UNIVERSITY OF THE SCIENCES IN PHILADELPHIA

# Medical Journal of Therapeutics *Africa*

**Volume 1 Number 1**
**January 2007**

***Malaria***

***Girl and boy in Zambia. Photo courtesy of Carl L Kalczuk.***

**KNOWLEDGE • COMMUNICATION • HEALTH**

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## *Welcome from the Editor-in-Chief*

Africa in the first decade of the 21st century is plagued with disease, of which the main killer is malaria. If malaria was a man and not a disease, it would be called an evil dictator and the deaths would be labeled genocide. So many deaths each year that the World Health Organization cannot estimate them, giving a figure of between 1 and 3 million world wide, of which the majority are in sub-Saharan Africa.

We are compiling the *Medical Journal of Therapeutics Africa* for readers in the United States and Africa. The medical journal articles are aimed at pharmaceutical industry professionals, the magazine articles are aimed at non-science trained professionals. We have a goal for a third audience, the general audience, and we are exploring broadcast video options for that. We wanted our first issue to explain what malaria is, who gets it, what other diseases have the same symptoms, what efforts are being made to prevent and treat it and why Americans should be appalled that it is a threat to a single life.

The pharmaceutical industry in the United States evolved from an unregulated industry in which snake oil was sold as a miracle cure into an industry regulated by acts of Congress which understand that medicines are so dangerous that anyone prescribing or dispensing them has to go through years of rigorous training.

Arguably the regulated pharmaceutical industry started in 1821, when University of the Sciences in Philadelphia (USP) was started (as the Philadelphia College of Pharmacy) by men of science who recognized the need to train professionals in scientific method to understand both how to deliver clean, consistent doses of therapies and the physiological effects of pills and potions given to heal. In 1997, when the Biomedical Writing programs were started, USP was the first to recognize medical writers as pharmaceutical industry professionals whose job is to compile and describe pharmaceutical data.

On behalf of the editors in the Biomedical Writing Programs, I welcome you to our pages. I invite all pharmaceutical industry professionals to contribute manuscripts and to work with us in our goal to establish of a regulated pharmaceutical industry throughout the continent of Africa.


***Billboard advertising anti-malaria mosquito nets in Botswana. Photo courtesy of Mark Travis.***

# INSTRUCTIONS TO AUTHORS

For consideration by the editors and the editorial board, all manuscripts must be written according to the uniform requirements for manuscripts submitted to biomedical journals, which are posted on www.icmje.org.

Our style and editing guidelines can be obtained from the editor-in-chief. In brief, add only 1 space between sentences, number the references sequentially in the text and list the references in the same style as PubMed.

The preferred manner of submission is as an attachment on an e-mail, with pictures of figures and tables sent camera-ready as high resolution jpg files. Under special circumstances, manuscripts will be accepted by posted mail or fax.

We accept letters, review articles and articles giving original research. Original data articles need to be in the form Abstract (200 words maximum), Introduction, Methods, Results, Discussion. Data articles should generally have under 3,000 words.

Magazine articles are narratives and have no proscribed structure; accompanying photographs are encouraged. They may be as short as 200 words or as long as 10,000 words, however, they must be focused and tightly written.

We do not pay for medical journal articles or for magazine articles. You will retain the copyright for your journal or magazine article when you assign to us rights to publish your article in an issue of *Medical Journal of Therapeutics Africa.*

Each data and magazine article is reviewed by at least 2 members of the editorial board and the editor-in-chief, and outside reviewers as the need arises. We adhere to the requirement of the National Library of Medicine for inclusion of journals in their database is that “neither the advertising content nor commercial sponsorship should raise questions about the objectivity of the published material.”

All articles published are required to meet the standards of the National Library of Medicine. Our major criteria for selecting each article are scientific merit, relevance to our target audience quality of writing, and relevance to the topic focus of the issue.

We invite submission of articles reporting any data or information that will nurture the dialog between pharmaceutical industry professionals in Africa and the United States. These articles will include clinical and pre-clinical studies, reviews of current clinical and pre-clinical studies, discussion of devices and medications, case reports.

Submissions of review articles and case reports must be preceded by communication with the editor-in-chief. We also invite submission of letters to the editor-in-chief, which should address observations relevant to the pharmaceutical industry, including novel manufacturing plants, interpretations of drug, device and biologic regulations, summaries of marketing campaigns, press releases about therapies.

