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Journal of Nigerian Medical and Dental Consultants Association of Niger Delta University Teaching Hospital

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Content Pages

EDITORIAL: THE NEW FACE OF NDMJ

Tubonye C. Harry, FRCOG, FRCP, FWACS
Editor-in-Chief

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The rejuvenated NDMJ is now online. This has been a bold step on the part of the newly reconstituted editorial board. The current work-plan for the NDMJ is to aim for quarterly publication of hardcopies but publications ahead of print online.

The intent is to bring medical research real-time. Our peer-review process is rigorous and timely. Mean time of receipt to acceptance is 31 days.

In this current edition we have the Lead International Editorial Board member sharing with us a digest of his career as an obstetrician and gynaecologist in the Niger Delta culminating as a Vice-Chancellor and a trainer cum mentor to many. A lot to learn from this commentary[1].

The NDMJ will be publishing in part the Dean's Lecture series, an excellent initiative sponsored by an Educational Grant from Pfizer Pharmaceuticals. In this edition we have published excerpts of the 2nd Pfizer Guest Lecture[2], and others in the series[3,4,5,6].

There will be a mix of original articles, review articles, commentaries, case reports and audit reports. News items relevant to practice will be periodical excerpted in the journal with the relevant copyright permissions were applicable.

A charge of $50.00 processing fees is proffered to sustain our policy of open access.

The NDMJ is non-profit under the management of the Medical and Dental Consultants Association of Nigeria, Niger Delta University Teaching Hospital, Okolobiri Chapter. None of the Editorial Team receive any form of remunerations.

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WE REAP WHAT WE SOW.

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University of Medical Sciences, Ondo

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SUMMARY

This is an account of the work of Kelsey Harrison given by the man himself (1933 -), a pioneer undergraduate at University College Ibadan (1951-55), an obstetrician and gynaecologist, a researcher, a teacher, a relief worker during the Nigerian civil war of 1967-1970, a sort of social activist, and a cricket fan. At University of Ibadan in the 1960s, his researches were focused largely on the elucidation of how severe anaemia affects the mother and her baby. The results of this work led to the world-wide adoption of the treatment of this life threatening condition by the use of rapidly acting diuretics combined with direct blood transfusion instead of by the more elaborate and costly exchange blood transfusion. At Ahmadu Bello University (ABU) Zaria, his work analyzing 22,774 consecutive deliveries from 1976-1979 at ABU Teaching Hospital and published as a supplement to the British Journal of Obstetrics and Gynaecology (BJOG) in 1985 turned out to be a major factor in the launching of the global safe motherhood movement. At University of Port Harcourt (1981 – 1998) where he became that university's vice chancellor, his powerful advocacy for better health for women was important and the ideas therefrom are still hugely relevant

INTRODUCTION

Coming under the influence of many good people, as I did, I went into medicine, specialized in obstetrics and gynecology, and then took to practicing, teaching and researching. Fellow Nigerian colleagues and I were all pioneers, whose working life coincided with some great events in our country and in international maternal health. It is some of these events and my own contributions that I wish to share with you believing as I do that this sharing of experiences especially in a budding university community is important for various reasons, not least, the acquisition of knowledge for improvement of our society. We reasoned that the correct application of information generated through our research in Nigeria, would lead to improvement in the health of our women. This then is an account of some research seeds, how we acquired the seeds, how they were planted, how they grew into fruition and who benefitted. We reckon that we led an interesting life. The events are told in two of my books. One is an autobiography (1), and the other is a compilation of some of my research publications from 1966 to 2010 (2).

MY MENTORS

I count myself fortunate in having many mentors in my career. Eight were outstanding.

Ethel Taylor of Abonnema was my mother. She told me in my early teens why she preferred hospital based maternity care available at Aba, in Abia State to local traditional birth attendants (TBA) at Abonnema in Rivers state. She died aged 91 years in 2001.

Chief Anthony Karibi Bob Manuel of Abonnema was my surrogate father, a top man in the administrative arm of the colonial civil service in the 1920s and 1930s. His archives drew my attention to the success of the Church Missionary Society in reducing maternal mortality in its area of influence in parts of Eastern Nigeria in the 1940s (3). He died in 1972 aged 92 years, heart broken by our bitterly fought civil war of 1967 - 1970.

William Simpson, an Englishman, was in charge of Umuahia Government College, where I received my secondary education from 1946 to 1951. He counselled me successfully to study medicine, not civil engineering, my preferred choice when I was a teenager. He went to great lengths to inculcate modesty and character building as the two previous mentors did. He died in 1959 at his home in UK aged 58.

Dr. Mason Thomas Dokubo Braide of Bakana qualified as a medical doctor in Glasgow University. He spent his entire career in various capacities in the Nigerian Civil Service. Touched by the awful state of women's health, he singlehandedly collected data on over 2000 women in Eastern Nigeria. Some were circumcised, the rest were not. He compiled his observations into a thesis and was awarded the Doctor of Medicine degree by his alma mater in 1956. He titled it "a study of female circumcision in Eastern Nigeria: its medical significance". In it, he identified female circumcision in these words: "*It is a custom that causes a lot of suffering and ill health in African women. It is a custom that is bound to affect the span of life of African women adversely, on account of the associated obstetrical and gynaecological complications. It has brought misery and unhappiness to many husbands and wives. When critically analyzed, the practice has nothing to support the claims by its protagonists to perpetuate it. It is a primitive and barbaric custom. I condemn it in its entirety.*" The world bodies he then appealed to act to banish the harmful custom did nothing until now over 50 years later. Incidentally, the first caesarean operation I saw performed was by him at Obubra General Hospital in rural Eastern Nigeria in 1953. It was for the relief of obstructed labour and was successful. He died in 1995 aged 82 years.

John Bateman Lawson was the foundation professor of obstetrics and gynecology at University of Ibadan from 1953 to 1969. Later as Vice President of the Royal College of Obstetricians and Gynaecologists in London (RCOG), he was responsible for overseas affairs at the College. Generations of health care workers in and outside UK benefitted enormously from his work towards the betterment of women's health in developing countries. Women with vesico vaginal fistula (VVF) have cause to be grateful to him. He died aged 75 years in 1997.

William Charles Wallace Nixon was professor of obstetrics and gynecology in University of London at University College Hospital. A thoughtful and humane man, who, while I was a London undergraduate medical student, helped to groom me towards what I eventually became. More importantly, he personally taught trained and researched towards improving the welfare of women from all back grounds. He initiated and directed the 1958 National Perinatal Mortality Survey of England and Wales. It was the first of its kind and it led to many changes nationally and worldwide, in maternity care. He died aged 62 years in 1966.

Frank E. Hytten is an Australian, a qualified medical doctor, a pioneer and top researcher and writer in the field of Human Reproductive Physiology. He is judged to be the most influential editor of the BJOG. Now aged 92, he and I still keep in close touch.

Finally, there was Niilo Hallman, a Finn. He was Professor of Paediatrics at University of Helsinki in Finland. While serving in that capacity, he became the moving spirit in the modernization of the Finnish health system. In later years, his support for the creation of maternal and child health clinics in rural Africa became legendary, and in the case of Zaria, the support came always when it was most needed. He died in 2011 aged 94 years.

THE IBADAN YEARS 1960 – 1972

My time in Ibadan began with me as one of only three house officers in the 107 bedded department of obstetrics and gynecology at University College Hospital (UCH), and ended when I rose to the post of a professor in the same department, and left. The department handled about 3000 deliveries annually with a large proportion of complicated deliveries. Consultant staff strength was never more than six. The facilities provided were sufficient to allow us to cope, although we were occasionally stressed.

The subject of maternal deaths dominated much of the department's activity. We all realised that the death of a woman during pregnancy, labour and / or soon after her delivery, from largely preventable conditions, was awful. The medical causes were anaemia, complicated abortions, obstructed labour, eclampsia, infections, and hemorrhage or excessive bleeding. Severe anaemia was by far the commonest cause of maternal death. Lawson, our chief, encouraged a multidisciplinary approach to the study of the subject.

These studies revealed that poor nutrition especially folic acid deficiency, malaria and sickle cell disease were the principal causes. When anaemia became extreme, exchange blood transfusion, not straight blood transfusion, was needed to raise the low haemoglobin level quickly without killing the patients through overloading the failing anaemic heart. But exchange blood transfusion was too complicated and costly to set up and use in rural settings where the patients first reported for treatment. While I was still a house officer, I suggested that a group should be tasked with the responsibility of undertaking rigorous research to look for a simple method of transfusion to replace the complicated exchange transfusion. The small group made up of me and Mr. A. I. Kadiri, the senior laboratory technologist of the department, measured the major changes in the circulation severe anaemia produced (4) and in the end, devised the method of combining direct blood transfusion with a rapidly acting diuretic, ethacrynic acid. It worked as well as exchange transfusion (5) which it has since replaced worldwide. Frusemide is now preferred to ethacrynic acid.

Two years later, we showed for the first time that anaemia in the mother impaired the growth of her baby in the womb, and that the correction of the anaemia during pregnancy led to catch-up growth of the baby (6); an issue of enormous public health interest in and outside this country. Meanwhile, collaborating with haematologists and morbid anatomists we observed, carefully documented, and reported the dangers of sickle cell disease during pregnancy, and how to treat them (7). An important offshoot of these endeavours was the establishment of a quality research laboratory for the department of obstetrics and gynecology in 1970. I believe it still thrives.

While we were still based in Ibadan, there were other fruitful activities. One was the care we took of poor village women in and around University of Ibadan in illustrating how to run a community based maternal health service properly. Another was the pioneering of the use of anti-cancer medicines in treating one particular rare cancer in women - malignant trophoblastic disease. Suffice it to say that these and other additional duties made heavy demands on our time, but we still managed to carry out our routine clinical and teaching duties without compromising ourselves.

It has to be said that in Ibadan living and working conditions in terms of availability of facilities, and supporting infrastructure and personnel were almost at par with what I experienced during my undergraduate medical training in London from 1955 to 1959. The basic elements needed to take care of ourselves and look after the patients were provided and they functioned properly. All in-patients were hospital fed and without charge. Nursing standards were high. The whole place was vibrant, racially mixed at work and in private, with blacks, whites and Asiatic. Rented accommodation provided by both the university and its teaching hospital was good. There were no mobile telephones in those days, nevertheless, communication was not too bad. Outside, other forms of support such as facilities for children's education and recreation were good and easily affordable. We even made out time to resume playing cricket for Nigeria and went on tours to Ghana, Sierra Leone and Gambia. Throughout, hospitality on and off the fields of play was lavish. We were full of joy.

THE ZARIA YEARS 1972 – 1981

In 1972 I received the invitation to come to Zaria to replace Professor Jocelyn Moore, an elderly British lady in charge of the department of obstetrics and gynaecology. There, the acute shortages of everything and the sight of large number of women having their babies under intolerably bad conditions, with too many dying, were our constant worry. We vowed to bring about improvements based on the real needs of these women and their newborn babies. To this end, over 3 years, (1976-1979), my team and I obtained detailed information from all 22774 mothers who delivered at our hospital or were admitted there soon after delivery elsewhere. The mothers were from over 120 different ethnic groups, and half were Hausa - Fulani. The youngest was only 9, and the oldest was 50. The shortest was 1.16 metres in height, and the tallest was 1.93 metres. Some of the mothers had had over 24 previous deliveries. The singleton babies produced weighed 3.08 kg on the average. There were also twins, conjoined twins, triplets and quadruplets. There were 238 maternal

deaths and 2718 perinatal deaths giving an overall maternal mortality ratio of 1050 maternal deaths per 100,000 deliveries, and a perinatal mortality rate of 116 perinatal deaths per 1000 babies born. The principal medical causes of death were the same as in Ibadan and elsewhere in Nigeria, only that the delay on the part of the women in reporting to hospital for effective treatment made things very much worse. I should add that unlike Ibadan, complicated abortion was very rare.

More importantly the survey revealed that non-medical factors contributed hugely to the very bad situation. These non-medical factors were those which acted in combination, and made it impossible for women to have decent medical and obstetric care when they needed them. They included poverty, lack of formal education, adverse cultural, ethnic, and religious influences, inadequate health and physical infrastructure, and poor logistics. Having established these myriad of factors responsible for much of the huge loss of life among the mothers and their newborn babies in that society, and backed by the results of the analysis of these "unique and valuable data" obtained, we concluded that the real problem to be faced was not so much medical as sociological, and that universal formal education is *the* important key towards the needed solutions (8). Our findings were published as a special supplement to the October 1985 issue of the BJOG titled "Child-bearing, Health and Social Priorities: A survey of 22,774 Consecutive Hospital Births in Zaria, Northern Nigeria. Supplement 5." (9) It ran into 119 pages in 14 chapters, with tables, figures, and appendices totaling 129. From conception to publication took 13 years.

Besides, high maternal mortality, another worrying issue was the scale and severity of the horrific injuries some women sustained during unsupervised complicated deliveries at their homes. By far the worst of these injuries is VVF, a condition whose victims continuously leak urine through their vagina wetting their lower limbs from buttocks to toes, day and night. VVF carries with it, serious reproductive, social and economic consequences which the work of a dedicated sociologist in Zaria, the late Dr. (Mrs). Margaret Murphy, a Scot, helped to unravel in great detail (10, 11). VVF occurs all over Nigeria, but it is commonest in the North. The basic fault is that in the affected women the space in the bony birth canal through which the baby has to pass during labour is too narrow. In consequence labour becomes prolonged and difficult, with high risk of damage to the surrounding soft tissues in and around the vagina. But why is the space in the bony birth canal too narrow? The answer is that two basic entities are involved. The first is that the girls are not allowed to finish growing before childbearing starts. The second is that even when maturity is reached in terms of age, bony growth is hampered by the harsh conditions under which people have to live: there is poor nutrition, bad housing, frequent infections, and excessive physical work. More will be said about VVF later.

An original discovery made was that of growth during pregnancy in early teenage girls who had not finished growing when they became pregnant. Malaria and anaemia prevention by the use of antimalarial drugs, and iron and folic acid tablets taken throughout pregnancy made these underage girls grow even faster, with some having growth spurts during pregnancy. We reasoned that if the growth enhancing effect of antimalarial and anti anaemia measures is confirmed, it can become a way of preventing VVF in this country.

One would not have thought that information on stillbirths would open up important insights into the consequences of socio-economic deprivation. But it did. In Zaria, initially, there was strong opposition to the weighing of dead babies for cultural reasons. Eventually we arrived at a compromise. We provided separate sets of baby weighing scales, one set for babies born alive, another set for babies born dead and with torso intact, and the last set for babies born dead and with mutilated torso. We discovered that among babies born after prolonged labour had resulted in VVF the stillbirths were on the average much heavier than the live births. In all other situations, the reverse was the case in that stillbirths were lighter than live births. This reversal of the pattern of birth weight distribution in VVF carries implications.

One of such is the long-term consequence of pelvic contraction. In the growth-stunted adult woman, pelvic contraction is permanent. When she gets pregnant, her baby at term will either be small or big. If small, easy passage through the contracted pelvis will result in the birth of a small baby.

If her baby is big, the result is different. In this case, labour will be difficult, it may become obstructed which if neglected, results in damage to both mother and baby. The danger can be averted by timely caesarean operation with the birth of that big live baby. If the obstruction is allowed to persist for whatever reason, it will result at the end, in the birth of a baby of good size that is either born dead or born alive but severely damaged.

