1854-1918 wrote a textbook on Toxicology. In 1945 Rudolf Peters developed dimercaprol (British Antilewisite- BAL) as an antidote to arsenic war gases. Paul Muller developed dichlorodiphenyltrichloroethane (DDT) from 1944-1946 and Willy Lange and Gerhard Schrader in 1952 developed organophosphorus insecticides.

There is now heightened public concern about the effects of chemicals, radiation and technology in general on human health and environment. In 1945 the Allied Forces dropped atomic bombs in Hiroshima and Nagasaki whose grave consequences contributed to ending the second world war. The effects are still being felt in those cities since their citizens suffer more from certain diseases associated with a fallout from the bombs e.g. the leukaemias. In 1985 the leakage of methyl isocyanate (MIC) from a factory in Bhopal, India led to exposure of its citizens, death and legal action against the American Company which owned the factory. In 1986 radiation leakage from an atomic plant in Chernobyl, Russia led to deaths and dismantling of the plant. With industrialisation and mechanisation there has been increased pollution of the environment. Acid rain, ground water pollution and toxic waste dumps are now familiar terms in the modern world and are indications of the consciousness of the press and media to alert people to the unseen dangers in the environment. Nigeria is not left out of all these. Toxic waste dump in Coco, Delta State a few years ago most probably contributed to the early demise of some of its inhabitants.

History of Clinical Pharmacology

Clinical Pharmacology grew out of severe adverse reactions to drugs like thalidomide. As medicine emerged from that of Galen (A.D. 131-201) who preached polypharmacy, teleology, pragmatism and dogmatism it enjoyed a rebirth of the scientific spirit in the tradition of Hippocrates (460-370 B.C.) and Aristotle (384-322 B.C.). Paracelsus (1493-1541) was perhaps the most notable early physician to reject Galenical tradition of medicine and witchcraft and advocate experimentation. Although alchemy, philosophy and astronomy remained his pillars of faith, among his traditions can be found the precursors of chemical pharmacology and experimental therapeutics.

His successors in the 16th and 17th centuries included outstanding scientists like Harvey (1578-1657), Descartes (1596-1650), Sydenham (1624-89) and Malpighi (1628-94). Sydenham more than anyone else since Hippocrates emphasised the importance of clinical examination and observation in the nosology of disease. However, for a long time, except for the introduction of mineral baths and chemicals, therapeutics remained largely a mixture of quackery and faith healing. Medicines were mostly botanicals, ground bones, powdered excrements of animals and insects.

The 18th century brought further emphasis on observation and classification in the sciences. This was accompanied by the emergence of surgeons and physiologists like Hales (1677-1761), Hunter (1718-83), Priestley (1733-1804), Lavoisier (1743-94) and Cruikshank (1745-1800). The major thrust of clinical medicine was on bedside diagnostic technique, and correlation with postmortem findings. Blood letting, emetics and cathartics were the favoured medicines. They were mostly ineffecive and sometimes produced harmful results. Unfortunately many of the harmless medicines were associated with improvement and received the stamp of efficacy when they were in reality mere placebos. Such uncritical labels have passed from generations to generations and even till today are accepted mainly on faith or authority.

The 19th century saw organised scientific advancement. Claude Bernard (1813-78) is said to have introduced modern era of scientific medicine when he said "We give the name experimenter to the man who applies methods of investigation, whether simple or complex so as to make natural phenomena vary, or so as to alter them with some purpose or other"[19] . The

high ethical and moral standards of the period inhibited significant human experimentation and ensured that scientifically oriented clinical researchers turned to laboratory animal models for their investigations. Among the limitations of this approach is species variation which makes it not always possible to duplicate models of animal disease in man and *vice versa*. The thalidomide disaster confirmed that only man can serve as the ultimate model to establish the efficacy and toxicity of any new drug to be used by man. Ignorance, folly and superstition surrounded the 'healing arts' and Sir William Osler (1849-1919), an eminent clinician termed this phenomenon "therapeutic nihilism". Physicians succumbed to the tyranny of authority and based their treatment mainly on biases of the healer and sometimes of the healed, anecdotal descriptions and testimonials rather than on experimental science.

It is now known that scientific methods can be applied to measure drug responses in man. Modern clinical investigators have emerged who are competent and comfortable both in the laboratory and at the bedside.

Clinical Pharmacology

Clinical Pharmacology is a discipline concerned with the safety and effectiveness of drugs in man. It includes three principal approaches to medical investigation and teaching[20]. The first is the study of pharmacokinetics and mechanism of action of drugs in man; the second is the study of drug actions to investigate the pathology of diseases of a particular organ system in man. These two approaches previously involved Pharmacologists and Clinical Investigators neither of whom may have a primary interest in or the tenacity for evaluating the efficacy of a drug in a patient. A Clinical Pharmacologist is concerned with the interdigitation of therapeutics with the basic pharmacological principles. He applies research methodology, biostatistics and clinical acumen. He tries to overcome the barriers that inhibit the application of the scientific method to therapeutics. The third approach deals with documentation of the safety and efficacy of drugs in man. In fact this is now embodied in an even newer subdiscipline called Pharmacoepidemiology. Recognition and concern for this problem emerged along with the pharmaceutical revolution and the resultant drug explosion of the 20th century. New antibiotics and chemotherapeutic agents were

developed necessitating the development of clinical trials for their evaluation[21-25].

Clinical Trials

A Clinical Trial is a simple experiment designed to answer a precisely framed question to find out the effectiveness and safety of a new drug or treatment measure. It is only the well trained Clinical Pharmacologist who can conduct a meaningful controlled clinical trial. A controlled clinical trial compares treatments in patients by controlling or equalising all variables except the drugs to render the trial results convincing. A controlled clinical trial ensures that the comparisons we make are as precise, as informative, and as convincing as possible[26,27]. Retrospective analysis had previously established the value of dramatically effective drugs such as penicillins for pneumococcal pneumonia, insulin to prevent diabetic ketoacidosis, glucose to reverse hypoglycaemia, potassium to reverse hypokalaemia or citrus fruits to cure scurvy. These days most drug trials must be more carefully designed if real but subtle benefits are to be demonstrated.

Drug Disasters and Pharmacoepidemiology

The safety and efficacy of drugs in man became prominent when disasters associated with drug administration began to occur in epidemic proportions. The first documented disaster was associated with an epidemic of renal failure in the USA resulting from a brand of elixir of sulfanilamide dissolved in diethylene glycol[28]. This led to the 1938 Food, Drug and Cosmetic Act in the U.S.A. In November 1956 a non-barbiturate sedative and hypnotic, thalidomide (α - phthalimido - glutarimide) was first marketed as "Contergan" for use in a wide range of conditions including influenza, functional disorders of the stomach and gall bladder, mild depression, insomnia, menstrual tension, nausea of pregnancy and angina. It was promoted without sufficient evidence, as a safe and effective drug to be used during pregnancy. The resulting tragedy of some 10,000 severely deformed babies, many of whom were born without limbs, led to heightened awareness of the potential of drugs to produce damage to the foetus- teratogenicity. [From Gk teras=monster;