We will accept for submission for consideration by the editorial board articles sent as attachments to e-mail letters. Please first send an e-mail with a cover letter, then send a second e-mail with the article attached. We will only lay out articles for publication if the manuscript has been prepared in Microsoft Word or equivalent word-processing program.

When we accept the article for review, we will e-mail you a form which you need to sign, stating that you are the senior author of the article under review and that all tables and figures are either original or you have permission to reproduce them. We also need you to give us permission to publish the article in *Medical Journal of Therapeutics Africa*.

Send articles to: Dr SJ Dodgson, Editor-in-Chief
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***Photo courtesy of Mark Travis.***

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# THE EVOLUTION OF CLINICAL TRIALS

"A drug tragedy in Europe, the births of thousands of deformed infants whose mothers had taken the new sedative thalidomide, focused public attention on pending U.S. legislation to further strengthen the Federal Food, Drug, and Cosmetic Act. The Drug Amendments of 1962, passed unanimously by the Congress, tightened control over prescription drugs, new drugs, and investigational drugs. It was recognized that no drug is truly safe unless it is also effective, and effectiveness was required to be established prior to marketing ..... Drug firms were required to send adverse reaction reports to FDA, and drug advertising in medical journals was required to provide complete information to the doctor -- the risks as well as the benefits." from www.cfsan.fda.gov

If a manufacturer wants to sell a drug, device or vaccine for use in humans, the manufacturer has to convince the United States Food and Drug Administration that the product works the way the manufacturer claims, and any harm to humans is offset by greater benefits. The way the manufacturer proves this is through clinical trials.

According to the United States government website ClinicalTrials.gov, a clinical trial is "a research study in human volunteers to answer specific health questions". Clinical trials have been the tools for determining whether a therapy works better than nothing for decades, perhaps for millennia.

The first recorded clinical trial was of the biblical Daniel testing the effects of a diet of pulses rather than meat: "In the third year of the reign of Jehoiakim king of Judah came Nebuchadnezzar king of Babylon unto Jerusalem, and besieged it...And the king appointed [4 children] a daily provision of the king's meat, and of the wine which he drank: so nourishing them 3 years, that at the end thereof they might stand before the king...But Daniel purposed in his heart that he would not defile himself with the portion of the king's meat, nor with the wine which he drank [and said to the king]... Prove thy servants, I beseech thee, 10 days; and let them give us pulse to eat, and water to drink. Then let our countenances be looked upon before thee, and the countenance of the children that eat of the portion of the king's meat: and as thou seest, deal with thy servants. So he consented to them in this matter, and proved them 10 days. And at the end of ten days their countenances appeared fairer and fatter in flesh than all the children which did eat the portion of the king's meat. Thus Melzar took away the portion of their meat, and the wine that they should drink; and gave them pulse." (King James Bible, Daniel Ch1 ).

Daniel's requirement for food that differed from the munificent diet given by King Nebuchadnezzar follows the requirements for open-label clinical trials and was far more successful than most modern clinical trials.

The results from Daniel's unintentional clinical trial were clear cut and did not require imported specialist statisticians to prove that the sponsor's therapy was better than standard care; which is what I observed once when I was working as a medical writer in a small pharmaceutical company in New Jersey. This analysis did not impress the US regulatory body, the Food and Drug Administration (FDA), and the sponsor's new drug application (NDA) for marketing authorization was rejected.

The 3 phases of modern clinical trials are defined according to progression through development. These phases are defined by US statute. Posted on www.FDA.gov are the sections from the Code of Federal Regulations, Title 21, Volume 5.

Simply, the FDA wants to know when, why and how much of each new drug is given to any human. Phase 1 trial protocols are designed as part of the Investigational New Drug (IND) application with volunteers (healthy or with the indicated disease) taking defined doses of drug for a defined time to determine drug doses, pharmacokinetics and side effects of taking this therapy. When the new therapy is determined safe, volunteers with the disease which the new drug is designed to treat are enrolled in phase 2 clinical trials. They are either given placebo or drug. When the minimum dose for maximum effect is calculated, volunteers with the disease are enrolled in larger numbers in phase 3 clinical trials and given placebo or the optimal dose for a defined time. If the drug is still believed to be safe and effective after the 3 trial phases, and if the pharmaceutical company is ready to market the drug, all the documentation associated with development and clinical trials is packaged according to United States FDA requirements and a New Drug Application is filed.