It is well known that in general, heavier babies are superior to their lighter counterparts in terms of their potential for growth and physical and mental development. We therefore postulated that in a population where obstructed labour is common, the surviving babies might not be the best babies. Furthermore, because of the bad conditions in which those inferior babies are reared – bad housing, no prevention against infection, excessive physical work, and bad nutrition – these inferior babies in their adulthood become growth stunted, and give birth to more damaged babies. So the end result of pelvic contraction is damaged babies that grow up to be damaged adults who in turn produce the next generation of damaged babies. Obviously, emergency obstetric care cannot break this horrible cycle because it does not correct the underlying fault, which is pelvic contraction. Only fixing the politics and sustaining the needed social change, will. For as long as the cycle is allowed to persist, there is this dreadful thought that superior babies die, and inferior babies survive. This thinking is only a hypothesis, but in the prevailing circumstances in Nigeria, it sounds plausible.

The overall message from this Zaria Maternity Survey is that there are four key factors for banishing maternal mortality and morbidity. First, living conditions must improve to the point at which the vast majority of people are healthy. Second, all pregnant women must receive basic but professional antenatal care. Thirdly, measures must be taken to ensure that pregnant women who develop life-threatening complications get effective treatment if necessary operative interventions, before it is too late. Fourthly, records must be kept for audit and other purposes.

BEYOND IBADAN AND ZARIA

Major events that affected the whole of Nigeria happened in the years I lived and worked in Ibadan, Zaria and Port Harcourt. These events impacted on our work and living conditions, and on the living conditions of the society at large. In the 1960s and 1970s, there was first the Nigerian civil war, and second, the great Sahel drought. In the 1980s, it was the effects of the adoption of structural adjustment programmes (or SAP for short).

Our civil war did much damage throughout the Eastern Region. Before the war, there were impressive human and infrastructural investments. During the war, these developments were halted and some were completely wrecked. Afterwards, support was needed to start afresh as it were. I became a relief worker. In the process, though still on the payroll of Ibadan University, I voluntarily gave the needed expert assistance on the spot in Port Harcourt in rebuilding the maternity services that had been destroyed through military action. Furthermore, partly through our efforts, the government of the Rivers state established the Rivers State School of Nursing and Midwifery.

Nigeria next lurched from a man-made disaster which the civil war was, to a natural disaster. There was severe drought in the entire Sahel region of West Africa including Nigeria. For the best part of 1970s, crops and livestock production failed, food became scarce, and food prices being uncontrolled rose sharply (12).

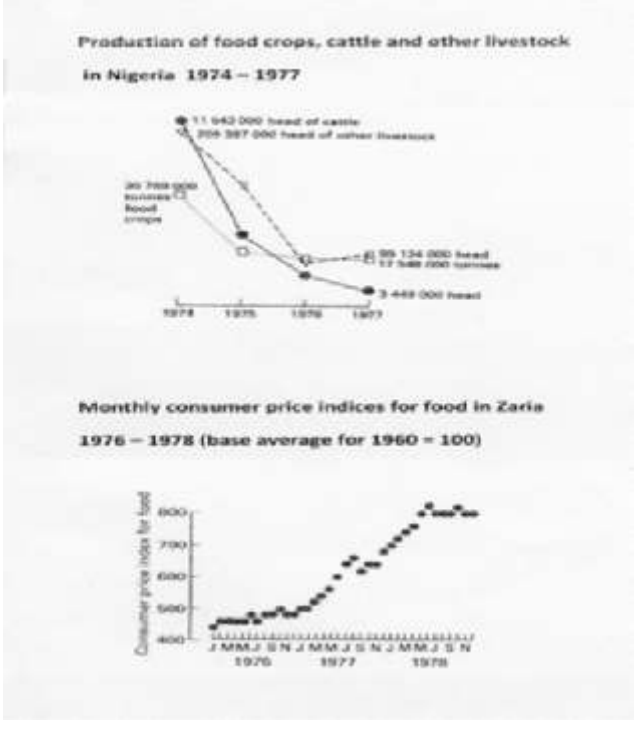

Figure 1 PRODUCTION OF FOODCROPS, CATTLE AND OTHER LIVE STOCK IN NIGERIA 1974 – 1977 AND MONTHLY CONSUMER PRICE INDICES FOR FOOD IN ZARIA 1976 - 1978 (BASE AVERAGE FOR 1960 = 100).

In fact, at the height of that period of extreme economic hardship - June to August 1977 - the price of staple foods suddenly doubled. For example, yam sold at 50 kobo per kg whereas before, it was 30 kobo per kg: cow meat was N3.3 per kg whereas before, it was N1.7 per kg. A similar pattern of price fluctuations was reported for beans, garri and to a lesser extent guinea corn. Looking at our Zaria data, we observed that the proportion of low birth weight babies being born also rose from around 23% to 40% for a subset of the population (12).

Table 1. RETAIL PRICES OF STAPLE FOODS AND FETAL BIRTH WEIGHT IN ZARIA. JANUARY 1976 TO DECEMBER 1977.

Staple Food Prices and Fetal Birth Weight in Zaria. January 1976 -December 1977

	Jan 76 - June 77	Sep - Oct 77	Nov - Dec 77
Price of Yam in kobo per kg	25	50	< 50
Price of Cow Meat in Naira per kg	1.6 -1.9	3.3	< 3.0
% Low Fetal Birth Weight	17 -23	40	23

Data from Port Harcourt showed the same trend though less marked. If these data from these two centres represent what happened countrywide at that time - late 1970s - then one might argue that since the damage from acute food insecurity can be passed on to children of the future, Nigeria must have been in trouble from this cause (too many low birth weight babies) and its consequences for decades later. The consequences are well known: they are irreparable brain damage, with delayed motor and social development, and learning difficulties, among others. Above all, the whole thing warns us that action or inaction today has long term impact.

So, of the three national disasters that befell us in 1960s to 1980s, I have discussed two, namely civil war and drought in the context of reproductive health. I now go on to the third, namely, SAP.

STRUCTURAL ADJUSTMENT PROGRAMMES

From the perspective of those of us who have to deal with maternity care in developing countries, the World Bank and International Monetary Fund promulgated Structural Adjustment Programmes (SAP) are not something we can ever forget. In the 1970s, like the rest of sub Saharan Africa, Nigeria got itself into serious economic difficulties. The existing fiscal arrangements were no longer able “to balance the books”. So, beginning in the 1980s, SAP (13) was introduced for the stated purpose of halting poverty, and for paying the debts owed to our creditors, mainly powerful international banks abroad. But SAP policies were prejudiced against social welfare. Hence, their implementation helped to precipitate the sort of catastrophe in which virtually all social, educational, economic and public health gains made in the 1960s were wiped out. Weakening of government structures, reduction of state machinery, drastic reduction in the size of the public sector, worker retrenchment, increasing private sector involvement, devaluation of the naira, and charging of user fees for cost recovery in health care were all part of SAP. The consequences were damaging. Socioeconomic inequality widened, a tiny few got very rich, while the rest became very poor. The scale of impoverishment was huge and was of a magnitude never seen before by most adults. It became even more offensive as corruption levels soared. The results on maternal and child health and education in Nigeria were catastrophic, and till today, over 30 years later, full recovery is nowhere in sight. In terms of maternal mortality and morbidity, data from Zaria revealed what happened when user fees began to be charged (14). In 1983 when hospital treatment was free, the number of hospital deliveries was 7450, nearly 20 % were complicated labours, and there were 48 maternal deaths. In 1988 when user fees began to be charged in full, the number of hospital deliveries dropped to 2991, the proportion of complicated labours rose to 63 %, and the number of maternal deaths rose to 75. The experience in Port Harcourt where I was then based was even more terrible. The cost of an uncomplicated caesarean

section was equivalent to nine month's average salary, and there were no proper records kept of the fate of those unable to afford the payment demanded by the hospital authorities. The truth was that women were dying in the hands of good doctors because they could not pay the user fees charged. Unclaimed corpses piled up in front of UPTH mortuary as impoverished relatives were not able to afford the fees charged to claim the corpses of their loved ones. Public education probably fared worse. All in all, it was a sorry sight, and one I would never wish on any institution or country.

PORT HARCOURT YEARS AND BEYOND 1981 –

The years we were based in University of Port Harcourt (1981-1998) were the most difficult. I was the university's vice chancellor for 3 years only (1989-92). Throughout, provisions for staff and student accommodation and academic work were grossly inadequate, and the increasing activities of the secret cults meant more insecurity. Even so, we made out time for the promotion of advocacy for better maternal health in developing countries. With generous sponsorship from several donor agencies, we travelled widely within and outside Nigeria acting like town criers on this issue of how to make women's lives better.

Within Nigeria, the Nigerian National Task Force on VVF was formed in July 1990. It was initially led by Amina Sambo from Kano. I succeeded her as President in 1996. We were 15 members initially. The task force which later became National Foundation on VVF worked to increase advocacy and to building of the needed capacity to deal with thousands of women with VVF awaiting surgical repair and rehabilitation. Support came initially from Ford Foundation, joined later by the Federal Ministry of Health, and other philanthropic groups. Since then, the WHO and other powerful international organisations and many donor agencies have taken over this concept and extended it to some African and Asian countries.

Next we facilitated an important UK Government sponsored joint project between Liverpool School of Tropical Medicine and University of Port Harcourt with Professor N.D. Briggs as its local coordinator. Based at K-Dere in Ogoniland, it was on the nature and pattern of non-fatal illnesses in women. Although the project ended nearly two decades ago, the University of Port Harcourt still benefits from it.

Then, there were the numerous invitations to write and publish. Among them, one gave me the greatest pleasure. It was an editorial for the African Journal of Reproductive Health on its debut in 1997 (15). It was titled “Maternal Mortality in Nigeria: the real issues”. Since then, under the competent editorship of Friday Okonofua, the influence of this journal continues to grow, whereas some other Nigeria-based journals have packed up.

THE GREATEST SEEDS AND HARVESTS

World reacts to the results of the Zaria Survey. International health experts reacted very quickly to the results of the Zaria Survey. Within one month of the publication of these results, WHO summoned its first interregional meeting on the prevention of maternal mortality. The purpose was to raise world awareness of the problem and how to tackle it. I noticed that at the meeting which took place at the headquarters of WHO in Geneva, each of us 40 or so participants from over 25 countries received a free donation of the published Zaria Maternity Survey. And in February 1987, the World Safe Motherhood Initiative was formally launched in Nairobi, Kenya. The aim of this initiative was to help reduce the existing high levels of maternal mortality and morbidity world - wide especially in developing countries. Empowering women, the setting up of efficient antenatal care, working referral systems, and emergency obstetric care, and an increased acceptance of family planning were seen as the corner stones for improving reproductive health. Its implementation gave fairly good results elsewhere but not in Sub Saharan Africa and most certainly not in Nigeria, where estimated maternal mortality ratio still exceeded 600 per 100,000 births. When progress became painfully slow, a rethink took place at the highest international level. Heads of UN agencies, development partners, research funders, and health foundations met and were confident that things could work better and that achievement through fresh goals was possible.

UN Millennium Development Goals 2000 replaced the safe motherhood initiative, but the truth was that we were stuck. There was not much to show for the combined efforts made by national and international bodies. By then I had left Nigeria for Finland on retirement but received regular information on the state of maternal health in Nigeria.

WE WERE STUCK

In faraway Finland, news kept reaching me that the poor state of maternal health at home had worsened. Trust in conventional maternity care was severely eroded. Good organization and proper communication between those concerned in maternity care had all but disappeared. In this tough situation, more and more of our women who could afford the cost travelled abroad to have their babies. Those who could not afford the cost remained at home but increasingly put their trust in TBAs, Pentecostal churches, and even faith healers. I felt rage and anger for our expectant mothers.

Something had to be done. On Africa Day 23 March 2007 at the Royal College of Obstetricians and Gynaecologists in London I presented a very short paper titled "Thoughts on making safe motherhood work better". In it, I expressed my concerns over the deteriorating situation in maternal health. All the efforts being made were coming to naught. I gave what I thought was the most important reason why: simply put, we are looking at and dealing with the wrong end of the problem of high maternal mortality and morbidity.

THE UNDERLYING DISEASE IN NIGERIA

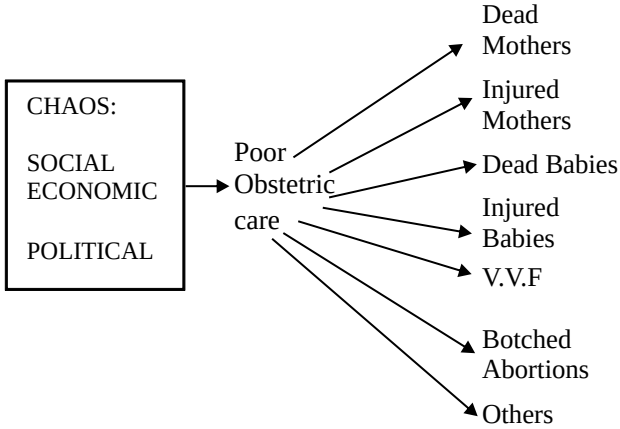

FIGURE 2. CHAOS: THE UNDERLYING DISEASE IN NIGERIA

Dead and damaged mothers and infants make up a cluster of conditions resulting from one thing, very poor obstetric care. Very poor obstetric care is, in turn one result of the chaotic health, socioeconomic and political systems, which is the major underlying disease. It is the disease, which has to be treated. Hence, the need is to turn things round to ensure that most things in the public domain work to the general benefit of society.

During this lecture in London older top people present recognized that we in Nigeria were in the same situation as we were in 1979 when I spoke on the same subject at that same venue. It meant we had worked and published on this subject for nearly 30 years yet there was little on the ground in Nigeria to show for it, except perhaps unregulated private practice, which is part of the chaos, mentioned earlier.

It is clear than an individual no matter how energetic, no matter how dedicated, can succeed without support from like-minded followers. So my hope is in the coming generations. But things can change quickly, and they have in Ondo.

SUCCESS AT LAST: ONDO UNDER GOVERNOR MIMIKO'S LEADERSHIP

Dr. Olusegun Mimiko, a trained physician and politician became the governor of Ondo State in 2009. He then declared loudly and with absolute conviction that improving social welfare, including education, and reducing deaths of women and children would be among his priorities. The policies and strategies would be aimed at the removal of barriers to safe motherhood. Attention would be paid to the avoidance of delays encountered by pregnant women in seeking, reaching and receiving quality health care at both primary and secondary levels. He would provide skilled personnel for government health centres and hospitals, and ensure that through efficient administration of the resources provided, the results would improve. The promise was kept and the results exceeded my highest expectations in that maternal mortality ratio dropped from one that was above the average for Nigeria (600 per 100,000 deliveries) to around 100 per 100,000 deliveries. There is still a long way to go compared to the results elsewhere, for example,

Finland, where the ratio is 5 maternal deaths per 100000 births. Nonetheless, a break-through has been achieved. Governor Mimiko's administration has transformed ideas into actual deeds. This ground breaking achievement is worth celebrating but at the same time we should also see it as having brought pressure on all sectors of health care in this country to do their job. So, henceforth, this can no longer be regarded as mission impossible.

CONCLUSION

Finally, permit me to end on a somewhat personal note. Please do not for one moment assume that there were no mistakes that were made along the path we carved out for ourselves. On the contrary, there were plenty, and indeed, some were inevitable. However, on this occasion, we ask you to join us in marking and celebrating the successes achieved. The overall point is this: individually or collectively, and in life, we reap what we sow.

ACKNOWLEDGEMENTS

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THE ELECTROCARDIOGRAPHIC "LEAD 1 SIGN" AS AN INDICATOR OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE – REPORT OF 2 CASES.

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ABSTRACT

Two patients with chronic obstructive pulmonary disease (COPD) who had the "lead I sign" are described. The "lead I sign" is a highly specific ECG marker of chronic obstructive pulmonary disease (COPD) and has been rarely documented in any other condition. The diagnosis of chronic obstructive pulmonary disease should strongly be suspected when the "Lead I sign" is present even in the presence of cardiac disease.
In resource poor settings where investigative procedures and equipment are a rarity the 'lead 1 sign' will be very helpful in the management of COPD patients.