Drug Disasters and Causes

DESCRIPTION OF DISASTER	CAUSE	DATE
renal failure	diethylene glycol	Y1938 Y1991
phocomelia (flippers instead of limbs)	thalidomide ('Contergan')	Y1963
aplastic anaemia	chloramphenicol	Y1967
myelo-optic-neuropathy (SMON)	clioquinol	Y1980
vaginal adenocarcinoma	diethylstilboestrol for threatened abortion	Y1971
oculomucocutaneous syndrome	practolol	Y1975
fatal bone marrow depression	phenylbutazone/ oxyphenbutazone	Y1977
death from liver disease	ticrynafen and benoxaprofen	Y1980
anaphylactoid reaction	zomepirac	Y1987
acute renal failure	suprofen	Y1989
hypoglycaemia	human insulin	Y1990
suicide	fluoxetine	Y1990
death	fenoterol	Y1989
arrhythmias	terfenadine	Y1992
hypertension, seizures and strokes	bromocriptine postpartum	Y1990

genein=to produce]. The 1962 Kefauver-Harris amendments were a response to the infamous "thalidomide disaster," in which children with phocomelia (flippers instead of limbs) were born to mothers who had taken the drug thalidomide ('Contergan') during the early weeks of pregnancy[29]. The late 1960s, 1970s and 1980s also witnesssed a series of major adverse drug reactions. These included aplastic anaemia with chloramphenicol[30], subacute myelo-optic-neuropathy (SMON) caused by clioquinol especially

among Japanese[31], vaginal adenocarcinoma in young women whose mothers had received diethylstilboestrol for threatened abortion[32], oculomucocutaneous syndrome caused by practolol[33], fatal bone marrow depression caused by phenylbutazone and oxyphenbutazone[34], death from liver disease caused by ticrynafen and benoxaprofen[35,36], anaphylactoid reaction caused by zomepirac[37], acute renal failure and flank pain caused by suprofen[38]. Others are birth defects from isotretinoin[39], memory and other central nervous system disturbances with triazolam[40,41], hypoglycaemia from human insulin[42,43], suicidal ideation from fluoxetine[44,45], death from fenoterol[46,47], cancer from depot-medroxy progesterone[48], arrhythmias from terfenadine and astemizole[49,50], hypertension, seizures and strokes from postpartum use of bromocriptine[51,52]. These and other serious but uncommon drug effects have led to the development of new methods to study drug effects in large number of patients. Academic investigators, the pharmaceutical industry, the Food and Drug Administration, and the legal community have turned to the field of epidemiology, which is the study of the distribution and determinants of disease in populations. Thus the joining of the field of clinical pharmacology with epidemiology has resulted in the development of a new field called Pharmacoepidemiology. It is the study of the use of and the effects of drugs in large numbers of people. It is the science underlyng postmarketing surveillance. The Table below shows potential contributions of Pharmacoepidemiology.

A. Information which suppplements that available from premarketing studies - better quantitation of the incidence of known adverse and beneficial effects
   a. Higher precision
   b. In patients not sudied prior to marketing e.g. children, elderly, and pregnent women
   c. As modified by other drugs or illnesses
   d. Relative to other drugs used for the same indication
B. New types of information not available from premarketing studies
   1. Discovery of previously undetected adverse and beneficial effects
      a. Uncommon effects
      b. Delayed effects
   2. Patterns of drug utilisation
   3. The effects of drug overdoses
   4. The economic implications of drug use
C. General contributions of Pharmacoepidemiology
   1. Reassurances about drug safety
   2. Fulfillment of legal and ethical obligations

Contributions

My work has been centred mainly on Nigerian hypertensives. My colleagues and I have used our knack for painstaking investigations to advance the treatment of hypertension in blacks and we have been involved in the clinical trials of a number of antihypertensive drugs used in Nigeria today. Because of my concern for those with the complications of untreated or badly treated hypertension I was instrumental in the establishment of a strong clinical pharmacology and renal unit in the Department of Medicine of the Lagos University Teaching Hospital. The efforts of members of this unit catalysed by some prevailing factors resulted in the Hospital Management Board establishing the Dialysis Centre in 1981. In spite of numerous obstacles the Dialysis Centre is still functioning. We have trained many doctors , nurses and dialysis technicians, in the centre, who are now working in other public as well as private hospitals all over the country.

Since we now live in a world where advances in therapy and quality of treatment delivered by the physician is determined by our knowledge of basic science, we have tried to apply basic pharmacological knowledge to the management of diseases like shigella dysentery, cholera and malaria and to work out the pathophysiological basis of the management of hypertension in blacks. Our group has carried out basic and clinical studies on now well known drugs like frusemide ("Lasix") and cotrimoxazole ("Septrin") and elucidated both their well known and uncommon side effects. During the clinical trial of cotrimoxazole for the treatment of shigella dysentery we observed that some of the patients complained of constipation after two or three days treatment with the drug at a time when the bacteria were still present in the stool. On the isolated guinea pig and rabbit intestinal strips we showed that cotrimoxazole has a direct inhibitory effect on intestinal motitlity and tone not mediated by autonomic innervation. This is the explanation for the side effect of constipation in many patients receiving the drug for other infections.

We also showed quite clearly the inhibition of sodium and salicylate transport under the influence of furosemide in the rat intestine. Several studies on sodium transport in blacks have shown a defect in the transport of sodium and potassium in the red cells of black hypertensives compared to Caucasians. It is therefore not surprising that black hypertensives respond very well to diuretics as a first line form of treatment. We have also shown that in handling sodium Nigerians can be subdivided into three groups. The first group are those who consume normal amount of sodium and excrete almost all of it; they have normal blood pressure. The second are those who consume normal amount or a lot of sodium and retain most of what they consume; they have high blood pressure. The third group are those who consume a lot of sodium but can excrete all or even more than they consume; these have normal blood pressure but may occasionally have low blood pressure when exposed to severe dry weather. Earlier in my career I showed that patients with severe renal impairment respond to high dose frusemide by losing fluids through the gut thereby losing their accumulated oedema fluids.

Rational drug use

Rational drug use involves the use of the right drug in the right dose and dosage form at the right dosing interval for the right duration of time. Rational prescription implies that the therapist encourages compliance by doing the above with due consideration of cost and ensuring that the patient knows why, how, and when to use both prescription and non-prescription drugs[53]. At present there is a large amount of irrational drug use in Nigeria. When drugs are not used rationally the incidence of medication errors with consequent adverse reactions to the patient increases. It was Napoleon Bonaparte who once said "I do not want two diseases, one nature made and the other man made". Reasons for irrational therapy include:

1. lack of appreciation that no drug is free from toxicity and that potent drugs can cause serious morbidity and mortality
2. lack of awareness that potential drug reactions increase proportionally to the number of drugs given
3. little familiarity with the principles of controlled drug evaluation

4. lack of effective professional programme for continuing education in pharmacotherapy
5. lack of objective well organised and concise drug information
6. considerable dependence on the pharmaceutical industry and professional advertisers for drug information and education

Voltaire once satirically described physicians as "men who prescribe medicines of which they know little to cure diseases of which they know less, in human beings of which they know nothing".

Examples of Iatrogenic Disease

By iatrogenic disease is meant a disorder directly attributable to medical or surgical intervention be it physical or psychological. For example fears implanted in a patient's mind by the examiner's manner or injudicious remarks come into this category. It is usually said that "one who does not learn from history will often repeat the same mistakes". However, one must have knowledge of the history before one can learn from it. Below are some examples of iatrogenic diseases encountered during my practice (not all of them were my patients!) in Nigeria documented in the hope that my colleagues can learn from them.