Pharmaceutical therapies may be further tested after they are FDA-approved, these post-marketing clinical trials are known as phase 4 clinical trials. Phase 4 trials are also run by pharmaceutical company wanting to explore the effectiveness of their drug in treating diseases other than the 1 for which the FDA approved it (http://prsinfo.clinicaltrials.gov/definitions.html). Phase 4 trials can be risky: the results of a phase 4 trial of the pain reliever rofecoxib, resulted in its withdrawal from the market in September 2004, and, 6 months later, the withdrawal of another of its class, valdecoxib, from another

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pharmaceutical company.

I wanted to know how clinical trials progressed from being odd things that biblical heroes impressed potentates with to being complex and legal mechanisms by which all therapies and devices are tested. The James Lind Library, launched in 2003 by The Royal College of Physicians of Edinburgh, is an online resource for tracking clinical trials, www.jameslindlibrary.org. The first recorded clinical trial they report is the biblical Daniel's, the second was from 11th century China and the third from 16th century France. But the Edinburgh surgeon James Lind (1716-94) who investigated the best treatment for scurvy and from whom the library takes its name was probably the first person clinical investigator running a controlled clinical trial of the modern era

"On the 20th of May 1747, I selected 12 patients in the scurvy, on board the Salisbury at sea. Their cases were as similar as I could have them. They all in general had putrid gums, the spots and lassitude, with weakness of the knees. They lay together in 1 place, being a proper apartment for the sick in the fore-hold; and had 1 diet common to all, viz. water gruel sweetened with sugar in the morning; fresh mutton-broth often times for dinner; at other times light puddings, boiled biscuit with sugar, etc., and for supper, barley and raisins, rice and currants, sago and wine or the like. Two were ordered each a quart of cyder a day. Two others took 25 drops of elixir vitriol 3 times a day ... Two others took 2 spoonfuls of vinegar 3 times a day ... Two of the worst patients were put on a course of sea-water ... Two others had each 2 oranges and 1 lemon given them every day ... The 2 remaining patients, took ... an electary recommended by a hospital surgeon ... The consequence was, that the most sudden and visible good effects were perceived from the use of oranges and lemons; 1 of those who had taken them, being at the end of 6 days fit for duty ... The other was the best recovered of any in his condition; and ... was appointed to attend the rest of the sick. Next to the oranges, I thought the cyder had the best effects ...". Taken from Dr James Lind's "Treatise on Scurvy" published in Edinburgh in 1753, and quoted by Dr Peter Dunn (1997;76;64-65 Arch. Dis. Child. Fetal Neonatal Ed )

Dr Lind reacted to a problem which had not been in existence before improvement in sail engineering enabled ships to leave land and sail oceans and seas without landing for months. However, his interpretation of his clinical trial results was right in general and wrong in specifics; he concluded that citrus fruits prevented or cured, which is correct, but he suggested this effect was through their action on the digestive processes, which is not correct. How Dr Lind interpreted his results is irrelevant; after a lag of 50 years, directly because of James Lind, British sailors' rations included citrus fruits.(Cook DG. Postgrad Med J. 2004;80:224-229)

After the report of this scurvy trial in 1753, the number of reports of clinical trials increased. The number of clinical trials reported in journals indexed by the US National Library of Medicine has steadily increased since 1950, when "A controlled investigation of streptomycin treatment in tuberculosis" was reported by Long and Ferebee (Public Health Reports vol 65 pp1421-51). During 1974, 175 papers had "clinical trial" in the title and "controlled" in the keywords, this had increased to 215 during 1984, 715 during 1994, and 1,945 during 2004.

Clinical trials became required by law as governing authorities began recognizing a need for regulating pills, potions and ointments in the early 20th century. The FDA was founded in 1862 as a scientific institution and became a law enforcement organization after the US Congress passed the Food and Drugs Act in 1906. After that, legislation progressively demanded more accountability for marketing food and drugs, and clinical trials of drugs increased. The changes in the law are known as the Kefauver-Harris Drug Amendments 1962.