Key words: "Lead I Sign", Chronic Obstructive pulmonary Disease (COPD), Electrocardiograph (ECG).

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a common illness among Nigerians[1, 2, 3]. The respiratory and cardiovascular systems are so intimately related that changes in one sooner or later cause changes in the other. Functional and structural changes of the respiratory system greatly influence cardiovascular functions in patients with COPD[4]. Some studies reported changes in the activity of the heart including P-wave axis and amplitude, rightward displacement of QRS and T-axis, reduction of amplitude of QRS complex in limb and precordial leads, sinus tachycardia, right bundle branch block (RBBB) among COPD patients[5, 6]. In clinical practice, COPD is defined by its characteristically low airflow on lung function test[7].

COPD influences the electrical events of the heart in the following basic respects[8] – the voluminous lung has an insulating effect and thereby diminishing the transmission of electrical potential to the registering electrodes. The heart descends to lower position due to lowering of diaphragm. This will alter the position of heart relative to the conventional precordial electrode positions. The right ventricle and right atrium becomes compromised due to a reduction of pulmonary vascular bed.

This will result in right ventricle hypertrophy and dilatation as well as right atrial enlargement.

The typical ECG changes in COPD are (1) prominent P waves in leads II,III and aVF (2) rightward shift of the QRS axis in frontal plane (3) poor progression of the R wave in the precordial leads (4) low voltage of the QRS complexes especially in the left precordial leads, and (5) the "lead I sign".

In patients with COPD, the frontal plane P, QRS and T wave axes are not infrequently directed at around +90. However, they are directed precisely or almost perpendicular to the standard lead I axis. As a result, lead I reflect either absent or very low amplitude P, QRS, T wave complexes giving the appearance of a minimally disturbed baseline. This ECG phenomenon is known as the 'lead I sign". The "lead I sign" is a highly specific ECG marker of chronic obstructive pulmonary disease (COPD) and has been very rarely documented in any other condition[7].

In 1965, Fowler and co-workers reported 15 patients with severe pulmonary emphysema with cor-pulmonale and found 5 of them (33%) showing the "lead I sign". They went ahead to propose very strict arbitrary criteria for the diagnosis of the "lead I sign". These were the presence of isoelectric P wave in lead I combined with a very small QRS complex of less than 1.5mm total deflection and a T wave of less than 0.5mm in lead 1[9]. ECG changes in COPD and their possible mechanism include (1) low voltage graph (QRS complex <5mm in standard lead). This is thought to be due to the insulating effect of hyper inflated lungs and lowered position of the heart (tubular) with respect to electrodes (2) Right axis deviation of QRS with clockwise rotation.

This is due to rotation of the heart on horizontal and frontal plane. (3) right atrial (P-pulmonale) and right ventricular hypertrophy (Decreased voltage of R in leads V_1 and V_2 with R:S>1). This is secondary to development of pulmonary hypertension and subsequent development of cor-pulmonale, (4) poor progression of R wave in chest lead from V_1 to V_6. Hyperinflated lungs push down the heart with respect to electrodes, which record low voltage. There is a clockwise rotation shifting the transition zone leftwards resulting in poor voltage in precordial leads. (5) SI, SII, SIII pattern. This indicates marked shifting of QRS axis to north-west region, that is, right superior quadrant. (6) The T wave may be inverted in lead V_1 or V_2 due to right ventricular hypertrophy (RVH). (7) There may be generalized ST depression with T wave inversion due to global hypoxemia. (8) Arrhythmias: supraventricular arrhythmias are more common than ventricular arrhythmias usually due to generalized myocardial ischaemia complicating global hypoxia.

In 2011, Obasohan et al[3] showed clearly in their study that a shift of the electrical axis of the heart occurs in COPD patients mainly with the development of right ventricular hypertrophy (Cor-pulmonale), rather than the hyperinflation. In their series, 39 of the 92 Nigerian patients with COPD had associated cor-pulmonale, P wave axis greater than 90^0 present in 2 (19.1%) of 17 patients with COPD alone and 15 (41.7%) out of 36 with development of cor-pulmonale ($P<0.001$). The mean P wave axis was 64.7 ± 10.6 in those without cor-pulmonale while it was significantly shifted to the right (83.9^0) in those with cor-pulmonale

Case 1

KB was a 62 years old ex-soldier with background history of hypertensive heart disease who was admitted to hospital with cough, breathlessness and leg swelling of 4 weeks duration. He had smoked a packet of cigarette for over 25 years. He had severe dyspnea on minimal exertion and had had several admissions to hospital for acute episodes of breathlessness. He was on amlodipine. On examinations, he exhibited pursed lip breathing and a barrel shaped chest. Lung function test showed severe irreversible airflow limitation: FEV_1 36% predicted, FVC 75% predicted, FEV_1 / FVC = 30%. Arterial blood gases showed moderate hypoxaemia with mild hypercapnoea. Chest radiograph showed a cardiothoracic ratio of 1:2, hyperinflated lungs and flattened diaphrams. High resolution CT scan of the chest showed severe emphysema. Echo-cardiography demonstrated dilatation of the right atrium and ventricle on apical four chamber view.

The 12 lead ECG, (Fig1) which was recorded on admission to hospital showed sinus rhythm at a rate of 100 / min. The following features of COPD were present (1) prominent P waves in leads II, III and aVF (2) Poor R wave progression in the precordial leads. (3) depressed ST segment in lead II, III and aVF (4) A rightward shift of the mean QRS axis. The "lead I sign" criteria were met by the isoelectric P wave in lead I, small QRS complexes of less than 1.5mm in total deflection and T waves of less than 0.5mm in lead I.

Following his discharge from hospital, the patient has been on follow-up as an outpatient on *Prednisolone, Frusemide* and inhaled *Salbutamol* from metered dose inhalers.

Case 2

J.A.was a 61years old farmer with hypertensive heart disease presented with cough and sputum production, breathlessness and leg swelling of two weeks duration. He had been a patient with COPD and was also a heavy smoker (> 20 sticks per day) for over thirty years. About six weeks before presentation he was admitted to another hospital for acute exacerbation of COPD.

Examination showed he was in biventricular heart failure as indicated by elevated jugular venous pressure, hepatomegaly and pedal oedema. Examination of the heart revealed a rate of 108 per minute, blood pressure of 160 / 110mmHg. He had normal heart sounds and had no cardiac murmurs. The examination of the chest showed hyper-resonance to percussion, reduction in the areas of cardiac dullness, increased anterior-posterior diameter and reduced breath sounds.

The chest radiograph showed hyper-inflated lungs and flattened diaphragm in keeping with COPD. Pulmonary function tests were not done.

The 12-lead ECG (Fig 2) showed (1) sinus rhythm at a rate of about 100 / min with prominent P waves in lead V_1 suggesting right atrial enlargement (2) Poor R wave progression in the precordial leads (3) Depressed ST segment in lead II, III and aVF (4) A right axis deviation. The "lead I sign" criteria were met by the isoelectric P wave in lead I, small QRS complexes of less than 1.5mm in total depletion and T waves of less than 0.5mm in lead I.

He improved with *Frusemide, Lisinopril, and Salbutamol*.

Fig 1

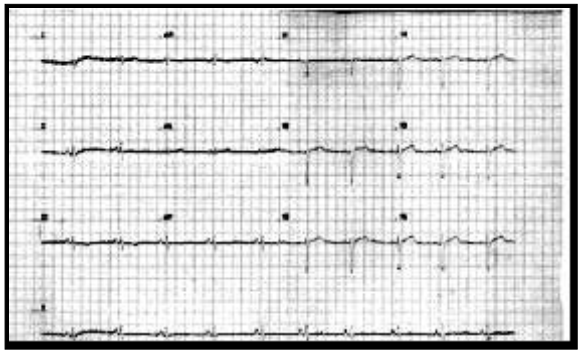
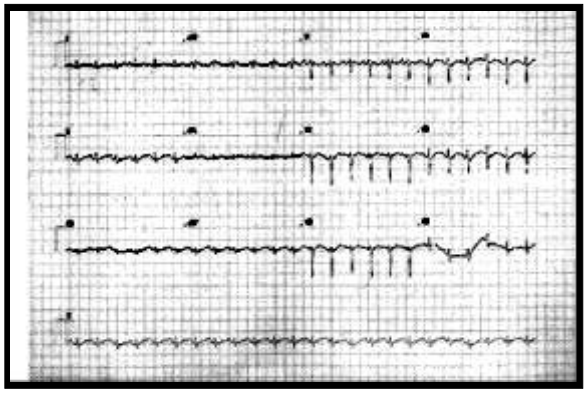


Fig 2



DISCUSSION

Fowler et al[9] reported 15 patients with severe pulmonary emphysema with cor-pulmonale of which 5 (33%) showed the "lead I sign". In the 13 patients that were used as control (who had pulmonary thromboembolism or idiopathic pulmonary hypertension), only one showed the "lead I sign". This patient had normal lung function tests. They then proposed very strict arbitrary criteria for the diagnosis of the "lead I sign" consisting of isoelectric P wave in lead I combined with a very small QRS complex of less than 1.5mm total deflection and a T wave of less than 0.5mm in lead I. The two patients described above clearly met these criteria. However, more recently Schamroth described the "lead I sign" as been reflected by "absent or very low amplitude P, QRS, T wave complexes giving the appearance of a minimally disturbed baseline" without any specification of the cut-off values for the amplitude of these three wave forms[10]. The 'lead I sign" is a highly specific indicator of COPD, being rarely seen in other conditions[8]. The two cases presented above both had in addition to COPD, - hypertensive heart disease similar to the coexisting cardiac condition reported by Yip et al[11].

In our setting where investigative procedures and equipment are a luxury, the diagnosis of chronic obstructive pulmonary disease should be strongly suspected when the "lead I sign" is present on electrocardiogram.

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THE RISING BURDEN OF NON-COMMUNICABLE DISEASE AND FOOD AS MEDICINE.

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INTRODUCTION

As opposed to communicable diseases, non-communicable diseases (NCDs) are those diseases that cannot be transmitted from one person to another. These conditions which are chronic (cause a protracted period of impaired health), cause dysfunction or diminution of the quality of life and develop over relatively long periods of time. They usually persist for the life-time of the person affected and so place a massive burden on the individual's resources and that of the health system. The most common of these NCDs are cancer, respiratory diseases (chronic obstructive airway disease and asthma), cardiovascular diseases (heart attack and stroke) and diabetes as they account for approximately 70% of all deaths worldwide and 82% of all NCD deaths[1]. Cardiovascular disease (CVD) is the most common cause of NCD deaths (17.5 million annually), followed by cancer (8.2 million), respiratory diseases (4 million) and diabetes (1.5 million)[2,3].

According to WHO estimates, 38 million people now die from NCDs annually and of these, 75% (28 million) occur in low and middle income countries[1], a very steep rise from just under 40% in 1990[4]. About 16 million NCD deaths occur in people aged less than 70 years and 82% of the these “premature” deaths occur in low- and middle-income countries[2]. NCDs account for 48% of the healthy life years lost (Disability adjusted life years ? DALYs) worldwide versus 40% for communicable diseases, maternal and perinatal conditions and nutritional deficiencies, and 1% for injuries[1].

It is estimated that over the next 20 years, NCDs will cost more than US$ 30 trillion, representing 48% of global GDP in that time, and push millions of people below the poverty line[5]. By contrast, mounting evidence suggests that NCDs are preventable, meaning millions of deaths can be averted and economic losses reduced by billions of dollars if extra attention is paid to preventive measures such as healthy eating habits. A recent World Health Organization report states that population-based life-style adjustment measures aimed at reducing tobacco and harmful alcohol use, promoting healthy diet and improving physical inactivity, are estimated to cost US$ 2 billion per year for all low- and middle-income countries, which in fact translates to less than US$ 0.40 per person[5].

Healthy eating patterns are reported to result in lower circulating concentrations of inflammatory markers. A diet consisting of whole grains, vegetables and fruits, and fish will lower chronic low-grade inflammation. Meals rich in advanced glycation end products (AGEs) enhance oxidative stress and inflammation as do, saturated fatty acids and trans-mono unsaturated fatty acids. Poly unsaturated fatty acids especially of long chain n-3 variety are antinflammatory[6]

Inflammatory cells produce soluble mediators, such

as metabolites of arachidonic acid, cytokines and chemokines, which act by recruiting more inflammatory cells and producing reactive oxygen species (ROS). ROS can both induce changes in transcription factors, such as nuclear factor kappa B (NFKB), signal transducer and activator of transcription 3 (STAT3), hypoxia-inducible factor-1α (HF-1α), activator protein-1 (AP-1), nuclear factor of activated T-cells (NFAT) and NF-E2 related factor-2 (NrF2), which mediate immediate cellular stress responses, induction of cyclooxygenase-2 (COX-2), inducible nitric oxide synthase (iNOS). This sustained inflammatory / oxidative environment is self-perpetuating and can lead to endothelial dysfunction, vascular remodelling, altered tone and vascular inflammation. It may also result in the introduction of gene mutations and structural alterations of DNA that damage DNA, blockage of intercellular communication and modification of second messenger systems leading to cell proliferation or a decreased apoptosis, among other changes characteristic of chronic disease[7,8,9]

SOCIO-ECONOMIC AND PUBLIC HEALTH IMPACT OF NCDS

People of all ages and in all countries of the world, including children, adults and the elderly are all susceptible to the risk factors that lead to NCDs as these diseases are associated with ageing, rapid unplanned urbanization and globalisation of unhealthy lifestyles[1]. NCDs are commonest in people aged 40 and over but there are worryingly increasing reports of type 2 diabetes occurring more frequently in children in the Africa sub region. The WHO reports that this previously rare situation is now so common that in some countries in the region, children and adolescents are now responsible for approximately half of all newly diagnosed cases of type 2 diabetes[10].

About half of all those aged 25 years and older in sub-Saharan Africa already suffer from hypertension, an established precursor for strokes and heart attacks[1] and according to the Commission on Ending Childhood Obesity (ECHO) overweight prevalence in children aged less than 5 years has risen from 4.8% to 6.1% between 1990 and 2014 with the absolute number of children so affected in the same period, increasing from 31 million to 41 million. For lower middle-income countries however, the number of overweight children has more than doubled from 7.5 million to 15.5 million, over the same period. In Africa, the number of children under 5 years of age who are overweight has nearly doubled from 5.4 million to 10.3 million since 1990[11].

Although Communicable diseases and other conditions still predominate in sub-Saharan Africa, NCDs are projected to be the leading cause of death by 2030. Almost 30% of NCD deaths in low- and middle-income countries occur in people under age 60, at the peak of their economic productivity compared to only 13% in high-income countries. Also, in sub-Saharan Africa, people die on average 10 years earlier than in developed countries[10].

Non-communicable diseases are closely associated with poverty because they markedly raise household costs associated with treatment of these diseases that endure for the life of the sufferers. Additionally, the rising burden of these diseases will negate any poverty alleviation measures the Government may put in place. The result is that poor members of our society suffer a steady deterioration in their health and die earlier than the more affluent members of society mainly because they are more likely to seek quick but potentially harmful solutions to their health conditions such as herbal medicine, to use tobacco and alcohol and to consume unhealthy food.

The massive cost of NCDs resulting from lengthy and expensive treatments involving antihypertensives, antidiabetics and antineoplastic drugs, and the loss to death of breadwinners is dragging a large proportion of Nigeria's population into poverty yearly, and preventing development.