1. Ventricular fibrillation due to rapid *iv* injection of aminophylline: In 1965 a 28 year-old asthmatic in severe attack was attended by an enthusiastic house officer in the Casualty Department. He injected 250 mg aminophylline *iv* too rapidly and the patient blacked out. ECG confirmed ventricular fibrillation and she was resuscitated with iv hydrocortisone, iv Normal Saline, an antibiotic and hospitalisation for two weeks.
2. Sudden death due to chloroquine-induced hypotension: In 1964 a two year-old well nourished boy was treated for diarrhoea and dehydration with iv ½Normal Saline and 4.3% Dextrose in 0.18% Normal Saline. After rehydration the house officer who had been looking after him since 9:00 a.m. recommended that he be discharged home at 4:30 p.m. However the expatriate registrar who came to review all the cases in Paediatric Casualty before discharge or admission into the wards felt that the boy should have an injection of chloroquine before being discharged. He prescribed the injection which was given *im* by a sister. Within five minutes of administration of the injection the boy's mother gave a shrill cry of distress. The boy had fainted and he was in shock with

thready and feeble pulse at over 160/minute. All resuscitative measures with nikethamide, hydrocortisone and iv 4.3% Dextrose in 0.18% Normal Saline failed and the boy died. Nearly 30 years later febrile children given chloroquine injections in different parts of Nigeria suffered similar fate simply because insufficient emphasis was laid on the fact that chloroquine causes vasodilation. This effect summates with the vasodilation caused by pyrexia and toxins produced by malarial parasites.
The lesson here is that chloroquine injection should never be given to dehydrated and febrile children. Since chloroquine is well absorbed orally its use in children should be by this route.

3. Acute Renal Failure due to "Green water" poisoning: In 1982 a 32 year-old man being initiated into a religious group was given a bottle of "green water" to drink. After a few doses he developed oliguria and became toxic. He was admitted through Accident and Emergency Medicine Department to the Dialysis Centre. After three dialysis he went into the diuretic phase and on conservative treatment gradually recovered after two weeks hospitalisation. However a 45 year-old man who similarly ingested "green water" was not so lucky. He was brought into the hospital a week afterwards and he had both acute renal failure and liver failure. He died despite being treated by dialysis.

4. Postural hypotension due to antihypertensive drugs: A 30 year-old doctor was consulted by her 42 year-old former teacher in secondary school. Routine medical examination for insurance had shown her blood pressure was 170/110 at the first visit. She prescribed methyldopa 250 mg thrice daily, co-amilozide (fixed dose combination of amiloride 5 mg plus hydrochlorothiazide 25 mg) one tablet daily for her. Two days later the teacher fell while standing in her class room and she was rushed to the hospital casualty. She had lost 3 kg in two days. Blood pressure was 100/70 lying, pulse 108/min and 80/40 standing, pulse 120/min. The drugs were stopped and she was rehydrated with 1 litre of intravenous normal saline. Her mild hypertension was later controlled on bendrofluazide 5 mg given on alternate days.

5. Diabetes mellitus caused by thiazides: A 48 year-old man was on treatment with one tablet co-amilozide daily for 15 months for mild hypertension 170/105. Routine check of his urine at clinic visit showed glycosuria and on questioning he admitted to excessive thirst since the past three months. An oral glucose tolerance test revealed a diabetic curve. The drug was stopped and salt reduction advised. Six months later the blood pressure

remained normal and a repeat oral glucose tolerance test was normal.

6. Gout due to "Brinerdin": A 79 year-old man who had been on reserpine-clopamide- dihydroergocristine for about 20 years for moderate hypertension presented with olecranon bursitis. Serum uric acid was 10.4 mg/dl. The drug was stopped and he was treated with probenecid 500 mg bid and allopurinol 100 mg daily. The bursitis resolved within three months. His antihypertensive therapy was changed to a calcium antagonist.

7. Penicillin induced pyrexia: A patient being treated for pneumonia with injection of crystalline penicillin responded initially with clearing of chest signs and fall in temperature from 39°C to 36°C within 4 days but from the 6th day the temperature rose again to 38°C and various investigations proved negative. Then a close look at the temperature chart showed that the pyrexia usually followed injection of procaine penicillin used for maintenance dose. The temperature settled and the patient improved when the drug was stopped.

8. Extensive Allergic maculo-papular eruptions (Stevens Johnson's syndrome) caused by cotrimoxazole: Cotrimoxazole was prescribed for a 64 year-old man who had upper respiratory tract infection. Forty eight hours after commencement of therapy he developed extensive itchy eruptions all over the body including the face and scalp. Enquiry showed that he had experienced fixed drug eruptions with phthalylsulphathiazole administered for diarrhoea 20 years previously but the attending doctor failed to obtain a drug history. He was treated with high dose prednisolone gradually tailed off over two weeks, and chlorpheniramine. The lesson is that a drug history must always be obtained and specific questions asked about a previous adverse or allergic reaction to any drug taken by the patient in the past.

9. Osteoporosis and stress fractures leading to paraplegia in osteoarthritic patient self medicating with prednisolone: An obese 55 year-old menopausal female .was not satisfied with the relief obtained from various non-steroidal antiinflammatory drugs (NSAIDs) prescribed by her doctor for osteo-arthritis of the knee joints. She consulted a pharmacist who prescribed prednisolone for her. Since she found great relief she over five years used prednisolone 5 mg twice daily bought from the same shop. One day she was alighting from her car when her leg got caught in a dangling seat belt. She stumbled, fell and developed paraplegia. Radiological investigation showed osteoporosis of all bones and a

stress fracture at 12th Thoracic and 1st to 3rd Lumbar Vertebrae. The lesson is that corticosteroids must not be prescribed by just anybody and once prescribed it must not be repeated without the doctor's consent.

10. Perforated DU caused by corticosteroids: A similar presentation in a 37 year-old long distance trailer driver resulted in symptomless duodenal ulcer which presented with sudden shock. Examination revealed that he had a perforated ulcer which was surgically treated.

11. Gas gangrene caused by unsterile injection needle in a patient who received chloroquine injection: A 15 year-old school girl was brought home to her mother from the boarding house on account of fever, vomiting and loss of appetite. Her mother consulted a trained nurse who lived nearby and she suggested to treat her for malaria with chloroquine injection. This was purchased from a neighbourhood chemist and administered by one of the personnel there into the right buttock. The girl improved initially but two days later she developed a swelling of the right buttock, thigh and leg. She was brought to the hospital emergency department in a shocked state. Examination showed a well nourished toxic girl with crepitus in the right buttock, thigh and leg. Radiological investigation confirmed that she had gas gangrene and she was in bacteraemic shock. She died before she could be taken to the theatre for surgery. The lesson is that injections should only be given after all the necessary sterile precautions have been observed. Unqualified personnel should not administer injections or man pharmacies or drug outlets.