The increase in clinical trial data led to the increasing number of jobs for medical writers in the pharmaceutical industry in Europe and the United States. The downside of the increase in clinical trial data has been the lack of control of how these data are reported; in a 2005 article published by the European Medical Writers Association (emwa.org), I described the practice of guest authorship in which healthcare professionals claim authorship credit for medical journal articles which they did not write from data they neither collected nor analyzed. This article attracted the attention of a journalist from the Wall Street Journal, and an example I quoted was given in an article she wrote (Dec 13, 2005. p p A1). The dialogue continues as clinical trials generate increasingly more data.

Medical writers understand medical science, clinical data and the rules and regulations of their reporting. My hope is these pharmaceutical industry professionals will have more control in the design of clinical trials and in the analysis of the data.

***by SJ Dodgson PhD***

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# FLORENCE NIGHTINGALE

Florence Nightingale was born in 1820 and died in 1910. She was cosmopolitan at birth, her first name resulted from a 2-year honeymoon in Europe by her wealthy English parents. Her parents gave her the anglicized name of Firenze, the Italian city of her birth. Her elder sister was born in a Turkish city we know as Constantinople, their parents gave her the Greek name for the city, Parthenope.

Florence Nightingale's *Letters from Egypt*, on archive in the Florence Nightingale Museum, attest to her interest in at least 1 country in Africa. European-style African hospitals have been influenced greatly by her life, and her name affects children in Africa today through the Florence Nightingale International Foundation Girl Child Initiative.

The inaugural issue of *Medical Journal of Therapeutics Africa* would not be complete without recognizing the contribution of nursing to the international pharmaceutical industry.

## My Hero Florence Nightingale

Ever since I can remember my mother told me stories about bombs and St Thomas' Hospital in London in the 1940s when my father was a medical student and my mother a young physician. Particularly memorable was "bomb duty" when medical students were told to climb onto the roofs of St Thomas', look through the night skies for bombers and unmanned bombs, and sound the alarm when something flew towards them.

On my last night of a visit to London in 2004 I walked west along the Thames and found St Thomas' on the south bank immediately opposite the Houses of Parliament: undoubtedly a prime target for bombs. I could imagine that imprecise aim could land bombs on St Thomas'. This happened more than once after 1940. One night when my father was on "bomb duty" his fellow medical student was killed. Over 60 years later, I was quietly remembering the student whose life stopped where I was walking, and enjoying the thought that the lives of my brothers and I started because my mother could not resist my father in the backdrop of the drop-dead gorgeous views across the Thames, when I saw a sign for the Florence Nightingale Museum.

Back in Philadelphia I found the link between Florence Nightingale and St Thomas'. Miss Nightingale responded to her nation's call after William Howard Russell's *Times* report about soldiers who had survived bayoneting and musket fire only to die in the makeshift hospital in the old Turkish Barracks in Scutari, on the outskirts of Constantinople. The news reports so appalled the British public that Sidney Herbert, the Secretary at War, asked a family friend to organize a group of nurses and take them to the wounded soldiers. Miss Nightingale's letter volunteering to do so crossed with his in the mail, and Miss Nightingale was soon where she was needed most. For 18 months her administrative genius in organizing nursing personnel, supplies, evacuations and hygiene resulted in decreased mortality while she was dealing with jealous male medical personnel, an active war and increasing fragility from chronic disease. Deeply thankful British citizens donated £45,000 into the *Nightingale Fund.* The fund financed the Nightingale Training School and Home for Nurses which opened in the rebuilt and re-located St Thomas' Hospital.

***Florence Nightingale's life tells us that the impossible is possible, and that a single focused individual without suffrage, title and university degree can influence the lives of millions, probably billions.***

After occupying space in the south end of London Bridge from 1215 until 1862, St Thomas' was reopened on its present site in 1871 by Queen Victoria (King's College London College Archives). St Thomas' was rebuilt with input from Miss Nightingale according to the principles of hospital design she described in her book *Notes on Hospitals*. The architect of the new hospital building, Sir Henry Currey, was a supporter of the "pavilion plan" of hospital design, which Miss Nightingale wrote was essential for correcting the 4 basic defects of hospital design which can be summarized as 1. Sick patients jammed together, 2. Limited space to move around 3. Limited ventilation and 4. Limited light. According to Dr GC Cook, Sir Henry's biographer, after Miss Nightingale's move into public consciousness the "pavilion plan" was widely accepted in British hospitals and coincided with greater inpatient survival (Postgraduate Med J 2002 78:352-9).