RISK FACTORS FOR NCDs

The risk factors for NCDs can be described as modifiable behavioural risk factors or metabolic or physiological risk factors. The very high rate of poverty in many countries in sub-Saharan Africa leads to high rates of infectious diseases and leads to non-communicable disease risk factors such as drinking, smoking and poor diet, driving a double burden of disease. Tobacco use, physical inactivity, unhealthy diet and the harmful use of alcohol are considered the most important modifiable behavioural factors that increase the risk of NCDs by the World Health Organization[12].

About 6 million deaths every year are attributable to tobacco use, including those resulting from the effects of exposure to second-hand smoke. This figure is projected to increase to 8 million by 2030. Inadequate physical activity is responsible for approximately 3.2 million deaths annually with harmful use of alcohol (which is defined as the presence of physical and/or psychological complications)[2], contributing another 3.3 million deaths annually. One million, seven hundred thousand deaths due to cardiovascular diseases were directly attributable to excess salt or sodium intake in 2010[3].

The risky behaviours described above lead to four major metabolic/physiological changes that elevate the risk of NCDs and they include: high blood pressure, overweight/obesity, raised blood glucose levels (hyperglycaemia) and raised levels of fat in the blood (hyperlipidaemia). Of these, the leading metabolic risk factor globally is high blood pressure (responsible for 18% of deaths worldwide), followed by overweight/obesity and hyperglycaemia[12].

PATHOLOGICAL BASIS OF NON-COMMUNICABLE DISEASES

The Role of Reactive Oxygen Species in the Development of NCDs

Oxidative stress is defined as a disequilibrium between production of free radicals and reactive metabolites, also called oxidants or reactive oxygen species (ROS) and their neutralisation by protective agents called antioxidants. During regular metabolic processes in the body, aerobic cells produce ROS such as superoxide anion (O_2^-), hydrogen peroxide (H_2O_2), hydroxyl radical (OH^-), and organic peroxides as normal products of the reduction of molecular oxygen[8,9].

All non-communicable diseases are linked in the sense that they are all associated with an increased inflammatory response, observed long before overt disease manifests. The sources of inflammation are varied and numerous and include microbial and viral infections, exposure to allergens, radiation and toxic chemicals, autoimmune and chronic diseases, obesity, consumption of alcohol, tobacco use, and a high calorie diet. In general, the longer the inflammation persists, the higher the likelihood of developing chronic disease (NCD)[7].

Ingestion of excess calories causes the mitochondria to be overloaded with glucose and fatty acids and an overproduction of acetyl coenzyme A (acetyl coA)[13], an important enzyme in cellular metabolism. Elevated levels of acetyl coA causes an increase in reduced nicotinamide adenine dinucleotide (NADH) generation from the tricarboxylic acid (TCA) cycle. The excess NADH increases electron production by Complex I of the mitochondrial electron transport chain and elevates membrane potential sufficiently to stall the activity of Complex III, resulting in a longer half-life for coenzyme Q. The longer half-life of coenzyme Q means it is available for a longer time to cause an increased reduction of oxygen to superoxide (O_2^-)[14].

Superoxide is unstable and is quickly converted to hydrogen peroxide (H_2O_2) in the mitochondria by superoxide dismutase. H_2O_2 undergoes a Huber-Weiss or Fenton reaction to produce a highly reactive hydroxyl radical (HO^-), which can oxidise mitochondrial proteins, DNA, lipids and amplify the effects of the superoxide-initiated oxidative stress[15,16]. ROS also activate redox-sensitive transcription factors which set off inflammatory cascades and cause the generation of more ROS (Figure 1).

Inflammatory cells produce soluble mediators, such as metabolites of arachidonic acid, cytokines and

chemokines, which act by further recruiting inflammatory cells and producing more reactive oxygen species (ROS). ROS can both induce changes in transcription factors, such as nuclear factor kappa B (NFKB), signal transducer and activator of transcription 3 (STAT3), hypoxia-inducible factor-1α (HF-1α), activator protein-1 (AP-1), nuclear factor of activated T-cells (NFAT) and NF-E2 related factor-2 (NrF2), which mediate immediate cellular stress responses, induction of cyclooxygenase-2 (COX-2), inducible nitric oxide synthase (iNOS). This sustained inflammatory/oxidative environment is self-perpetuating and can lead to endothelial dysfunction, vascular remodelling, altered tone and vascular inflammation. They may also result in the introduction of gene mutations and structural alterations of DNA that damage DNA, blockage of intercellular communication and modification of second messenger systems leading to cell proliferation or a decreased apoptosis, among other changes characteristic of chronic disease[7,8,9].

The impact of oxidative stress on pancreatic β cells is a diminished expression of glucose transporter type 4 (GLUT 4), which over time can support the onset of type 2 diabetes mellitus. In endothelial cells, oxidative stress causes the formation of peroxynitrite radicals which decrease nitric oxide levels and result in defective endothelial dependent vasodilation, which over time leads to cardiovascular disease[6].

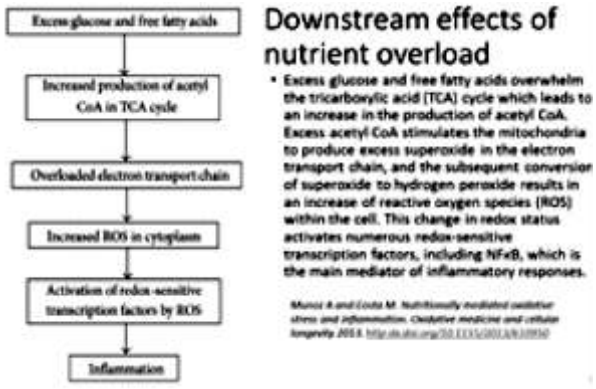


Figure 1: Downstream Effects of Nutrient Overload

PREVENTION AND CONTROL OF NON-COMMUNICABLE DISEASES

As described earlier, these conditions seem to be linked by a common pathological process and so solutions apply to all conditions. For a resource-poor country like ours, emphasis has to be placed on prevention. The WHO recommends that individuals adopt the following simple and inexpensive lifestyle adjustment measures:

1. Achieve and maintain a healthy body weight
2. Be physically active, engaging in regular moderate-intensity exercises for at least 30 minutes day on most days of the week, with a minimum of 120 minutes weekly.
3. Eat a healthy diet consisting of three to five servings of fruits and vegetables a day and a low content of sugar, salt, saturated fats and trans-fatty acids.
4. Avoid smoking or the use of tobacco in any form
5. Avoid harmful use of alcohol
6. Receive regular medical checks, including fasting blood sugar, blood lipids, PSA checks, mammograms etc.

Governments can help with fiscal policies that place a huge tax on the manufacture, importation and sale of sugary and high energy drinks such that their retail price goes up at least 20%. The reasoning is that low-income individuals who suffer most from the consequences of consuming these products are more likely to be dissuaded from purchasing them if their costs go up[10]. The WHO recommends that the revenues derived be invested in subsidising the cultivation of and cost of fruits and vegetables and by so doing encourage the consumption of fruits and vegetables. Additionally, fast food outlets should be made to use only oils that are free of saturated and trans fatty acids[10,12,17].

The most effective of these measures at ensuring that future generations are protected from non-communicable diseases is a change in our food culture. I will therefore focus the remainder of this paper in describing what constitutes a healthy diet.

FOOD AS MEDICINE

Food is defined simply as any substance that can be metabolised by an animal to give energy and build tissue. It is divided into macronutrients and micronutrients. Macronutrients are the classes of chemical compounds humans consume in largest quantities and which provide bulk energy. These are fat, protein and carbohydrate. Micronutrients are substances needed only in small quantities for normal body function and include vitamins and minerals.

Evolution of the human diet

The human diet has evolved through four stages, namely: the Miocene to early Pleistocene era, the Paleolithic era, the Neolithic era, and the Industrial Revolution. In the Miocene to early Pleistocene era, diets consisted of foliage, leafy vegetables, fruits, seeds and nuts and supplied high amounts of fiber, plant sterols, and vegetable proteins.

The diet of the Paleolithic man (Caveman) was not much different as it also consisted mainly of plant food but in addition, contained large amounts of animal protein derived from lean meat and seafood. The Paleolithic period ended about 10,000 years ago with the emergence of agriculture during the Neolithic period.

The Neolithic era was characterized by starchy foods in the form of grains and legumes as the main dietary staples. The diet also contained dairy products as well as vegetable oils such as olive oil. Neolithic diets were sources of large amounts of fiber, vegetable protein, and plant sterols.

The Industrial Revolution brought about the most significant change in the human diet, introducing the convenience and prepackaged foods including canned meats, condensed canned soups, hydrogenated vegetable oils, and refined grains, including white flour. A major consequence of the Industrial Revolution which has taken place over the past 200 years is a human diet rich in high glycaemic index carbohydrate sources (carbohydrate sources that cause a rapid rise in blood sugar), animal products, meat, saturated fat, and dietary cholesterol but deficient in legumes, vegetables, fruits and nuts[18].

The changes in the human diet over these past 10,000 years, it is now widely held, has adversely affected a number of dietary markers of health, including the amount of glucose in blood, fatty acid composition, macronutrient composition, micronutrient composition, acid / base balance, sodium / potassium ratio, and fiber content. It is also believed that these adverse effects have occurred because the changes that have taken place in our environment, including dietary and lifestyle shifts, have happened at a rate faster than the human genome could adapt to, and so humans are still biologically adapted to the environment of their ancestors[19]. This slow adaptation to modern diets (the basis of the paleolithic diet) has resulted in a multitude of chronic diseases in modern man, which our ancestors did not have.

Food as a remedy for illness or food as medicine became popular in the mid-1970s following publications by the gastroenterologist Walter Voegtlin and others. These scientists believed that adopting a nutritional plan based on the presumed ancient diet of the caveman of the paleolithic era that is known variously as paleolithic, caveman, stone age or hunter-gatherer diet, and that consisted mainly of wild plants and animals, protects against chronic disease. One of the major proponents of this diet, a Swedish scientist called Staffan Lindeberg did a number of studies, now collectively known as the Kitava Study, on the non-westernised population of Kitava, one of the Trobriand Islands of Papua New Guinea. These studies conducted between 1989 and 1993, found that the people of Kitava apparently did not suffer from stroke, ischaemic heart disease, diabetes, obesity or hypertension[20]. From about 1999, several doctors and nutritionists have argued in favour of a return to a paleothic diet or preagricultural diet and have formulated diets from modern foods that mimic the nutritional characteristics of the ancient paleothic diet[21].

Figure 2: Paleolithic Diet

Mediterranean Diet

The Mediterranean diet is a modern nutritional recommendation inspired by the traditional dietary patterns of Southern Italy, Greece and specifically the Greek island of Crete and parts of the Middle East (Morocco).

In addition to regular physical activity, the Mediterranean diet emphasises abundant plant foods and fresh fruits as the typical daily dessert, olive oil as the principal source of fat, dairy products (principally cheese and yoghurt) and fish and poultry consumed in low to moderate amounts, zero to four eggs consumed weekly, red meat consumed in low amounts and wine consumed in low to moderate amounts. Total fat in this diet is 25% to 35% of calories, with saturated fats at 8% or less of calories.

The highlights of this diet include high olive oil consumption; high consumption of legumes; high consumption of unrefined cereals; high consumption of fruits; high consumption of vegetables; moderate consumption of dairy products (mostly cheese and yoghurt); moderate to high consumption of fish; low consumption of meat and meat products and moderate wine (particularly red wine)[25] (Ellen Gouch, 2005). Red wine contains flavonoids with powerful antioxidant properties[26] (Martinez-Gonzalez et al., 2010).

I shall in the remaining part of this paper, outline the potential benefits and adverse effects of ingested food and food supplements; and present evidence that components of the diet of early man when consumed as functional foods (foods that are consumed as part of the normal diet and contain biologically active components which can enhance health or reduce the risk of disease) today will reduce the risk of obesity, stroke, ischaemic heart disease, diabetes, cancer and osteoporosis.

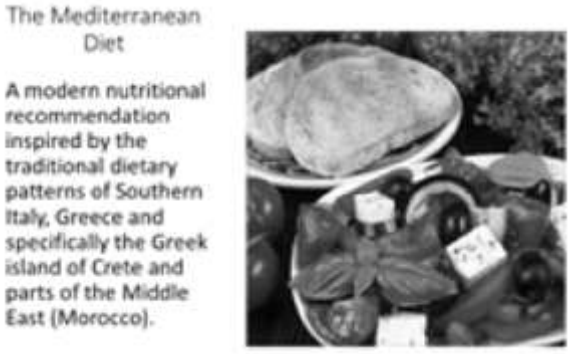


Figure 3: Mediterranean Diet

Evidence that food can be medicine

In the early 1950s the Rockefeller Foundation appointed Dr Leland Albaugh Field Director to investigate causes of high rates of death on the Greek Island of Crete. After systematically reviewing every aspect of life on Crete and comparing it to life in mainland Greece and America, Dr Albaugh reported that the rates of death in Crete were high, but the primary problem was poor public health infrastructure, poor access to good quality medical care and the availability of drugs to combat infections such as malaria, typhoid and dysentery. Importantly however, his data also showed that the adults of Crete had significantly better rates of heart disease than in America with 30% fewer deaths related to cardiovascular disease and just less than 30% deaths from cancer. Dr Albaugh's research showed that although Americans and the adults of Crete consumed similar daily calories, the food groups and nutrients for the main calories were different for the Crete and American adults (Table 1). Although the

significance of this finding was lost on the investigators at the time, it has now become the basis of a very popular functional diet called the Mediterranean diet.

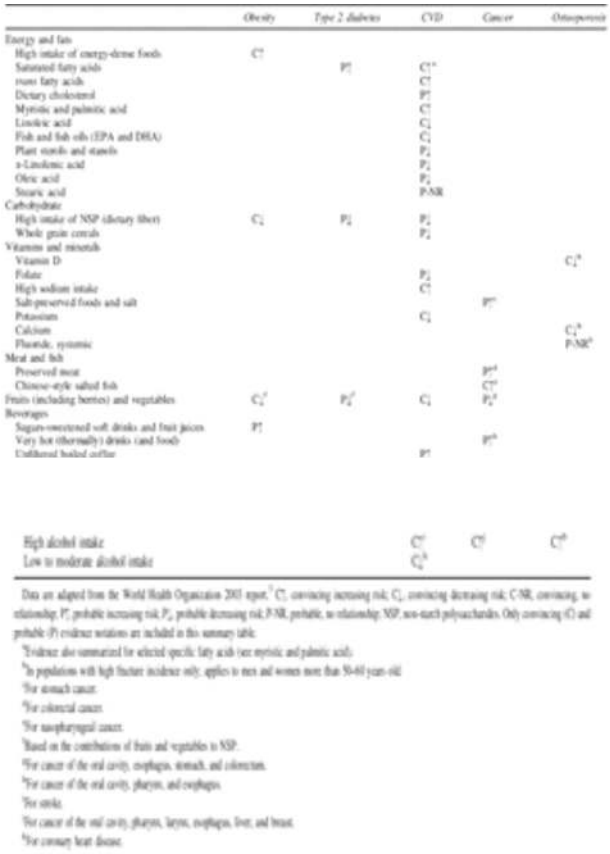
Table 1:
Sources of calories consumed by percentage in Crete Greece and United States in 1948

Food Group	Crete Fall 1948	Greece 1948-1949	USA 1948-1949
Cereals	39	61	25
Potatoes	4	2	3
Sugar and honey	2	4	15
Pulses and nuts	7	6	3
Vegetables and fruits	11	5	6
Meat, fish and eggs	4	3	19
Dairy products	3	4	14
Oils and fats	29	15	15
Wine, beer & spirits		not given	not given
Total calories per person per day	2,547	2,477	3,129
Sources of protein in the diet, by percentage			
Animal protein	24	19	66
Vegetable protein	76	81	34

Emphasis is the author's.