12. Penicillin anaphylaxis: A 40 year-old banker had a minor operation for an in-growing left big toe nail. He was put on daily *im* injection of procaine penicillin. Five minutes after the third dose of injection he fainted as he was about to enter his car. On examination he had hypotension with severe bronchoconstriction but fortunately he was revived with *iv* aminophylline, hydrocortisone and infusion of normal saline. He spent one week in hospital after this event. He later admitted using penicillin powder for treating minor wounds although he denied having received any previous injection. There have been previous episodes of penicillin allergy which resulted in death when such injections were administered by unqualified drug retailers who lacked knowledge of how to deal with anaphylactic shock. The lesson here is that a complete drug history must always be

obtained. Those who do not take a drug history will write more death certificates than discharge certificates.

13. Intra dialysis hypertension due to high sodium content of dialysis concentrate: A 63 year-old man who had been on chronic haemodialysis programme for four years and whose blood pressure had been controlled without antihypertensive drugs for one year developed accelerated hypertension during dialysis with a new batch of dialysis concentrate in a private hospital. Dialysis was prematurely terminated on the first occasion and antihypertensive drugs recommenced. Three days later his blood pressure at the commencement of dialysis was normal but rose to 190/115 within one hour of dialysis. A consultant was invited to see the patient and he confirmed the intradialysis accelerated hypertension and advised that the dialysing fluid be checked. The sodium content of the fluid was found to be much higher than expected. It was also found that all patients using the same batch of dialysis concentrate had intradialysis hypertension. The lesson is that one must regularly check that the composition of the dialysate fluid is within the accepted range.

14. Difficulty in finding the cause of allergy in a hypertensive diabetic receiving metformin, glibenclamide, nifedipine and multivitamin tablets. A 54 year-old female obese hypertensive diabetic was receiving metformin, glibenclamide, nifedipine and multivitamin tablets. After two weeks on the therapy she developed generalised body pruritus. She was managed with antihistamine cover while the drugs were stopped one by one in order to find which of them was responsible for the drug reaction. It turned out to be metformin.

15. Resistant tuberculosis in a patient who was using fake rifampicin bought from a drug store and in another who did not comply with drug regimen: A 23 year-old female had pulmonary tuberculosis and she was placed on rifampicin, isoniazid and streptomycin . After two months the streptomycin injection was stopped and she continued treatment with rifampicin and isoniazid. Despite compliance with treatment her condition deteriorated and her chest lesion got worse. She was admitted to the hospital and investigation showed that she had resistant tuberculosis. Her batch of rifampicin combined with isoniazid bought from a retail outlet was found to contain rifampicin 168 mg and isoniazid 95 mg instead of rifampicin 300 mg and isoniazid 150 mg per capsule. She was treated with hospital supplied rifampicin, isoniazid, ethambutol, ethionamide and streptomycin

since it was not possible to culture organisms from her sputum. She made a slow recovery and was discharged after three months in the hospital. The lesson here is "*Caveat emptor*" i.e. Buyers beware!

16. Thiazide induced diabetes with high renal glucose threshold: A 63 year-old male hypertensive who had for five years been controlled with reserpine-clopamide-dihydroergocristine ("Brinerdin") one tablet daily, atenolol 50 mg daily developed an ulcer over the lateral aspect of the left ankle. His urine was sugar free, so he was treated with amoxycillin- clavulanate and dry dressing in addition to the antihypertensive drugs. One week later he complained of polyuria and thirst. He had lost 4 kg in weight, his urine was still sugar free but random blood sugar was 11.4mmol/l (205 mg/dl). He was treated with metformin 500 mg twice daily but he did not respond to treatment until the reserpine-clopamide-dihydroergocristine was stopped.

17. Ignorance of Brand Name Composition: A 39 year-old female with established hypertension (BP was 190/120 and pulse was 82/min) lying and standing was begun on methyldopa 250 mg thrice daily and co-amilozide one tablet daily. Four weeks later her BP lying and standing was 175/110 (pulse 84 and 88). Reserpine-clopamide-dihydroergocristine was added to her therapy at a dose of one tablet daily. Two weeks later the BP was still 170/105 but she had developed glycosuria. Random Blood sugar was 10.2 mmol/l (184 mg/dl). Both co-amilozide and reserpine-clopamide-dihydroergocristine were stopped and isradipine 5 mg substituted. Four weeks later there was no glycosuria, her BP sitting was 130/80 (pulse 80) and standing was 125/76 (pulse 84). Two hour post prandial blood sugar was 5.8 mmol/l (105 mg/dl). This case demonstrates that the doctor did not realise that both drugs contained thiazide-like diuretics which have a flat dose response curve. Unfortunately, there was summation of their toxic effects while the beneficial effects had peaked.

18. Cerebral Infarction due to too rapid lowering of blood pressure in the elderly: A 68 year-old man was brought by his son who is a medical laboratory technologist to a primary care doctor on account of frequency of micturition with urgency. On examination the blood pressure was found to be 185/115. Methyldopa 250 mg thrice daily and co-amilozide one tablet daily were prescribed. After five doses of methyldopa the elderly man woke up to respond to an urgent feeling to urinate. He fell in the

toilet and hit his head against the water closet. When he was brought to Casualty his BP was 80/50 and pulse was thready and rapid at 112/min. He was given iv hydrocortisone and infusion of Normal Saline but although his blood pressure was raised to 130/90 mm Hg he died. At autopsy it was found that he had wide spread arteriosclerosis and had suffered cerebral infarction from too rapid lowering of his blood pressure. The lesson here is that the BP of the elderly should not be lowered too rapidly.

19. Asthma death caused by α and β adrenoceptor blocker: A 49 year-old poultry farmer whose asthma was usually controlled with salbutamol tablets and inhaler as well as iv aminophylline for more severe attacks developed mild hypertension. He was seen in the hypertension clinic and co-amilozide one tablet daily was prescribed. He was afterwards seen by a doctor in his wife's company clinic and the latter doctor prescribed labetalol in the erroneous belief that it was safe to use this drug in asthmatics since it possessed both α and β adrenoceptor blocking properties. About two hours after the second dose of labetalol he went into status asthmaticus and died before arrival in the hospital emergency department. The lesson here is that asthmatics must never be administered β adrenoceptor blocking drugs.

20. Nonsteroidal anti-inflammatory drugs (NSAIDs) by reducing the presence of vasodilator prostaglandins may increase blood pressure or nullify the effects of antihypertensive drugs. A 55 year-old female whose blood pressure was controlled on co-amilozide one tablet daily was receiving ibuprofen 200 mg daily for osteoarthrosis. After two weeks she complained of persistent severe frontal headache. Examination showed that the BP had risen to 190/120. The ibuprofen was stopped and amlodipine 2.5 mg daily was added to her treatment. The blood pressure three days later was 120/70. Amlodipine was stopped and BP has remained normal on half tablet of coamilozide given daily with advice on salt restriction.

21. A 7-month old boy was brought to the Children's emergency department because of persistent cough and fever of 3 days duration. The doctor after careful examination prescribed ampicillin syrup 5 ml (125mg) six hourly and Linctus scill opiate 5 ml eight hourly. The following day the boy was brought back to the hospital on account of lethargy and excessive sleep. The boy's teen age mother had given him the cough linctus every three hours because she was bothered by his cough. On examination the boy's respiration was depressed, he had pinpoint pupils both

signs of opiate overdose. He was revived with oxygen therapy, intravenous fluids and recovered after five days in hospital. The lesson here is that adequate communication with the patients or their relatives is important to prevent episodes of overdosing.