Nurses trained at St Thomas' were known as Nightingales, and when I visited the Florence Nightingale Museum in 2005, the frighteningly formidable, cheerful and well-groomed short lady volunteering behind the counter introduced herself as a Nightingale, which solved another riddle. On my fifth birthday in Manchester I was given a nurse's outfit, which I wore the rest of the day and wanted to forever. A red cape, a starched white cap and apron - gorgeous. My declaration that I wanted to be a nurse resulted in my mother standing me on her bed and telling me that I had better always remember this: no daughter of hers would ever be a nurse. My father smiled and shook his head: not a good idea. I concluded for years that my parents thought nursing was beneath my talents. I now understand that

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they spent the years of their professional training terrified by Nightingales and they were not about to incubate one in their own home.

Florence Nightingale was terrifying, how else could she have moved politicians and founded not only nursing but health administration, and changed hospital architecture? I believe she was also the first post-industrial medical writer, and the first modern hero of the medical writing profession. She excelled in regulations, statistics, and healthcare, and pretty much everything we teach our graduate students in the Biomedical Writing Programs. Like most medical writers, Miss Nightingale was mostly self-taught; she had started her career after soaking up all the education in nursing and mathematics available to a female with enlightened and wealthy parents. She left behind 200 publications detailing everything needed in a hospital for patients to survive their stays anywhere. In 1860 Miss Nightingale was the first woman elected Fellow of the Statistical Society for her contribution to army statistics and comparative hospital statistics. She was also a consultant in India without ever leaving London. My favorite papers, published in 1864 and 1874, she entitled *How People May Live and Not Die in India* and *Life or Death in India: With an Appendix on Life or Death by Irrigation.* She did not write about clinical trials, but clinical trials could not have become a part of healthcare without her work.

Miss Nightingale defined the nursing profession as no other profession has been defined before or since in her book published in 1860: *Notes on Nursing: What It Is and What It Is Not.* Women were not permitted to train as physicians in St Thomas' in 1871. They were only permitted to train in 1949, 5 years after my mother was hired as a young physician from Ireland. Miss Nightingale was not however defining a profession subordinate to that of a doctor but rather a parallel profession for women based on hygiene and hand-washing, concepts unknown to medical practitioners until Dr Ignaz Semmelweis suggested that they might be useful.

***Houses of Parliament in London from St Thomas' Hospital. Photo SJ Dodgson.***

The idea that hygiene was invented in the mid 1800s is nonsense. According to Mrs Mary Seacole's account of her work as a doctress in the front of the battle in the Crimea, her success in keeping her wounded soldiers alive resulted largely from learning from Jamaican traditional healers, including her mother, about the need for cleanliness in food and water and around the sick bed. Mrs Seacole's efforts in healthcare were heroic, her willingness to stay at the front of the battle and her lack of monetary award for her service despite her high connections, notable. She was not, however, a medical writer, hospital administrator or statistician. She was also not born wealthy; and, like most humans, was not a single-minded genius like Miss Nightingale. I recommend her book *The Wonderful Adventures of Mrs Seacole in Many Lands* which I bought from the Florence Nightingale Museum.

Many lessons can be learned by medical writers as we work together to define another new profession 150 years after Miss Nightingale's heroic achievements in the public eye. Miss Nightingale never had a hint of scandal, no breach of ethics, and she never took money to endorse a product or therapy. Until her death at 90, she was mostly an invalid, rarely seen in public, writing her many books and papers in her bed, and yet her audience was huge and paid attention to what she said. Even now, 97 years after her death, I find in the US National Library of Medicine hundreds of papers referring to her continuing influence on healthcare and healthcare institutions named after her in Turkey and London.

All these years after modern communications caused a public outcry which forced the British Government to legitimize a profession that had been around since babies were born to humans, Florence Nightingale's life tells us that the impossible is possible, and that a single focused individual without suffrage, title and university degree can influence the lives of millions, probably billions.

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***By SJ Dodgson PhD***

***Florence Nightingale International Foundation Girl Child Initiative at www.fnif.org***