A World Health Organisation (WHO) report published in 2003[27] (Table 2) summarised the links between diet and obesity, diabetes, cardiovascular disease (CVD), cancer and osteoporosis.

Table 2:
Summary of links between diet and obesity,diabetes, CVD, cancer & Osteoporosis



EVIDENCE OF HEALTH PROMOTING EFFECTS OF PALEOLITHIC AND MEDITERRANEAN DIETS

The nature of the Caveman and Mediterranean diets may have stimulated the design of therapeutic diets to manage chronic diseases in this and other countries[28,29,30]. Results from studies in human beings involving interventions using the Paleolithic or Mediterranean diet have been promising. For instance, a short term intervention trial using the Paleolithic diet by Osterdahl et al.,[29] in healthy human volunteers showed decreases in mean weight, body mass index, waist circumference, and systolic blood pressure. Additionally, dietary intake of fat, antioxidants such as vitamins C and E, and potassium-sodium ratio all showed favourable changes. Participants had adverse effects attributed to low levels of calcium because the Paleolithic diet excludes dairy products such as milk.

Another randomized, controlled, cross-over clinical study in the primary care setting, compared the Paleolithic diet with a commonly prescribed diet for type 2 diabetes. The Paleolithic diet resulted in lower mean values of HbA1c, triacylglycerol, diastolic blood pressure, body mass index, waist circumference and higher values of high density lipoprotein when compared to the Diabetes diet. Also, glycemic control and other cardiovascular factors were improved in both diets without significant differences[19]. It is also important to note that the Paleolithic diet was lower in total energy, energy density, carbohydrate, dietary glycemic load and glycemic index, saturated fatty acids and calcium, but higher in unsaturated fatty acids, dietary cholesterol and some vitamins.

The beneficial health effects of the Mediterranean diet are thought to be due to the eating of small portions, daily exercise and the emphasis on freshness, balance and pleasure in food. It has for instance been reported in the Seven Countries Study that Cretan men on a traditional Mediterranean diet consisting mostly of olive oil, large amounts of fruit and vegetables, fish and a moderate amount of dairy foods and wine, had exceptionally low death rates from heart disease, despite moderate to high intake of fat. The Lyon Diet Heart Study made some modifications to the Cretan diet by replacing olive oil with rapeseed (canola oil) increasing vitamin C-rich fruit and bread by 20% and decreasing processed and red meat. The researchers found that on this modified diet, mortality from all causes in the participants who had all survived a first heart attack, was amazingly reduced by 70%[31].

The British Medical Journal published a study in 2009 which reported that components of the Mediterranean diet, such as high vegetable consumption and low meat and meat product consumption, are more significantly associated with low risk of mortality than other components, such as cereal consumption and fish consumption[32].

As can be seen, all the health promoting nutritional plans described so far, contain fruits and vegetables and so before we make further progress let me quickly outline the health benefits of fruits and vegetables.

The culinary definition of vegetable is an edible plant or part of a plant but usually excludes seeds and most, sweet fruits. This usually means the leaf, stem, or root of a plant. Although botanically, a fruit is the ovary of a flowering plant, for culinary purposes, it is any edible part of a plant with a sweet flavor.

Apples like most fruits are naturally low in fat and calories, are filling and provide essential vitamins and minerals, fibre and other substances that are important for good health. A regular size apple has between 70-100 calories. Eating an apple when craving for candy or chocolate or other junk food such as doughnuts has a mellowing effect on blood sugar that suppresses the desire, since apple itself contains sugar but gives you only a quarter of the calories.

It is important to note however, that with fruits and vegetables, variety is just as important as quantity and that no single fruit or vegetable provides all the nutrients required to be healthy. The largest and longest running clinical trial to date, conducted as part of the Harvard-based Nurses' Health Study and Health Professionals follow-up study, involving 110,000 men and women whose health and dietary habits were monitored for 14 years, found that the higher the average daily intake of fruits and vegetables, the lower the risk of developing cardiovascular disease[33]. Combining the findings of this study with many other long-term studies in the United States and Europe and examining the effects on stroke and coronary vascular disease separately, the researchers found that individuals who ate more than 5 servings of fruits and vegetables a day, had approximately 20% lower risk of coronary heart disease and stroke when compared to people who ate less than 3 servings a day[34,35].

The Optimal Macronutrient Intake Trial for Heart Health (OmniHeart), a follow-up study to the Dietary Approaches to Stop Hypertension (DASH) study, which examined the effects of a diet rich in fruits, vegetables, and low-fat dairy products and which restricted the amount of saturated and total fat, found that blood pressure was lowered even more (DASH lowered systolic blood pressure by about 11 mmHg and diastolic blood pressure by about 6 mmHg) when some of the carbohydrate was

replaced with healthy unsaturated fat or protein[36]. A meta-analysis of studies and observational studies[37] has also found that consumption of a vegetarian diet was associated with lower blood pressure.

The link between fruits and vegetables and cancer is weak. In the Nurses' Health Study and the Health Professionals Follow-up Study for instance, over a 14-year period, men and women with the highest intake of fruits and vegetables (8+ servings a day) were just as likely to have developed cancer as those who ate the fewest daily servings (under 1.5)[33]. This is not surprising in the light of a very recent study which found that two thirds of all cancers are due to random genetic mutations[38]. A team of scientists from the Johns Hopkins Kimmel Cancer Center studied mutations that drive abnormal cell growth in 32 different types of cancer by developing a mathematical model for assessing the role of genetic copying errors in the development of cancer, using DNA sequencing and epidemiological data. Their results explain why people who lead a healthy life and have no family history of cancers may get the condition.

Several studies have reported [33,39,40, 41] that in men and women who were free of major chronic diseases, greater consumption of whole fruits – especially blueberries, grapes, and apples – is associated with a lower risk of type 2 diabetes but that greater consumption of fruit juice is associated with a higher risk of type 2 diabetes.

The indigestible fibre content of fruits and vegetables absorbs water and expands as it passes through the digestive system which can calm symptoms of an irritable bowel and, by triggering regular bowel movements, relieve or prevent constipation[42]. Diverticulosis may also be prevented by this bulking and softening action of insoluble fiber by decreasing pressure inside the intestinal tract[43]. Finally, it has been reported that eating fruits and vegetables can keep your eyes healthy, and may help prevent two common aging-related eye diseases—cataracts and macular degeneration—which afflict millions of Americans over age 65[44,45,46,47]. Lutein and zeaxanthin, in particular, seem protective against cataracts[48].

Antioxidant Supplements

It is thought that oxidation of low density lipoprotein in the blood contributes to heart disease, and initial observational studies found that people taking vitamin E supplements had a lower risk of developing heart disease. As a direct result, at least seven large clinical trials have been conducted to test the effects of antioxidant supplementation with vitamin E, in doses ranging from 50 to 600 mg per day. None of these studies found a statistically significant effect of vitamin E on overall number of deaths or on death due to heart disease. So, despite the clear role of oxidative stress in cardiovascular disease, controlled studies using antioxidant vitamins have observed no reduction in either the risk of developing heart disease, or the rate of progression of existing disease[49,50,51]

While some level of antioxidants, vitamins and minerals in the diet are required for good health, there is considerable doubt as to whether antioxidant supplements are beneficial or harmful and if they are actually beneficial, which antioxidants are needed and in what amounts. It is believed that excessive antioxidant levels may inhibit recovery and adaptation mechanisms and may also prevent many of the health gains that normally come from exercise such as increased insulin sensitivity.

Processed Foods

Refining is one of the measures by which processed foods are made. Refined flour has the brown husk of the wheat grain removed, leaving the white, refined starch found in white bread, white rice, pasta, biscuits and many other junk foods. Without the fibrous husk, refined starches are broken down quickly into glucose which is readily absorbed into the blood stream, causing glucose levels to rise quickly (hyperglycaemia) and inducing higher than normal levels of insulin secretion (hyperinsulinaemia) to bring it under control. Both these effects increase the risk of obesity and hypertension. Eating whole grains, such as, whole wheat bread, cereals, brown rice and barley with the bran surrounding intact, on the other hand, leads to a much slower absorption of sugar into the blood stream than occurs with refined starches and reduces the risk of obesity.

Additionally, refining destroys and devitalizes most good foods. Healthy unsaturated fatty acids are lost

during the milling process. Half the vitamin E is destroyed when the wheat germ and bran are removed. Refining wheat into flour removes between 50 and 93% of wheat's magnesium, zinc, chromium, manganese and cobalt. Approximately 50% of calcium, 70 percent of phosphorous, 80 percent iron, 50% potassium, 65% of copper, 80% of thiamin, 60% of riboflavin, 75% of niacin, 50% of panthotenic acid and about 50% of pyridoxine is lost[52].

Fast foods or junk foods are harmful because they are made from processed white flour and oils rich in trans-fats. Trans-fats are formed by the process of hydrogenation of vegetable oils to convert the readily oxidisable fatty acids such as linoleic acid into oxidation-resistant fatty acids. Oxidation of fatty acids makes vegetable oils rancid but the trans-fats (as opposed to cis-fats) that result from hydrogenation are unnatural and harmful. Trans-fats raise LDL- or bad cholesterol and lower HDL- or good cholesterol. Scientists do not yet know why, but the addition of hydrogen to oil increases blood cholesterol more than do other types of fats. It is believed that the addition of hydrogen to oil makes the oil more difficult to digest and the body recognises trans-fats as saturated fats. Junk foods (meat pies, doughnuts, sausages, and others foods prepared with hydrogenated oils including fried rice) are thus very high calorie (energy dense) meals which contain more fat, cholesterol, salt and sugar, fewer vitamins, minerals and other nutrients, than fresh food. Several studies have shown that apart from their nutritional deficiencies, fast foods promote weight gain. In addition, junk food consumption alters brain activity in a manner similar to addictive drugs like cocaine and heroin, leading to compulsive eating for pleasure[52].

What should we eat?

We could adopt a nutritional plan that is based on the Paleolithic diet or the Mediterranean diet, the components of which I have shared with you. However, doing so may pose significant challenges. For instance, the Paleolithic diet derives most of its macronutrients from wild game animal protein and we cannot very well, go out and catch an antelope or a grass cutter for lunch or dinner every time we are hungry. The Caveman diet also lacks Vitamin D and calcium because of the exclusion of dairy products. Some fears have also been expressed about the high salt content of some foods included in the Mediterranean diet, such as olives, salt-cured cheeses, anchovies, capers, salted roe, and salads dressed with extra virgin olive oil. More importantly, most of these diets are foreign to us and so the components are not readily available[52]

It may therefore, not be practical to convert solely to one or the other. It may however be easier and of greater value to us to evolve a diet plan that includes the health promoting components of these diets as functional foods and adopting a healthy lifestyle, to prevent chronic disease. The chart below, published by the Harvard School of Public Health summarises what we should be eating, drinking and doing[53].

Avoid junk food as much as possible. I say this because it may be near impossible to completely avoid these highly attractive and palatable dishes. Also avoid carbonated and sweetened soft drinks such as coke, sprite, malt drinks, alcohol (except moderate quantities of red wine) and tobacco. These things give you so much unwanted calories and actually contain harmful substances such as trans fatty acids and refined sugar. In place of food made out of white flour - white bread, cakes, biscuits, white spaghetti eat whole grains such as whole wheat bread, brown rice and whole grain pasta.

Use healthy oils such as olive oil and canola oil. Both of these oils are heart healthy and can be used for baking and cooking. However, olive oil is a wholly natural oil made by pressing ripe olives at cold temperatures to preserve the nutritional content and collecting their juices. Olive oil contains polyphenols, antioxidants and omega-3 fatty acids. Canola oil on the other hand is made from a hybrid of the rapeseed plant, and is a vegetable oil. Some people have reservations about canola oil because it is manufactured at high temperatures using processes that may involve the use of toxic chemicals such as hexane. It is de-gummed, deodorised, bleached and further refined at high temperatures. It is believed that these high temperatures may change the omega-3 content and significantly increase its content of trans fatty acids and saturated fats. Canola oil is however undoubtedly good for your heart and is endorsed by the British Heart Foundation.

Olive oil is available in the market in different forms. Extra virgin olive oil is the best and is collected from the first pressing of the olive. It contains the most nutrients. Virgin olive oil is collected from the second pressing. Oils derived from subsequent pressing are used to make light and pure olive oils, which may undergo further processing. It is recommended we eat fruits and vegetables with every meal, very day. Fill half your plate with vegetables at very meal and eat fruits and vegetables at snack time too. You should have at least 5 portions of fruits and vegetables each day. A portion of fruits or vegetable is: a dessert bowl of salad; a handful of grapes, cherries or berries; a glass of fruit juice (150 mls); two tablespoons of beans and pulses (lentils, kidney beans etc). Note that however much of fruit juice or beans and lentils you eat, you can only count these as one portion per day. One apple, one orange, one mango, banana, pear or other medium sized fruit; half a grape or avocado; one slice of a large fruit e.g. water melon or pineapple. To find out more about this or how much you need to eat for your weight, sex and physical activity level, please visit: http://www.cdc.gov/nutrition/everyone/fruitsvegetables/howmany.html

Eat healthy protein such as that derived from fish, poultry, beans and nuts. Limit red meat to small portions of pasture-raised beef and wild game meat. Remember that although the Caveman ate large amounts of meat, he was highly mobile (physically active) and also consumed large amounts of monounsaturated and polyunsaturated fatty acids, n-3 fatty acids and fruits and vegetables, all of which are believed to mitigate the adverse effects of high protein intake. Drink water, tea and coffee (with very little or no sugar), red wine, and freshly squeezed orange or some other fruit juice (at least one 150 ml glassful daily). Water contains no calories and the others all contain high amounts of natural antioxidants that have been proven scientifically to be beneficial. Avoid alcohol in the form of beer and spirits, sugary drinks (what we call mineral and malt drinks, including the diet versions.

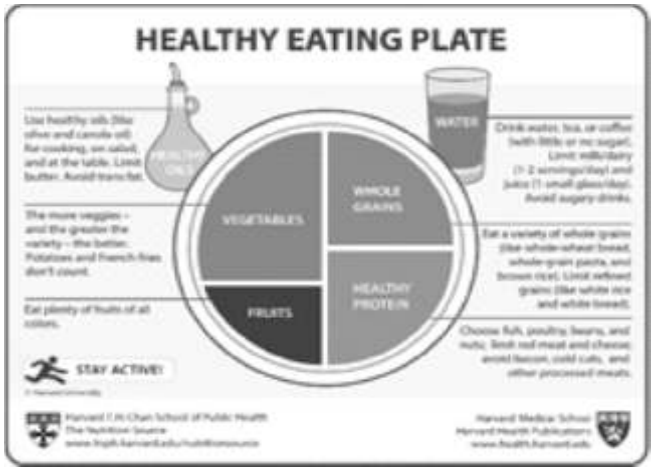
Finally, you must find time to exercise. It is recommended that you aim to take 10,000 steps a day but any amount of exercise daily is helpful. There are devices called pedometers that help you keep count of how many steps you have taken daily. The advantage in wearing them every day when you step out of your house is that you are consciously trying to meet a target and so you walk when you do not have to drive, you walk on the spot in your office while reading papers etc. You can get more information at www.cdc.gov/nutrition/everyone/basics/foodgroups.html and www.cdc.gov/nutrition/everyone/fruitsvegetables/index.html

How much should we eat?

You can get fat eating a perfectly healthy diet and so how much you eat is very important, whether it be fruits or vegetables alone or a Paleolithic or Mediterranean type diet. How much we should eat depends on many factors, including how tall we are, how old we are, whether we are male or female, our general state of health, what jobs we do, what leisure time activities we partake in, genetics, body size, body composition, and what medications we may be on. As a general rule, if we consume more than we use up by way of calories we gain weight and if the converse happens, we lose weight. There are certain other factors which may give you extra wiggle room on the amount you can eat: for example, if your food contains a lot of fiber you can usually eat more calories than if you eat food with a very low fiber content[53].