Drug Interaction as a cause of Medication Error

A drug interaction is the alteration of the action of one drug by the action of another drug present in the body as a result of co-administration or previous administration. Some drug interactions can be used for therapeutic benefit but many drug interactions manifest as toxicity. Pharmaceutical drug interactions occur when incompatible mixtures are given in the same syringe or as injection to the same site. The use of penicillin (an acid) with streptomycin (a base) in the same syringe results in reduced effective dose of either drug. Pharmacokinetic drug interactions may involve absorption, distribution, metabolism and excretion.

Absorption : Drug absorption from the gastrointestinal tract can be affected by interaction with other drugs. The mechanisms responsible may be due to alteration of gastric pH, gastrointestinal (git) transit time, and the formation of poorly soluble or inactive complexes.

Changes in pH

Most drugs have relatively large molecules and are either weak acids or bases; therefore they are ionised in solution. But because of their size they can only cross the mucosal lipid membranes of the stomach and intestines by passive diffusion and not through the minute pores in the membranes. Drugs are more readily absorbed in the unionised form. Changes in the git pH alter the degree of ionisation and thus the extent of passive diffusion. However, while ionisation reduces the diffusion phase it increases the dissolution phase. Absorption of tetracyclines is diminished in the presence of antacids containing calcium, magnesium and aluminium ions because of chelation and because of the poor solubility of the capsule in the alkaline medium provided by the antacid[54]. Iron reduces absorption of tetracyclines[55]. In cases in which dissolution is the rate limiting step, antacids may decrease the absorption of basic drugs and increase the absorption of acidic drugs. Thus sodium bicarbonate

increases the rate of absorption of aspirin (an acidic drug) while decreasing that of tetracycline (a basic drug).

Changes in GIT Transit Time

The gastrointestinal absorption of drugs is complicated by other factors, such as the presence of food and drugs with anticholinergic properties which reduce git motility. The delayed git emptying time caused by concomitantly administered anticholinergic (benzhexol, benztropine or biperiden) with levodopa to parkinson patients may result in insufficient absorption of levodopa and inadequate treatment of the condition. Increased retention of drugs in the stomach due to the presence of food can delay the onset of action of drugs which are not significantly absorbed until they reach the intestine e.g. metformin. However the bioavailability of poorly absorbed drugs like digoxin and dicumarol may be increased by tricyclic antidepressants with anticholinergic effects. This is due to the increased time available for dissolution and absorption. The reduced absorption of griseofulvin when administered with phenobarbitone is due to increased git motility caused by phenobarbitone. Phenobarbitone stimulates bile secretion which in turn stimulates git motility. The reduced drug-intestine contact time results in lowered plasma level of griseofulvin which is mainly absorbed in the intestine.

Formation of poorly absorbed complexes

Absorption of tetracyclines is diminished in the presence of antacids containing calcium, magnesium and aluminium ions mainly because of chelation. Antacids, owing to their large surface area , have also been shown to retard the absorption of iron and a number of drugs like sulphonamides, phenothiazines and nitrofurantoin. Iron and vitamin preparations containing zinc and ferrous sulphate reduce the absorption of tetracyclines[55] due to chelation. There is reduced absorption of lincomycin in the presence of kaolin-pectin mixtures when concomitantly administered[56]. Cholestyramine reduces the bioavailability of other drugs like thiazides, warfarin and digitoxin[57] .

Distribution

After absorption, drugs are distributed to the tissues and become available both for their intended receptors and at receptors determining adverse reactions[58]. Alternatively, drugs can be sequestered in the tissues in an inactive form, such as

bound to serum protein. Methotrexate, warfarin, diphenylhydantoin, salicylates, sulfonamides, antimalarials, phenylbutazone, tolbutamide and trichloroacetic acid (a metabolite of chloral hydrate) are among the drugs that are significantly bound to sites on serum protein. In this form, their availability may be inadvertently increased by the introduction of a second drug that displaces the first from its inactive site. Toxicity thus may arise from a drug given in a previously satisfactory dose after a second drug is introduced. This mechanism is particularly significant for drugs like warfarin and dicumarol, which are over 90% bound to protein. Factors influencing the concentration of an unbound drug include the serum concentration of the drug, the amount of plasma protein, the number of binding sites on the protein and the drug's binding affinity. When a second drug displaces only a fraction of the anticoagulant, the effective dose of free drug can readily be doubled, with consequent prolongation of the prothrombin time[59]. For example a displacement of 5% of a drug which was 95% bound to protein will double the percentage of the dose that is free to diffuse to the receptor site to 10%.

Oestrogens increase liver production of thyroxine binding globulin (TBG) and protein bound iodine (PBI). Hence women on oestrogen containing oral contraceptives have high PBI levels in the absence of other symptoms of hyperthyroidism.

Metabolism

Majority of drugs are metabolised in the liver. Competition for some of the conjugation pathways can cause one drug to interfere with the metabolism of another. The most frequent site, however, at which one drug can influence the metabolism of anohter is in the microsomal system of the liver. This system is stimulated (induced) by a wide variety of drugs as well as environmental compounds (DDT) and social drugs (cigarettes, marihuana). Conney and Burns have reviewed the exogenous compounds that affect the induction of this system in man[60]. The development of tolerance to ethanol in alcoholics can be attributed to induction of this system. As a consequence of this induction, alcoholics can have a high tolerance for other drugs, including the barbiturates[61]. A problem arises during acute alcoholic intoxication, when the normally active metabolism of drugs can be acutely diminished by the presence of alcohol. Under these circumstances the accustomed large dose of, for

example, a barbiturate may not be metabolised in the usual manner and a prolonged and accentuated effect can occur. Other frequently used drugs that induce this system include phenylbutazone, diphenylhydantoin and glutethimide. Diphenylhydantoin, phenylbutazone, digitoxin, meprobamate and steroids are more rapidly metabolised as the result of such induction. Of particular importance is the altered metabolism of the coumarin anticoagulants (warfarin and dicumarol) in response to these drugs.[59] In this connection, attention should be called to the barbiturates, which are apt to be used as a sedative while the patient is in the hospital having his anticoagulant dosage adjusted. When the patient leaves the hospital the sedative may be discontinued, causing a diminished microsomal metabolism of the anticoagulant. Under these circumstances the same dose of anticoagulant will have a greater effect, with a consequent increase in the danger of haemorrhage.

Enzyme inhibition may also be responsible for drug interaction. A drug may inhibit hepatic microsomal enzymes or compete for the same enzyme or coenzyme that metabolises another. Ethyl alcohol and trichloro-ethanol (a metabolite of chloral hydrate) compete for alcohol dehydrogenase and reduce the metabolism of each other. Genetic differences among patients can lead to altered drug response,[62] and in some instances genetic differences in drug metabolism can be responsible for decreased metabolism of a second drug; patients who are slow acetylators have an increased risk of isoniazid toxicity. Isoniazid inhibits the metabolism of phenytoin., and when taking isoniazid concomitantly patients have an increased risk of diphenylhydantoin toxicity[63]. Cimetidine inhibits oxidative enzymes and this leads to reduced metabolism of drugs which first require oxidation prior to conjugation. Diazepam is first demethylated (a form of oxidation) before it is conjugated with glucuronic acid. Monoamine oxidase inhibitors (MAOI) inhibit both hepatic and synaptic enzymes. If patients on these drugs eat food containing tyramine (e.g. cheese,) or take certain drugs they may experience dangerously high blood pressure because the tyramine in cheese releases catecholamines. MAOIs may also inhibit metabolism of antidiabetic drugs, tricyclic antidepressants, anaesthetics and narcotic analgesics. Anticholinesterases inhibit the metabolism of suxamethonium and this may cause prolonged apnoea. Magnesium sulphate also interacts with suxamethonium in the same way. Allopurinol inhibits the metabolism of

azathioprine, mercaptopurine and cyclophosphamide thus increasing their toxicity.

Excretion

Although drugs can be excreted through the biliary system, skin or lungs, only in renal excretion has the action of one drug been shown to alter the elimination of another. Most drugs and their metabolites are excreted by the kidneys. Like git absorption the passive excretion of drugs in the urine is regulated by the pKa (dissociation constant) of the drug and the pH of the tubular fluid. The effect may be at the glomerulus, where to the extent that drugs are strongly bound to protein they will not be filtered unless displaced from serum protein by another drug. Other interactions occur within the renal tubule, where diffusion back into the bloodstream is favoured for neutral molecules. Alkalinizing the urine with drugs like sodium bicarbonate puts basic drugs, e.g., quinidine, into the neutral form while putting acid drugs, e.g., salicylate, into the charged form. Urine acidifiers like ammonium chloride have the opposite effect. Thus, alkalinizing the urine tends to favour excretion of basic drugs and retention of acidic drugs.[64] Competition among various drugs (and normal metabolites) for the carriers that mediate transport across the renal tubule is another area of drug interaction. Two separate carrier systems, one for weak acids and the other for weak bases, have been identified.[65] Experimental verification of the possible importance of interactions at these sites has been limited to the acid drugs[66], which include salicylate, hippurate, probenecid, phenylbutazone, indomethacin, thiazide diuretics, acetazolamide, penicillin and the sulfonamides[67] The prototype for interaction at the renal tubule is that between penicillin and probenecid; probenecid was designed specifically as an inhibitor for penicillin excretion and now has been shown to block penicillin transport out of the cerebrospinal fluid in experimental animals[58].

Other Physiologic Mechanisms Of Drug Interaction

Another class of drug interactions comprises those that occur by virtue of competition between two drugs for the drug receptor itself. The morphine antagonists nalorphine and naloxone act directly at the receptor site in competition with morphine. This direct antagonism is the basis for the use of these drugs in clinical practice. The tricyclic antidepressants (TCA) compete with guanethidine for active transport into the adrenergic nerve ending.

The TCA is preferentially taken while guanethidine is not taken up and its antihypertensive effect ceases. Phenothiazines, TCAs, antihistamines, procainamde and quinidine have varying degrees of anticholinergic properties and when given concomitantly their actions may summate. Fatal adynamic ileus has occurred when phenothiazines are given with tricyclic antidepressants (TCAs) and antiparkinsonism drugs. Nonsteroidal anti-inflammatory drugs (NSAIDs) by reducing the presence of vasodilator prostaglandins may increase blood pressure or nullify the effects of antihypertensive drugs as described above (Case 20).

Other drug interactions occur because one drug alters a physiologic parameter that affects the action of a second drug. The thiazide and furosemide diuretics diminish the body stores of potassium and the resulting hypokalaemia leads to increased likelihood of digitalis induced cardiac arrhythmia [68]. Hypokalaemia reduces the antiarrhythmic effect of quinidine, procainamide, phenytoin, and lignocaine. Hypokalaemia may also produce prolonged paralysis in patients receiving nondepolarising muscle relaxants. There is also evidence that depletion of cardiac catecholamines by reserpine may increase the cardiac sensitivity to quinidine. Cyclopropane and other halogenated hydrocarbon anaesthetic agents sensitise the heart to circulating catecholamines and arrhythmias may result if adrenaline, amphetamine, ephedrine or other sympathomimetic is concomitantly administered. Propranolol by inhibiting glycogenolysis may prolong insulin-induced hypoglycaemia. By depleting the dopamine content of the brain reserpine may render levodopa ineffective in parkinsonism. Antibiotic combinations may be mutually antagonistic if a bacteriostatic drug which acts by ribosomal binding is administered together with a similarly acting drug to which an organism is resistant. Erythromycin, lincomycin and chloramphenicol demonstrate this type of interaction.

Drug Surveillance

Information about drug interactions and the mechanisms by which they occur can guide future therapeutic practices. Knowledge about possible mechanisms of drug interaction come to light often long after the drug has been in use. How does the clinician clearly identify drug interactions? It has been pointed out that adverse drug reactions are often erroneously ascribed to manifestations of the patient's disease and are apt to be considered merely as idiosyncratic responses[72]. One approach to

identifying drug reactions is the use of surveillance that is removed somewhat from the subjective factors that might influence the individual physician. Surveillance methods can be classified in several ways. Study of the reactions and their frequency in a group of patients taking a given drug is said to be *drug-oriented surveillance*.[73] *Event-oriented surveillance* is illustrated by a study that shows certain pathologic conditions are increased in association with the use of a given drug. This type of surveillance is illustrated by the finding that children born by mothers who had taken thalidomide[29] in the early stages of pregnancy had phocomelia and that diethylstilboestrol given to pregnant women was associated with the later development of cancer of the vagina in postadolescent daughters born of these pregnancies[32,74]. In these instances the events were linked to the offending drugs only because of the rarity of the conditions in the affected age groups and the alertness of the physicians who observed the cases. Similarly, the relative rarity of thromboembolic phenomena in young women made it possible to associate this condition with the use of the birth control pill[75]. A drug will only be considered as causative of a complication when the complication occurs with a frequency noticeably above the expected value within the population at risk. It will then be necessary to use appropriate epidemiological criteria to associate the presumed complication with the prior administration of the drug.

Patient-oriented surveillance: The characteristics of each patient and the drugs he has taken are monitored along with a variety of clinical events that might be caused by drugs. In 1989 children receiving injections of chloroquine injections in a number of children's emergency clinics in Nigeria died suddenly shortly after the drug had been administered. A closer look revealed that these injections were administered while the patients were still pyrexial. It is well known that chloroquine causes vasodilatation. In these cases death was most probably due to hypovolaemia due to severe vasodilatation caused by chloroquine and pyrexia in an anaemic patient. In principle, a correlation can be sought between a patient's prior medication and any of a variety of signs and symptoms that he may later have.

Similarly from 1981 to 1988 cases of acute renal failure due to poisoning with "green water" were treated in the dialysis centre of the Lagos University Teaching Hospital. Analysis performed on the causative water produced by a relation of one of

the patients showed that it contained among others copper sulphate. We were able to provide feedback to the group using the water to remove the dangerous constituent from the mixture and we have not encountered any such case for some time. Surveillance can place adverse drug reactions into perspective for the clinician.