Put simply, how much you eat is very closely linked to the types of foods you eat and your lifestyle. Also, how much each one of us should eat depends on what our aims are: to maintain our body weight, lose or gain weight, or prepare for some sports event. However, any focus on food quantity intake is closely linked with calorie consumption.

Calories are a measure of how much energy there is in the food we eat. By understanding calories, you can work out how much food you need to eat. Different foods have varying number of calories per gram of weight. There are resources on the internet to help you work out how much calories you should be consuming.



CONCLUSION

Non-communicable diseases long considered a result of the ageing process, are increasingly more prevalent globally with a disproportionately greater burden in Africa and other low- to middle-income countries. Worryingly, these diseases are now a lot more common in children. To curb this rising burden, which is capable of dragging many households into poverty and stalling development, Nigerians need mainly to modify their diet, exercise more, avoid harmful alcohol use and tobacco, altogether. We in the medical community have a massive responsibility to reduce the burden of NCDs and to help reshape food systems in line with the UN declared Decade of Action of Nutrition 2016-2025.

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PROSTATE SPECIFIC ANTIGEN (PSA) THROUGH THE LENS OF A COMMUNITY UROLOGIST

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ABSTRACT

In the second half of the 20th century, great strides were made in the diagnosis and treatment of many disease conditions. These advancements were seen prominently in the field of Cancer care as multispecialty and inter-disciplinary collaborative practice swayed and yielded interesting and useful but sometimes controversial results and phenomena. Prostate cancer detection and management using serum prostate specific antigen in combination with other measures engaged the attention, knowledge and skills of the practising community urologist. The literature on the use of serum PSA and the clinical experience in a community urology practice were reviewed. The various causes of elevated serum PSA and how these reflected in the care and outcome of treatment were observed. Controversies that has besought serum PSA since its discovery were reviewed in the context of its usefulness in the care of men likely to be affected by prostate cancer. The 'highs' and 'lows' in terms of prostate cancer detection, staging of disease and prognostication , and monitoring of treatment outcomes were evaluated. Refinement of PSA -PSA density, PSA velocity, the Free/Total PSA ratio, Age-/Race specific PSA as applied in community urology practice to improve the predictive utility of this serum antigen was examined. Almost half a century since its arrival in the community urologist's practice platform, the ability of serum PSA to detect prostate cancers that will cost life, and thereby allow early curative treatment is as yet not clear .Also it is now known that PSA is ubiquitous in several body fluids and tissues in both men and women. So it is not prostate tissue specific nor prostate cancer specific and can be found in men and women sera and ejaculates. It appears, its most useful role is in detection of recurrences after adequate treatment and in evaluating response to treatment. Maybe time has come to stir up further controversies in terminology and consider such as serum PCRAN (Prostate cancer related Antigen). No. The Community Urologist through his/her lens should consider the serum PSA at our current depth of knowledge as a tool for an opportunity for open, frank and thorough conversation with a patient and/or relatives who are concerned about or being investigated for prostate related concerns or cancer.

INTRODUCTION AND BACKGROUND

Remarkable advances in the care of people with different types of diseases were recorded in the second half of the 20th century. These were influenced greatly by proliferation of technology, information sharing and knowledge transfer embedded in interdisciplinary collaborative networks and practices. The field of Cancer Care - Oncology, has been impacted by improved Diagnostic Imaging techniques, Discovery and refinements of tumour markers for cancer detection and monitoring, Radiation, Novelty and refined chemotherapeutic agents and Radical Surgical techniques employing minimally invasive approaches. Success stories abound in the treatment of cancers of the breast, colon, uterine cervix and lung. There appeared to be increased enthusiasm in cancer detection through numerous cancer awareness and educational programs in the public, cancer screening in some specific cancers, increased publicity about cancers in both the grey and peer-reviewed literatures. The science and art of quality improvement and patient safety also thrived in this period and allowed us to question and measure outcomes of the different treatment modalities that were seen in this era. Of all the advances in urology

during this period, the use of serum PSA and Prostate cancer and arrival of incisionless electro shockwave stone treatment (ESWL) with or without anesthesia were two phenomena that caught most attention of the public and the media. The discussion of prostate disease appeared "to come out of the closet" among professionals and lay people. The use of serum PSA as a tumour marker for prostate cancer surged especially in North America, Europe, Japan and Australia. Increase in aging population in many countries further fuelled the desire for campaign in early detection, screening and treatment of prostate cancer. In this review, we examine the historical perspectives and controversies in the discovery and characterization of serum PSA. Its role in the detection and management of prostate cancer will be reviewed. The molecular biology of PSA, its functions in the body, its significance in Prostate cancer and other diseases of the prostate shall be explored. Controversies in the use of serum PSA for Prostate Cancer screening and the ubiquitous nature of PSA in various body fluids and tissues in men and women will be highlighted. The niche for PSA in the armamentarium of the community urologist for the care of patients with prostate cancer and / or prostate problems will be identified

Prostate cancer is the leading cause of cancer-related deaths in men above the age of 50 years after lung cancer, worldwide. There has been an increase in the number of cases diagnosed because of the use of serum PSA with other ancillary procedures such as digital rectal examination and ultrasound. This has raised a number of questions. With these tests are we able to detect prostate cancers that are lethal early enough to cure them? We know that from autopsy studies, a good number of men are known to die with prostate cancer, not from prostate cancer? Is there a role for screening and if there is, is it cost-effective, sensitive, specific and free of harm? Answers to these questions are available and / or are being refined as we move along with new knowledge and experience.

WHAT IS PSA?

The clinician, -urologist or general practitioner / family doctor, faces a number of questions when the PSA test is ordered. "What is PSA? What system does PSA affect? What does PSA test result mean? What is total PSA? And Free PSA? What is serum PSA? .Other questions that are often raised include the following: Is PSA really specific? Is PSA prostate tissue specific? Or is it prostate cancer specific? Is it men-specific? Through the lens of a community urologist, some of these questions will be addressed and others considered for another opportunity and platform for conversations

PSA is a glycoprotein enzyme encoded in humans by KLK3 gene. It belongs to the kallikrein 3 related peptidase family. It is produced in the epithelial cells of the prostate and secreted into the semen or ejaculate. PSA in the semen-ejaculate is said to assist in liquefaction of the ejaculate and fosters sperms to swim freely. It is also believed to play a role in dissolving cervical mucus thus allowing entry of sperms into the uterus to facilitate penetration of the ovum by the sperm at fertilization. PSA is present in varying small quantities in men with healthy prostate glands. It is often present in abnormal quantities in men with prostate cancer and other conditions of the prostate gland. It is also believed that PSA is ubiquitous, found in ejaculates of men and women contrary to previous concepts and beliefs. For several years, it has assumed centre stage over the previously used prostatic acid phosphatase as a preferred tumour marker for prostate cancer. From the onset of its characterization as a molecule in 1979 to its first application in clinical practice, its function as an ideal tumour marker has been under scrutiny. However, despite all the controversies, serum PSA testing has made a significant impact in our understanding and care of prostate cancer patients.

The absolute value of serum PSA when used in combination with digital rectal examination and an imaging study provide useful information about the extent of prostate cancer and its response to treatment. It appears to be a useful early detector of adenocarcinoma of the prostate. Its use as a screening tool remains controversial.

We shall review, through the lens of a community urologist, the following aspects of PSA:

i) Historical perspectives,
ii) Measurement of PSA and abnormal occurrences in different entities,
iii) Molecular biology and advances in PSA testing
iv) Recommendations for clinical use
v) PSA as a screening tool and other controversies.

HISTORICAL PERSPECTIVES OF PSA

It is thought that PSA as a glycoprotein antigen was discovered and given different names by different workers thus creating a controversy. Flocks et al (1959) were said to have experimented with antigens in the prostate. Ten years later, Albin et al (1969) reported the presence of precipitation antigen in the prostate. In 1971, Mitsuwa et al, identified a unique protein in the semen and called it -Gamma semino-protein. In 1973, Li and Belng, isolated a protein E1, from human semen in an attempt to find a novelty technique for fertility control. Sensibaugh G F. (1978) identified a semen specific protein P30, but found it was similar to E1 protein and occurred in the prostate. It was considered a potential new marker for semen identification in forensic medicine. In 1979, Wang MC et al described the purification of a human PSA antigen in serum .In 1980, Parsidero et al were the first to synthesize the serum PSA molecule while Stamey et al were the first to start clinical use of serum PSA. With these varied claims for the discovery and characterization of the PSA, its use in clinical practice has continued to attract attention

MOLECULAR BIOLOGY OF PSA

PSA is produced as a proenzyme (pro-PSA) by the secretory cells (acini) of the prostate gland. It is then secreted into the ductal lumina where the propeptide is removed to release active PSA. The active PSA undergoes proteolysis to produce inactive PSA of which a small proportion enters and circulates in the blood stream as an unbound, free PSA. Active PSA can also diffuse directly into the blood stream where it is rapidly bound by protease inhibitors. Men with normal prostates, have a majority of free PSA in serum reflecting the mature protein that has been made inactive by internal proteolytic cleavage. In contrast, this cleaved fraction, is relatively decreased in patients with prostate cancer. Therefore, the percentage of free or unbound PSA is lower in the sera of men with prostate cancer compared with those men that have a normal prostate: Several factors are known to impact normal PSA serum levels.

AGE – SPECIFIC PSA RANGES.

In men with normal prostates, serum PSA reflects the amount of glandular epithelium and ultimately, the prostate size. Thus, as the prostate size increases with age, the PSA concentration rises, increasing at a faster rate as we grow older. Therefore, different normal references is available based on the age .The following ranges have been suggested:

Age (years)	PSA (ng/ml)
40-49	0.00 - 2.5
50-59	0.00 - 3.5
60-69	0.4 - 4.5
70-79	0.00 - 6.00

Age -specific reference ranges have been in use to help improve specificity and positive predictive value in cancer detection and screening. However, it is noted that the use of a higher upper range of normal for older men reduces the sensitivity for detection of prostate cancer while the specificity is increased.

RACE-SPECIFIC SERUM PSA

Men with normal prostates from different ethnic and racial groups have different average serum PSA levels .For instance, Black men without prostate cancer tend to have higher PSA values than Caucasians who have no cancer. Men from Indian and Far East origins, having even lower average serum PSA values

OTHER EFFECTS ON NORMAL RANGE

Weight appears to be associated with PSA concentrations. In population -based studies, men with no prostate cancer tend to have lower serum PSA concentrations if they have increased body mass index (BMI).

MEDICATIONS

Several classes of medications are known to affect serum PSA levels. Finasterisde and Dutasteride , inhibitors of 5-alpha reductase ,produce approximately 50% or greater reduction in serum PSA during the first 3 to 6 months of therapy and this is known to persist as long as the medication is

continued. This effect is probably as a result of direct interference by these agents in the intra cellular androgen response mechanism. Other pharmaceuticals that can lower PSA levels include NSAIDs, Statins; and Thiazides. These are small changes. The impact of these agents on PSA levels remains to be defined .However, these potential changes should be kept in mind when evaluating PSA levels in patients who are on these agents who may require additional therapies.

RANDOM VARIATIONS

As various factors tend to be associated with the release of serum PSA from the prostate gland and the variability seen with different assay methods , elevations with different serial measurements may not always be clinically significant .This is a good reason for thorough discussion with the patient and a need for repeat serum PSA test before any intervention..

CAUSES OF ABNORMAL SERUM PSA VALUES OTHER THAN PROSTATE CANCER

With a half -life of 2.2 days, elevations of serum PSA seen in different benign conditions, will have different recovery intervals .Digital rectal examination (DRE) is known to produce minimal changes such as 0.26 to 0.4 ng / ml. So PSA can be measured immediately after DRE.

Vigorous ejaculation can produce upwards PSA levels by up to 0.8 ng / ml which can return to normal levels within 48 hours.

Bacterial prostatitis can cause elevation of PSA in the serum that may return to normal values 6 to 8 weeks following resolution and appropriate antibiotics .Biopsies for elevated serum PSA may sometimes reveal asymptomatic inflammation in the prostate.

Prostate biopsies may result in elevation of serum PSA by a median of 7.9 ng / ml within 4 to 24 hours following the procedure, returning to normal values 2 to 4 weeks after the procedure. Transurethral resection of the prostate and procedures such as urethral dilatation, may cause similar disruption. These levels remain elevated for a median period of 3 weeks.

Acute urinary retention may be associated with elevated serum PSA and levels are expected to decrease 90% within one or two days. An abnormal serum PSA found at the time of acute urinary retention should be repeated 2 to 3 weeks following removal of catheter and / or resolution of the problem

CASE 1

A 60 year old man presented with mild LUTS and mild elevation of PSA 5.7 (normal= 0-4.0) ng / ml. DRE -smooth, non-tender, no nodules .Prostate size on u / s = 40 cc. Patient was anxious about prostate cancer. Requested, consented to and had a biopsy. Biopsy results = BPH with areas of chronic prostatic inflammation. Patient treated with long-term low dose antibiotics. 3 months following completion of treatment, patient felt well, LUTS resolved, repeat serum PSA =2.1 NG / ML

MOLECULAR BIOLOGY AND REFINEMENTS IN PSA TESTING

Since its arrival in the worksheet of the urologist as test for early detection of prostate cancer about 35 years ago, its limitation as an ideal tumour marker, has made it an object of intense basic science and clinical investigations. Several concepts have been developed and tested, with the goal of improving the clinical use of serum PSA by improving its specificity and yet preserving its sensitivity. These techniques include PSA DENSITY, PSA VELOCITY, AGE-RACE SPECIFIC PSA REFERENCE RANGE, and FREE / TOTAL PSA RATIO.. It is well known that PSA is present in the human serum in several molecular forms and that the concentration of free and complexed PSA (PSA bound to alpha -1 antichymotrypsin) may vary according to specific pathologic entities in the prostate gland.

The refinements and modifications of PSA testing are expected to be useful in further disease detection and screening procedures like biopsy when the total PSA is 2.5 to 10.00 ng / ml. This is the range in which decisions regarding further diagnostic testing are more difficult.

PSA DENSITY

The use of PSA Density is defined mathematically as total serum PSA (ng / ml) divided by the volume of the prostate gland (cc.) . It is based on the assumption

the PSAD calculation would theoretically adjust for the portion of PSA resulting from BPH , providing reference values above which increased chances of a patient having prostate cancer would justify further investigations. Though a promising concept, subsequent evaluation have indicated some limitations .While early studies suggested that PSA Density will allow us to distinguish benign from malignant prostate conditions, subsequent reports found considerable overlap in PSA densities in these groups .Catalona et al (1994) in a multicentre study compared PSA density and total PSA for early detection of prostate cancer and found almost 50% of the cancers would have been missed using 0.15ng / ml as a cut-off for biopsy.