Other Causes of Medication Errors

Prescriber Caused

- Failure to fully examine patient and make a definitive diagnosis before prescribing
- Lack of knowledge of the pharmacology of drug(s) prescribed
- Lack of awareness of drug's potential for adverse reactions
- Polypharmacy
- Failure to obtain complete drug history from patients
- Failure to consider patient's disease state
- Failure to consider genetic make up of patient
- Failure to prescribe generically and to adequately communicate with patient
- Failure to write legibly hence making it difficult for pharmacist/nurse to dispense

Pharmacist /Dispenser Caused

- Failure to communicate with patient correct dosing regimen
- Failure to discuss with prescribers when prescription is not legible or understood
- Failure to label drug packages - Secrecy in drug name disclosure
- Dispensing expired drugs/fake drugs
- Giving counter instructions to those of prescribers
- Profit motivation
- Prescribing without adequate knowledge of disease

User caused

- Consuming more drugs than prescribed
- Using drugs more frequently than prescribed
- Confusion about dosing regimen of different drugs
- Consulting different prescribers concomitantly without full disclosure

Non-compliance
Using left over drugs
Using expired drugs
Sharing drugs with patient with similar symptoms but not necessarily same disease

The Solution

Ideally, every secondary health care facility should have a clinical pharmacologist. Government should train more clinical pharmacologists, pharmacoepidemiologists and clinical pharmacists. Scholarships and bursaries should be provided for medical and pharmacy graduates who wish to enter into these specialties. Since all doctors, no matter their subspecialties, prescribe drugs the Nigerian and West African Postgraduate Medical Colleges should encourage all faculties to teach and ask questions on aspects pertaining to safe drug use at all parts of their examinations. Education and re-education in the process of rational prescribing should be carried out regularly. All practising doctors and pharmacists should attend scientific conferences and refresher courses annually and attain minimum credit hours before practising licences are renewed. Government and the Pharmaceutical Society of Nigeria should ensure that pharmacists are always present at licensed drug stores.

There should be proper education of medical students and interns in pharmacotherapy. Rational prescribing should include the following steps:

Step 1: Defining Patient's Problem
Step 2: Specifying Therapeutic Objective
Step 3: Verifying suitability of your P(ersonal)- treatment ----- Efficacy, safety, cost
Step 4: Starting treatment ..... non drug and drug
Step 5: Giving information, instructions and warnings
Step 6: Monitoring the treatment until it is stopped

Prescription Writing

The following information is mandatory on a prescription

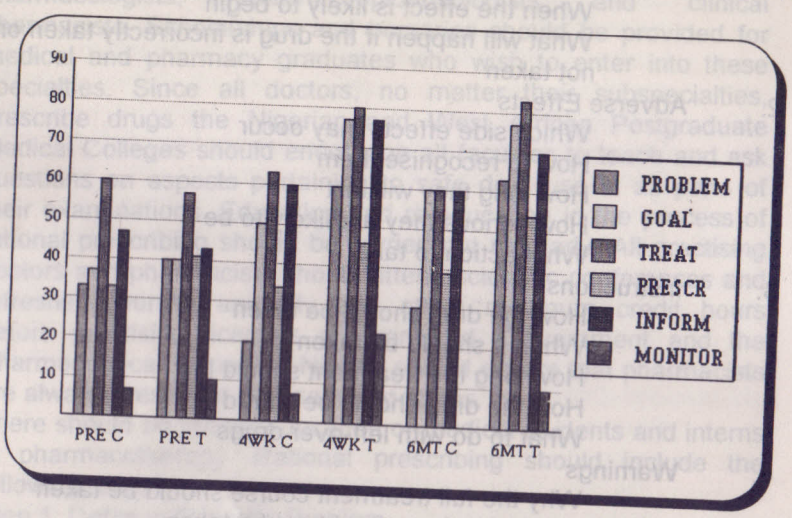
1. Name and address of Prescriber (with telephone number (if possible)
2. Date of Prescription

3. Generic Name, (sometimes also Brand Name), form and strength of the drug
4. Dosing regime and duration of treatment
5. Information to be written on the package label
6. Prescriber's Signature (full or abbreviated)
7. Name, age, gender and address of patient

Minimum Patient Information

1. Effects of the drug
   - Why the drug is needed
   - Which symptoms will disappear and which will not
   - When the effect is likely to begin
   - What will happen if the drug is incorrectly taken or not taken
2. Adverse Effects
   - Which side effects may occur
   - How to recognise them
   - How long they will last
   - How serious they are likely to be
   - What action to take
3. Instructions
   - How the drug should be taken
   - When it should be taken
   - How long the treatment should last
   - How the drug should be stored
   - What to do with left-over drugs
4. Warnings
   - Why the full treatment course should be taken
   - When the drug should not be taken
   - What is the maximum dose
5. Future Consultations
   - What information the prescriber will need at next visit
   - When to come back
   - In what circumstances to come back earlier
6. Everything Clear?
   - Ask patient if everything is understood
   - Ask the patient to repeat the most important information
   - Ask the patient if he has any questions for you

	PRE_C	PRE_T	4WK_C	4WK_T	6MT_C	6MT_T
PROBLEM	33	40	20	60	30	63
GOAL	37	40	50	77	60	77
TREAT	60	57	63	80	60	83
PRESCR	33	41	34	46	39	54
INFORM	47	43	60	77	60	70
MONITOR	7	10	7	23	0	10



GUIDE TO GOOD PRESCRIBING IN LAGOS, NIGERIA
RETENTION EFFECT

Table 1 Number of students

	Control groups			Study groups		
	All	Incl	Excl	All	Incl	Excl
Groningen	9	9	0	7	7	0
Kathmandu	10	8	2	10	8	2
Lagos	20	19	1	20	18	2
New Delhi	20	17	3	18	15	3
Newcastle	16	15	1	20	19	1
San Francisco	13	7	6	16	5	11
Yogyakarta	20	18	2	20	19	1
Total	108	93	15	111	91	20

Table 2 Patient problems used in tests

Test	Open questions		Structured questions
T1	A		X
T2	A	B	Y
T3	A	C	Z

T1=pre-test; T2=post-test; T3=6 months post-test

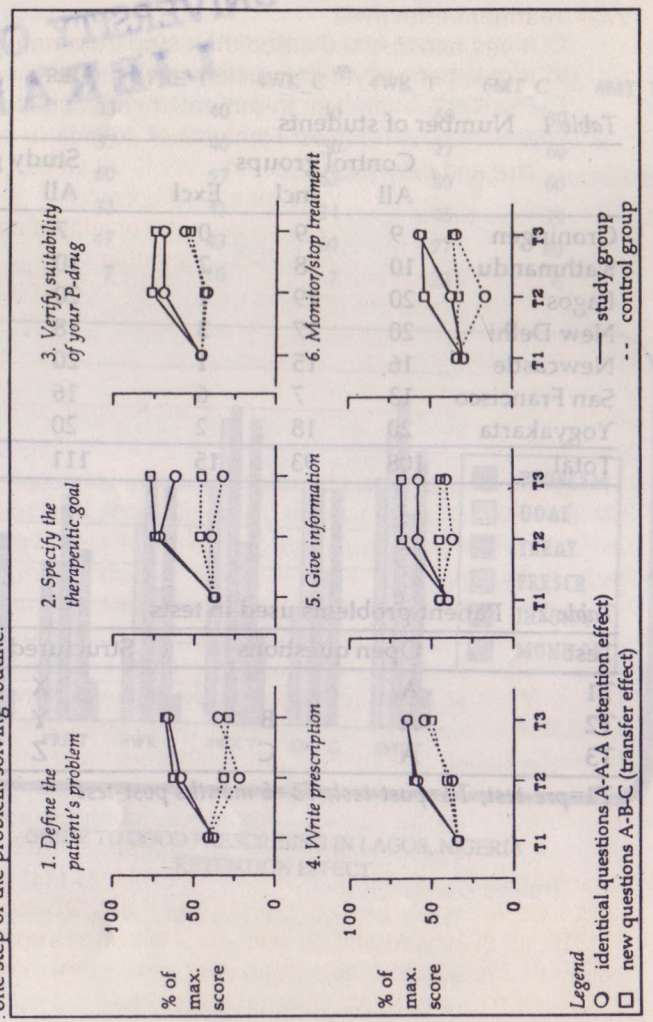


Figure 1
Scores for open questions A-A-A (retention effect) and A-B-C (transfer effect). Each panel represents one step of the problem solving routine.

Monitor and stop treatment

Was treatment effective?

a. If yes and disease cured then stop treatment

b. If yes, but not yet completed: Any serious side effects?
No: treatment should continue
Yes: Reconsider dosage or change drug

c. No, and disease not cured: Verify all steps
Was diagnosis correct?
Was therapeutic objective correct?
Was P-drug suitable
Was patient correctly instructed?
Was patient compliant with instructions?

Monitoring or auditing performance with drug utilisation surveys

The performance of prescribers and dispensers can be monitored by periodic drug utilisation surveys and the results of such exercises fed back to them. This type of peer auditing helps to reduce prevalence of irrational drug use and ultimately improves service to patients as well as reducing wasteful misuse of drugs due to costly but not necessarily better drugs being favoured.

In 1989 the International Network for Rational Use of Drugs (INRUD) was established as a cooperative organization consisting of health care researchers (doctors, pharmacists, nurses, social scientists, administrators and relevant health professionals) whose primary goal is to promote the rational use of pharmaceuticals. It now covers five countries in Africa (Ghana, Nigeria, Tanzania, Uganda, and Zimbabwe) and five in Asia (Bangladesh, Indonesia, Nepal, Phillipines and Thailand). Its activities are coordinated by Management Sciences for Health (MSH) in Washington DC and the Harvard Drug Policy Group. International support has been received from WHO, DANIDA, SIDA, USAID and PEW Charitable Trusts.

Objectives of Inrud

To achieve its goal INRUD Nigeria has been pursuing the following objectives:

1. to popularise the Essential Drugs Concept.

2. to Improve knowledge of the principles and practice of the Essential Drugs Programme at country and local levels.
3. to promote knowledge, attitudes and practices that would lead to better prescribing, dispensing and use of drugs.

A recent major achievement of INRUD is the development, in collaboration with WHO Action Programme on Essential Drugs (APED), of Health Facility Drug Use Indicators, which are intended to be standardized managerial tools to characterize the drug use situation in any health care system. Previously, inter-facility or cross-national comparisons of drug utilization have been hampered by inconsistent data collection methods. Following successful field trials supported by WHO in five developing countries - Indonesia, Bangladesh, Nepal, *Nigeria (by our group in Lagos),* and Tanzania - the indicators methodology was published as a manual entitled: "How to Investigate Drug Use in Health Facilities" by WHO in early 1993. The manual provides objective measures to describe the drug use situation in a region, and also suggests follow-up activities intended ultimately to improve utilization, including:

* further investigations of the nature and causes of priority drug use problems;
* design of managerial and educational interventions to solve or improve identified problems.

Information, Education and Communication

Many people are still not aware that once they have any of the chronic non-communicable diseases like hypertension "Treatment is for Life". Government should contribute more to the efforts to inform, educate and communicate with the population at large on the importance of using drugs only when necessary and complying with doctor's advice once disease has been diagnosed. On many occasions we have seen patients diagnosed ten or more years previously as suffering from hypertension or diabetes. They turn up with endstage kidney failure simply because they failed to continue to take their drugs in the erroneous belief that since they no longer had any symptoms they had been cured. Government should purchase daily columns in all print media circulating in the country and use such to convey health care messages to the people. Slots should be purchased in all the radio and television stations during prime time so that similar messages can be

conveyed. A stitch in time saves nine is true for health as it is for items of clothing.

Economic Empowerment

Many patients cannot afford the cost of drugs and although they suffer from chronic diseases they must cut corners in order to feed themselves and their families. The present economic situation has made it impossible for many people to be able to afford the cost of antihypertensive drugs. Some have in earnest had to appeal to their doctors to see what can be done about cutting corners by substituting less effective but cheaper drugs. Government can help to assure the availability of affordable drugs of good quality by taking the following measures:

1. reduce the import duties on essential drugs
2. reduce the import duties on pharmaceutical raw materials
3. reduce the import duties on machinery for drug manufacture
4. reduce the import duties on equipment for drug quality assurance
5. subsidise the cost of treatment for chronic diseases in truly indigent persons
6. increase the purchasing power of the populace by strengthening the Naira in relation to other currencies

Enforcement of Drug Laws

Government can also help to improve the drug availability and drug use situation in the country by enforcing the drug laws, and promoting clinical pharmacology and clinical pharmacy by awarding scholarships to graduates who wish to specialise in these disciplines.

Pity the Folks

I am aware that the Petroleum Trust Fund has set aside appreciable funds for servicing Health as well as Essential Drugs and Vaccines. I wish to humbly suggest that it is important to spend a small fraction of the allocation to ensure that the drugs supplied meet the requirements of the WHO Certification Scheme

on the Quality of Pharmaceutical Products Moving in International Commerce. The objective of the scheme is to assure that pharmaceutical products are safe, effective and of adequate quality when received. In order to promote effective implementation of the scheme, procurement and registration personnel should be familiarised with the scheme through orientation and training programmes. Exporting countries should be made to subject their pharmaceutical products for export to the same standards of control applied to locally consumed products. By doing so Government would be ensuring that the money it is spending is being used to provide quality drugs for its people and would therefore be seen to be really pitying the folks.

CONCLUSION

It can be seen from the above reports that Medication Errors are a problem, but many such occurrences are glossed over and never discovered or reported. Appropriate solution will not be found until more prescribers are made aware and the extent of the problem is carefully evaluated. As illustrated medication errors and adverse reactions themselves have extensive consequences[76] from serious disability to death. Many of these consequences may be due to drug interactions; support for this idea comes from the observation that the likelihood of an adverse reaction of a given drug is increased in patients who are taking a large number of other drugs[77,78]. However, it must be recognised that patients who receive more drugs are generally sicker than those taking fewer drugs and it may be their greater illness that makes them more susceptible to the adversities of drug therapy[79].

The consequences of medication errors can be minimised only if the doctor or prescriber is parsimonious in his use of drugs. **He should limit his prescriptions to those drugs he knows well and for which there is a clear therapeutic indication.** Additional drug information needed for specific therapeutic situations should be obtainable from services which should be in place in Drug Information Centres located in Teaching Hospitals or Reference Schools of Pharmacy in the Colleges of Medicine. Adverse drug reactions and medication errors and mishaps will doubtless be discerned if clinicians have a high index of suspicion. However, **the physician who uses only drugs he understands for clear therapeutic indications is less likely to provide the case reports for such mishaps from among his patients.**

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MEDICATION ERRORS AND DRUG TRAGEDIES: CASEBOOK OF A NIGERIAN CLINICAL PHARMACOLOGIST/NEPHROLOGIST

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