PSA VELOCITY

PSA Velocity is defined as the rate of change in serum PSA over time. This concept was developed to improve the ability of the clinician to distinguish BPH from prostate cancer and to identify men with prostate cancer likely to have progressive disease – slow or fast. This concept suggests that an elevated serum PSA that continues to rise may be indicative of prostate cancer. Carter et al in a longitudinal study found that a PSA velocity of 0.75 ng / ml per year separated patients with prostate cancer from those with BPH or no disease with a specificity of 90% and 100% respectively. A further study from the same group found that when PSA was <4ng / ml, a PSA velocity of >0.35ng / ml per year measured over several years was associated with a high risk of death from prostate cancer 15 years later. Another group (D' Amico et al) found that a PSA velocity of >2 ng / ml per year in the year prior to diagnosis was associated with an increased risk of death from prostate cancer after radical prostatectomy or radiation therapy. In clinical practice, the usefulness of PSA velocity is limited by the variability in serum PSA at different times in the same patient whether there is cancer or not. A longer period of observation and testing may reduce the general variation but the prolonged testing period may increase the anxiety for the patient

SERUM FREE and BOUND PSA

It is well known that Prostate cancer is associated with a lower percentage of free PSA in the serum compared with any benign condition of the prostate. The Free / Total PSA ratio has been useful to improve sensitivity of cancer detection when the total PSA is in the normal range (4ng / ml) and to increase specificity of cancer detection when total PSA is in the " gray zone" (4.1 to 10 ng / ml). Free PSA may be useful for risk stratification in men with prostate cancer. A lower percentage of free-to-total PSA may be associated with more aggressive tumour. However, as with total PSA there is no absolute cut-off ratio that reliably differentiates prostate cancer from BPH. The optimal cut-off value PSA is unclear and depends on whether optimal sensitivity or specificity is sought .The higher the cut-off value, the greater the sensitivity (i.e. fewer missed cancers), but the lower the specificity (greater number of false positives)

RAISING THE ACCURACY OF PSA TESTING

The need for an accurate tumour marker comes with the concern of unnecessary biopsies with attendant complications and costs. On the other hand is the risk of missing a treatable cancer. With the doubts about the benefits of screening in Prostate cancer. a better tumour marker will be welcome. Consensus on the use of these refined by-products of PSA is lacking and none of them have been shown to reduce the number of unnecessary biopsies nor improve clinical outcomes. The total PSA cut-off of 4.0 ng / ml is an acceptable value as it balances the trade-off between missing important cancers at a curable stage and avoiding detection of clinically insignificant cancers and the anxieties and complications of unnecessary biopsies. Tumour markers that can predict aggressive tumours will form a centre stage in the diagnosis and management of prostate cancer.

RISK STRATIFICATION AND STAGING

Men with prostate cancer may be characterized as LOW, INTERMEDIATE and HIGH RISK for developing metastatic disease, or dying of prostate cancer(Gleason scoring) and the stage of the disease based on low one of the three variables -Serum PSA, Gleason Scoring and Staging TMN0,

RISK	PSA (ng/ml)	GLEASON SCORE	CLINICAL STAGE
LOW	<10	6	<T2A
INTERMEDIATE	10.1 - 20	7	T2A
HIGH	>20	7/8	T3/C

Given the relative simplicity of the D'Amico criteria, other predictive models of risks stratification based on mathematical probability constructs exist or have been proposed to allow better matching of treatment decisions with disease features. Studies are being conducted into the incorporation of multi parameters with MRI imaging results into nomograms that rely on PSA, Gleason Grading and Tumour Stage.

POST TREATMENT MONITORING

Serum PSA levels are monitored periodically , for example, every 6 to 36 months, after treatment for prostate cancer- more frequently in patients with High risk disease and less frequently in lower-risk disease. If surgical therapy is successful at removing all prostate tissue and cancer, serum PSA becomes undetectable within a few weeks. A subsequent rise in PSA level>0.2 ng / m l. is generally regarded as a signal of recurrent disease. After radiation of any type, some PSA levels may be detectable, even when treatment is successful .This makes it more difficult to interpret the results of PSAs

PROSTATE CANCER SCREENING

Clinical guidelines for prostate cancer screening vary and are controversial due to uncertainty as to whether the benefits of screening outweigh the risks of over diagnosis and over treatment. In the USA, the US Food and Administration had approved the PSA test for annual screening of men 50 years and above. The patient needs to be informed of the risks and benefits of PSA before performing the test .Serum PSAs between 4.1 and 10 ng / ml are considered suspicious for prostate cancer and consideration to confirm abnormal test with a repeat serum PSA .If indicated prostate biopsy should be done to confirm tissue diagnosis. In Canada, there is no general consensus regarding screening. Rather primary health care providers and urologists are encouraged to discuss prostate cancer detection with their patients up and older than 50 years and the benefits and risks of PSA testing. In the UK, the National Health Service (2005) does not mandate nor advise PSA Test but allows patients to decide based on their doctors' advice. A review commissioned by the US Preventive Services Task Force concluded that “PSA based screening results in small or no reduction in prostate cancer specific mortality and is associated with harms related to subsequent evaluation and treatment, some of which may be unnecessary or more simply “the potential benefit does not outweigh the expected harms “in patients not already diagnosed or being treated for prostate cancer. While PSA testing may help 1000, men in a 1,000,000 avoid death due to prostate cancer; 4,000 to 5,000 men in 1,000.000 would die from prostate cancer after 10 years even with screening .This means that screening may reduce prostate cancer deaths by 25%. Expected harms include; anxiety for 100-200 receiving false positive biopsy results; pain and potential complications. For those found to have prostate cancer, frequent over diagnosis is common because most cases of prostate cancer are not expected to cause symptoms.

Since expected harm relative to risk of death from prostate cancer are perceived by patients as minimal , men found to have prostate cancer usually up to 90% of men will opt to receive treatment

PSA IN OTHER BIOLOGIC FLUIDS AND TISSUES

It is now clear that the term PSA is a misnomer. It is an antigen but it is not specific to the prostate nor to prostate cancer. Although present in large amounts in prostatic tissues and semen, it has been detected in large amounts in other body fluids and tissues.

CONCENTRATIONS OF PSA IN HUMAN BODY FLUIDS

FLUID	PSA (ng/ml)
Semen	200,000 - 5.5 million
Amniotic Fluid	0.60 - 8.9 8
Breast Milk	0.47 – 100
Saliva	0
Female urine	0.12 – 3.72
Female Serum	0.01 - 0.53

In women, PSA is found in female ejaculate at concentrations roughly to that found in male semen. Other than semen and female ejaculate, the greatest concentration of PSA in biological fluids are detected in breast milk and amniotic fluids. Low concentration of PSA have been found in the urethral glands, endometrium, normal breast tissue, and salivary gland tissues. PSA is also found in women who have breast cancer, lung cancer and in some patients with renal cancer. Tissue samples can be stained for PSA in order to differentiate the origin of malignant cells that may have spread away from the primary site.

CONCLUSIONS

Since coming on stage in the clinical urology world, it has been embattled with controversies. Attraction from the media have been galore. It has been a great leverage for bringing prostate out of the closet. Despite its refinements (PSA Density, PSA velocity, Free / Total PSA, Free and bound antigen), it has failed to meet the criteria for an ideal tumour marker. Its use and application in community urology practice to detect prostate cancer early has broken some barrier and created questions and controversies not ideal for a screening tool. Its use in tandem with Gleason grading and disease stage has ben one of the highlights of its application to clinical urology. It is a good tool for monitoring treatment of prostate cancer and detection of recurrence or castrate resistant cancer. Amidst the controversies about the discovery come information the after all PSA is ubiquitous in both male and female ejaculates. It is not prostate tissue specific; neither is it prostate cancer specific. May be time has come for a new name PCRAN (Prostate cancer related antigen)

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APPLICATIONS OF MOLECULAR BIOLOGY IN MEDICINE

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INTRODUCTION

Molecules are the building blocks of life, and variety the spice. It is variation of molecules in their genes that underlies the differences between living things in general, plants and animals, and individuals. Most of molecular biology is actually molecular genetics and has to do with these differences in the genome. In applying molecular biology to medicine, genomic differences are exploited in advancing the understanding, diagnosis and treatment of illness.

This article is a discussion of how molecular biology is applied in:

- understanding the cause and mechanisms of disease
- diagnosis and treatment of illness
- forensic medicine or medico-legal practice
- pre-implantation genetic testing and diagnosis in embryos
- population genetics.
- ameliorating resistance to tyrosine kinase inhibitor drugs
- deciphering and utilizing information written in the alphabets of life

Understanding the Cause and Mechanisms of Disease

Molecular biology has facilitated understanding of the cause of many diseases, such as cancers and other neoplasia. Genes are of cardinal importance in the development of neoplastic diseases. This is because neoplasia are, essentially, disorders in which there is uncontrolled cell division; and genes are crucial in the control of cell division. Molecular biology has revealed that malignant disorders of cell proliferation arise in many cases when there is an abnormality of a gene that codes for a protein or micro-RNA which plays a role in cell division [1]. The cardinal importance of genes in development of cancers and other neoplasia is illustrated by the fact that a cell which does not have a nucleus (and therefore has no genes) does not become neoplastic or cancerous. The mature red blood cell and the blood platelet are very good examples. No known disease is caused by neoplastic transformation of the mature red blood cell or platelet. These cells do not undergo neoplastic transformation because they contain no genes. By contrast, the immature erythroid cell in bone marrow which has a nucleus and genes – the erythroblast – is known to undergo neoplastic transformation; leading to erythroleukaemia (Di Gugliemo's Disease). Similarly, the nucleated cell in the bone marrow which gives rise to the blood platelet – the megakaryocyte – does undergo neoplastic transformation; leading to acute megakaryoblastic leukaemia. Genes found to be abnormal (mutated) in cancers and other neoplasia code for substances that have important roles in cell division. An example is *C-MYC;* which codes for a transcription factor and is found to be abnormal in Burkitt's lymphoma. Other examples are *JAK2* and *ABL* that code for enzymes that attach phosphate groups and so activate proteins that transmit the signal for cell division.

. Two of the genes that have been found to be abnormal in breast cancer – *BRCA1* and *BRCA2* - code for DNA repair enzymes. If a cell cannot repair its DNA or genes when these are damaged; it will accumulate genetic abnormalities and become prone to neoplastic transformation.

If the product of a gene has a role in the control of cell division, the normal function of the product may either have the effect of stimulating or suppressing cell proliferation. The abnormality (mutation) that occurs in such a gene may lead to *gain of function* of

gene. An example is the abnormal *ABL* which, joined to nucleotides in the BCR gene, has a product with greater enzyme activity than the normal ABL. The more active abnormal enzyme activates the proteins that transmit signals for cell division far more than the normal cell enzyme. So, the effect of the genetic abnormality that leads to the neoplastic disease called chronic myeloid leukaemia is a *gain of function* of the gene product. When such a gain of function leads to a neoplasm, the gene is called an oncogene. On the other hand, if the effect of the gene abnormality that leads to neoplasm is a *loss of function* of the gene product, the gene is a *tumour suppressor gene.* Examples are *BRCA1* and *BRCA2* genes that, when mutated, their protein products lose function as DNA repair enzymes.

In the light of the above, many neoplasia are indeed genetic disorders. These genetic disorders are usually *acquired* after the spermatozoon fertilizes the ovum to form a zygote; and so affect somatic (non-germ) cells such as the pluripotent haemopoietic stem cell in chronic myeloid leukaemia, or breast epithelial cell in breast cancer. Since the haemopoietic stem cell is not involved in formation of the zygote (i.e it is not a germ cell) the genetic abnormality that causes chronic myeloid leukaemia is not transmitted from a parent to the offspring. This situation is different from sickle cell disease or haemophilia in which the genetic abnormality is present in the germ cells (sperm or ova) involved in formation of the zygote; as a result of which the offspring are born with the genetic disorder [2,3]. In other words, the abnormal gene is inherited and the disease is *congenital,* not acquired as in chronic myeloid leukaemia. Molecular biology has led to the understanding that many neoplastic diseases are acquired genetic disorders of somatic (non-germ) cells. It is for this reason that abnormality of DNA or gene is associated many conditions / factors that predispose to neoplasia: ionizing radiation, chemical carcinogens such as alkylating agents, Down's and Fanconi' syndromes, paroxysmal nocturnal haemoglobinuria and myelodysplasia.

Another group of genes (distinct from conventional tumour-suppressor genes and oncogenes) also contribute to the neoplastic process. MicroRNA genes, unlike other genes involved in cancer, do not encode proteins [1,4,5]. Instead, the products of these genes consist of a single RNA strand of about 21 to 23 nucleotides. With a length of 21-23 nucleotides, they are very small or 'micro' compared with the much longer messenger RNAs which contain hundreds or thousands of nucleotides. The function of miRNAs is to regulate gene expression. A microRNA molecule can anneal to a messenger RNA (mRNA) containing a nucleotide sequence that complements the sequence of the microRNA. This way, the microRNA blocks translation of the messenger RNA (protein synthesis) and / or causes degradation of the mRNA, i.e regulates expression of the gene from which the messenger RNA was made.

With this background information about microRNA genes, let us consider how they contribute to the development of neoplasia. RNA quantitation studies of various neoplastic cells show that they may over-express, or under-express, specific microRNA genes. For example, *miR-15a and miR-16-1 are deleted or down-regulated* in most indolent cases of chronic lymphocytic leukaemia; and *miR155* gene is overexpressed in aggressive CLL, diffuse large B-cell lymphoma, carcinoma of the breast and colon [4,5]. Since a microRNA inhibits gene expression, if its own gene is up-regulated in a neoplasm, one can infer that it inhibits a tumour-suppressor gene; in other words, its effect is similar to that of an oncogene. On the other hand, if a miRNA gene is down-regulated in cancers, its effect is like that of a tumour-suppressor gene; because its normal function is probably to inhibit an oncogene. The function of microRNA genes depends on their targets in a specific tissue. A miRNA gene acts as a tumour suppressor in a given tissue if its miRNA inhibits an oncogene; it can act as an oncogene in another tissue if its miRNA inhibits the messenger RNA of a tumour-suppressor gene. Many microRNA genes occur in parts of chromosomes that are rearranged, deleted, or amplified in neoplastic cells. Parts of the genome consistently involved in chromosomal rearrangements in cancers but do not code for 'oncogenes' or 'tumor-suppressor genes' appear to contain microRNA genes.

Diagnosis of Disease

Diagnosis of disease has largely gone molecular. It is expected that, as more and more diseases are characterised at the molecular level, the trend

towards molecular diagnosis will continue; eventually becoming the norm. Specific diagnosis of haemoglobinopathies and various malignancies is currently based on demonstrating the genetic abnormality unique to those conditions. Specific diagnosis of sickle cell anaemia, for example, depends on demonstrating that the A=>T mutation is present in the two beta-globin genes in the individual. Such molecular diagnosis is preferred because it is more exact or specific, and allows a more accurate description of the relationship between genotype and phenotype. Various malignancies are currently diagnosed by demonstrating the genetic abnormality unique to each condition. Examples are:

MALIGNACY	GENETIC ABNORMALITY
acute myeloid leukaemiaacute promyelocytic	translocation from chrom 8=>21 t(8;21) t(15;17)
leukaemiaacute monoblastic leukaemia	inversion / del 16 trisomy 8
erythroleukaemiaBurkitt's type	t(8;14) t(2;8)t(8;22)
ALLbreast cancer	mutations of BRCA1 / BRCA2

Therapeutics and the Pharmaceutical / Biomedical Industry

The prototype of targeted molecular therapy developed by the pharmaceutical industry is treatment of chronic myeloid leukaemia with imatinib – an inhibitor of the overactive bcr-abl tyrosine kinase that drives cell proliferation in this neoplasm. Imatinib works by occupying the grove in the abl part of bcr-abl where ATP normally binds, and prevents ATP from donating a phosphate to tyrosine residues in the substrate signal transduction proteins within the cell. By preventing the activation (phosphorylation) of molecules that transmit the stimulus (signal) for cell division, tyrosine kinase inhibitors such as imatinib, nilotinib and ponatinib, reduce neoplastic cell proliferation and confer clinical benefit in chronic myeloid leukaemia.

With the success story of tyrosine kinase inhibitors in treatment of CML, targeted molecular therapy for myeloproliferative neoplasia has been tried using inhibitors of the mutant JAK2; but the clinical benefits have not matched that of TKIs in CML.

Considering the role of microRNAs in development of neoplasia, inhibiting microRNAs might be beneficial in the treatment of neoplastic diseases. For example, targeted inhibition of microRNA-191 has potential for therapy of ALL or AML with 11q23 translocation and those solid tumours in which this miRNA is overexpressed.

Forensic Medicine

Molecular biology is applied in the identification of individuals in forensic medicine or medico-legal practice. For example, DNA analysis to demonstrate the presence of specific genes that are expected to be inherited by a child from a parent, or the absence of such genes that are expected to be inherited, is used to help a court of law determine the probability that an individual is a parent, sibling, or other types of blood relative of another person.

In addition, matching of specific genes in DNA extracted from the biological sample (such as buccal mucosal swab, saliva or blood) taken from a suspect with the same genes in DNA from a forensic specimen (such as semen, hair or blood) could help in identifying the culprit during the investigation of a crime.

Population Genetics

The prevalence of specific genes in different human populations could be used to assess if there is any ancestral relationship between them. Such population genetics data can help historians and archeologists trace the migration of peoples from one geographical region to another, over the past centuries.

Pre-implantation Genetic Diagnosis

After in-vitro fertilization (test tube baby) DNA is extracted from a single cell taken from the embryo at about the 16-cell stage (embryo biopsy) and analysed to determine if the embryo has or does not have a specific desirable gene, or an abnormal or disease-causing gene. The embryo that has the desired gene or does not have the abnormal gene is then implanted in the uterus for further development. This process of pre-implantation genetic diagnosis could be used to produce 'designer babies' that are:

(a) potential donors of organs or haemopoietic stem cells for transplant to particular individuals (e.g, siblings) because they have the same HLA genes.

(b) babies who do not have the gene for specific diseases, such as sickle cell anaemia or haemophilia.
(c) babies of preferred gender; either because being a female means that the child is unlikely to have haemophilia A for example, or the parents desire a male or female child.
Developments in molecular biology make it imperative that current and future generations of doctors will practice medicine at a far more molecular level than their predecessors. To meet these challenges, tt is necessary that medical students and practising doctors are equipped with the knowledge and skills required for molecular medicine.

Molecular Insights In Chronic Myeloid Leukaemia, Gastro-intestinal Stromal Tumours and Their Treatment with Tyrosine Kinase Inhibitors

As mentioned previously, chronic myeloid leukaemia (CML) is caused by uncontrolled multiplication of a pluripotent haemopoietic stem cell and its progeny which have acquired an abnormality of the gene encoding the tyrosine kinase enzyme ABL. Incidentally, gastro-intestinal stromal tumours (GIST) also result from uncontrolled cell division caused by abnormality of the gene (*C-KIT*) for another tyrosine kinase that is very similar in structure and function to ABL. As a result of these similarities, CML and GIST can be effectively treated with drugs that inhibit both ABL and C-KIT tyrosine kinases; ie tyrosine kinase inhibitors (TKIs). Response to TKIs is affected by biological variables dependent or independent on the molecular structure of the tyrosine kinase. Variables not dependent on the molecular structure of the tyrosine kinase include activities of the Organic Cation Transporter-1 (Oct-1) which carries imatinib into cells, and the cell drug efflux pump MDR1 (ABCB1). Variables dependent on the molecular structure of the tyrosine kinases include mutations in their genes that result in changes in amino acid sequence of the tyrosine kinase enzyme proteins; and thereby resistance to their inhibitors. As would be expected, rational design of tyrosine kinase inhibitor drugs to overcome the effects of amino acid changes in tyrosine kinases caused by their gene mutations ameliorates or overcomes resistance to these inhibitor drugs.

The story of resistance to tyrosine kinase inhibitors reminds one of bacterial resistance to antibiotics; and the sobering observation that, despite the intense therapeutic war humans wage against pathogenic bacteria, antibiotic-resistant bugs have not been vanquished! So, we have had first, second, third, and even fifth generation cephalosporins! With reports of resistance to ponatinib, one of the most recently developed tyrosine kinase inhibitors [6,7], it is obvious we are travelling along that familiar road of drug resistance. Therefore, there is need for alternative strategies to reduce or overcome resistance to TKIs.

Instead of developing more and more tyrosine kinase inhibitors modeled after the prototype imatinib, alternative strategies to address resistance to these drugs are being investigated [8-13]. These strategies include combining allosteric inhibitors of tyrosine kinases with drugs such as imatinib which occupy the ATP-binding sites (or kinase domains) of these enzymes, destroying the tyrosine kinase oncoproteins (such as bcr-abl) by unleashing their natural enemy protein phosphatase 2A, and engineering disruptive mutations of the coiled-coil domain of bcr-abl required for dimerization and activity of this enzyme.

Molecular Alphabets of Life and their Applications to Medicine

Biomolecules could be considered as 'letters' used to form chemical compounds or 'words' that convey biological information. Whereas only linear polymers can be formed by nucleotides (DNA or RNA) and amino acids (proteins), these 'letters' of the genomic and proteomic alphabets are able to form far less number of 'words' and convey bioinformation than sugar molecules of the carbohydrate alphabet (such as glucose) that form both linear and branched polymers; e.g glycogen and starch.
By comparing the capacities of the genome, proteome, and glycome to convey bioinformation, the limitations of the genomic and proteomic alphabets are appreciated; and the structural versatility of sugar molecules recognized as a plausible explanation for the fact that biological information is more extensively written in the

carbohydrate alphabet [14].

To date, advances in molecular biology and their applications to medicine have focused on genomics and proteomics more than glycomics. As a result, the glycome is less generally understood than the genome or proteome, and the potential applications of glycomics to medicine less widely appreciated in comparison with genomics or proteomics. To address this imbalance, more light is shed on the glycome as the third alphabet of life by drawing extensively on how the versatility of carbohydrates in forming covalent bonds with a wide variety of chemical moieties enables them to carry an enormous diversity of biological information, interact with many bioactive molecules, and thereby modulate body structure or function

The numerous interactions of the glycome with bioactive moieties may go wrong; leading to disease. On the bright side, understanding of the molecular lesions that cause disease could be applied in making specific diagnosis [15]; and presents opportunities for targeted molecular therapy to physicians. There are potential molecular targets for treatment of conditions ranging from cancers, sickle cell and autoimmune diseases; through inflammatory, cardiovascular and thrombotic diseases, to infections such as *Helicobacter pylorus*, HIV and Ebola.

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THE ENDOCANNABINOID PHYSIOLOGICAL CONTROL SYSTEM: EMERGING TARGET FOR THE DEVELOPMENT OF NOVEL THERAPEUTIC AGENTS

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INTRODUCTION

Cannabis is one of the most commonly used and abused drugs in the world. Its use is more than those of cocaine, heroin and the amphetamines combined (UNODC, 2012).

For example, it is estimated that about 3.9% of global population (aged 15-64) used cannabis in 2011 while the estimate for the amphetamines, cocaine and opiates combined is 1.13% (UNODC 2011).

Cannabis has the longest recorded history of human use. Cannabis plant has been exploited for medicinal, agricultural, recreational and spiritual purposes in diverse cultures for thousands of years (Mechoulam, 1986).

The use of marijuana as a recreational drug has been reported to be due to its ability to alter sensory perception and cause elation and euphoria, most vividly described by the 19th century French poet, Charles Baudelaire, in his book, *Les Paradis Artificiels* (Iversen, 2000). However, the ability of extracts of cannabis to produce a variety of pharmacological actions other than its psychoactive properties, had been recognized as early as the third millennium BC, when Chinese texts described its usefulness in the relief of pain and cramps. In ancient India, the anxiety relieving effect of marijuana had been recorded more than 3000 years ago (Mechoulam, 1986).

The therapeutic use of cannabis in medicine was introduced in Western medicine in the 1st half of the 19th century (Zuardi. 2006).

At the turn of the 20th century, several pharmaceutical companies started marketing cannabis products for various medical conditions. However, by the middle of the 20th century, the use of cannabis was almost abandoned because of variations in potency of cannabis extracts, unreliable responses, introduction of more reliable pharmaceutical alternatives, experience of important adverse effects and global legal restrictions to cannabis (Fankhauser, 2002).

Cannabinoids are a group of terpenophenolic compounds present in cannabis. The best known is delta -9-tetrahydrocannabinol (THC). Cannabis smoke contains more than 460 compounds (ElSohly and Slade, 2005) out which 107 originate from the plant. These compounds that are peculiar to cannabis are known as phytocannabinoids (ElSohly and Waseem, 2014).

Two of the major constituents of cannabis (phytocannabinoids) are delta - 9-tetrahydrocannabinol (THC) and cannabidiol (CBD), both of which have been reasonably well characterized.

THC is the major constituent and predominant psychotropic component of cannabis.

THC is largely responsible for important adverse effects of cannabis such as psychosis (Gaoni & Mechoulam, 1964, Onaivi, 2009).

CBD, another major constituent of cannabis has opposite effects and ameliorates adverse effects of cannabis including psychotic symptoms (Bhattacharyya et al. 2010).

Cannabinoid –like compounds are endogenous in humans and animals and are known as endocannabinoids.

Two of the endocannabinoids, *anandamide* and *2 – arachidonoyl glycerol (2- AG)* have been identified and characterized. The Endocannabinoid Physiological Control System (EPCS) previously unknown until about two decades ago are elaborate and ubiquitous. The system is involved in a variety of physiological and pathological conditions. The fundamental role they perform in human

development, health and disease is unfolding (Mechoulam & Parker, 2013, Fride, 2008).

Endocannabinoid Signaling System

Physiological and pharmacological studies provide evidence that endocannabinoids are involved in the regulation of neurotransmitter release through activation of presynaptic CB1 receptors. The system appears to exert a powerful modulatory action on retrograde signaling associated with cannabinoid inhibition of synaptic transmission. The extensive distribution of CBrs in most biological systems provide the EPCS with broad signaling capabilities which may explain the numerous behavioural effects associated with cannabis use (Freund, Katona, Piomeli, 2003, Ohno-Shosaku et al., 2011).

EPCS consists of endocannabinoid ligands, their synthesizing and degrading enzymes, their protein transporters and their receptors (Onaivi, 2009). They are particularly abundant in various parts of the brain involved with activities such as behavior and cognition, body movement coordination, reward, learning, memory, etc.

As a result of increased understanding of the cannabinoids signaling system, there has been tremendous increase in research on potential medicinal uses of cannabis.

Available evidence implicates EPCS in a variety of physiological functions including, regulation of cell development and growth, nervous functions, modulation of immune function, reproduction, feeding behaviour, appetite, movement, memory, learning, blood pressure, pain, etc. (for reviews see, Pacher et al., 2006, Mechoulam & Parker, 2013, Pertwee, 2005).

Consequently, modulating the activities of the EPCS has great therapeutic potential for a wide range of different diseases and pathological conditions, including mood and anxiety disorders, movement disorders such as Parkinson's and Huntington's diseases, neuropathic pain, multiple sclerosis, spinal cord injury, cancer, etc. (Xian et al., 2013, Di Marzo, 2008, Pacher et al., 2006, Mechoulam, 2006, Pertwee, 2014).

Licensed cannabis-based medicines

Three cannabis – based products have been approved for clinical uses in several countries.

Dronabinol (Merinol®): approved for relief of anorexia associated with weight loss in patients with HIV / AIDS, Chemotherapy-induced nausea & vomiting (CINV).

Nabilone (Cesamet®): approved for CINV

Nabiximols (Sativex®): an extract of Cannabis of equal THC and CBD contents formulated as sublingual / oromucosal spray (approved for relief of spasticity in multiple sclerosis).

Other conditions for which clinical trials have been performed include neuropathic and cancer related pain (Wright and Guy, 2014 for a review).

Cannabis-based therapeutic agents at various stages of development and clinical trials include *CBD* (Colon Cancer, Alzheimer Disease, Glioma , Antianxiety, Antipsychotic, Schizophrenia, Anti-inflammatory, Antidepressant.

Cannabis preparation (reduced risk for diabetes, sickle cell disease, Carren et al. 2015, Abrams, 2014); for pain, adjunct to opioids (Lucas 2012); Epidiolex for treatment - resistant epilepsy, IACM Bulletin May 2015); CBR_2 agonists (Reduced rejection of organ transplant, Kenter et al, 2015); *Anandamide* (Tardive Dyskinesia, Ropke, 2014

Cannabis use-associated psychopathology

Several studies provide evidence that heavy use of cannabis is an independent risk factor for developing psychotic symptoms. This risk increases considerably in vulnerable persons such as persons with pre –existing psychiatric disorders (Andersson, et al., 1987; More et al, 2007).

The mechanism by which cannabis produces this effect is not fully understood.

Owing to the potential important therapeutic uses of cannabis, many countries have approved clinical uses of cannabis (Medical Marijuana). New policies liberalizing access to cannabis are being adopted in many countries and may likely result in substantial increase in the availability and use of cannabis in the general population and increased risk for cannabis use-associated psychopathology.

Animal models may provide information that may assist in elucidating the mechanism involved in cannabis use-associated psychopathology and in the management of cannabis use associated psychosis.

In attempt to contribute to the elucidation of the mechanism of cannabis – associated psychopathology, a simple animal model for evaluating the behavioural responses of rats exposed to cannabis smoke was developed (Obianwu and Ibeh, 2010).

Acute exposure of rats to cannabis smoke

significantly attenuated d-amphetamine - induced locomotion and stereotypy behaviours while sub-acute exposure enhanced them (Obianwu, Ikeh and Eroje, 2014). The results may indicate that exposure to cannabis smoke predisposes the animals to amphetamine - induced psychopathology. They also provide information that may assist in elucidating the mechanism involved in cannabis use-associated psychopathology.

The animal model may also be useful in evaluating samples of cannabis for potential to produce psychotic symptoms.

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MEDICO-LEGAL ASPECT OF HIV

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INTRODUCTION

The Acquired Immunodeficiency Syndrome (AIDS) was first reported in the United States of America in 1981. It has now assumed the status of a pandemic disease because it has been reported in practically all countries of the World. It is also an exponential disease. It is the most widely debated disease of this century because of non-availability of cure and consequent mortality of full blown cases. There are highly politicized controversies about the origin of AIDS, the Western Powers maintain that AIDS originated from the continent of Africa. The amount of ongoing medical research on various aspects of AIDS in practically all countries of the World is considerable. The developed countries are spending millions of dollars on this disease and there are encouraging results. Most of the research in AIDS in the developing countries is funded by the donor agencies from the developed countries and the implications are obvious. It is now known that in multiracial communities like the USA, the incidence of AIDS is on the decline in white communities. This is just to buttress the fact that our health is in our hands and also to congratulate the organizers of this seminar for bringing the problem of AIDS to the fore. The increase in HIV infection poses serious challenges not only to the medical services but also to the legal system. Two main reasons why medical professionals study Law and Ethics:

First to help function at the highest professional level by providing competent and compassionate health-care to patients.

Secondly, to help avoid legal problems that can threaten our ability to earn a living.

SYNOPSIS OF THE BODY OF KNOWLEDGE ON AIDS

It is important to highlight some of the accepted facts about this disease before a discussion on the medico-legal aspects for obvious reasons. Legal problems usually arise from the body of knowledge on issues, this is why witnesses are made to swear to an oath before giving oral evidence in Courts of Law. The Courts are also guided by published statements on any issue in dispute. It is known that ignorance of the Law is not an excuse in Law, so also is ignorance of published facts on any issue, not an excuse if the issue is in dispute.

Therefore medical knowledge should also be furthered by the reading of medical journals and articles, it was held in Crawford V Charing Cross Hospital that an anesthetist who had failed to read an article in the Lancet (a leading medical journal), describing the risks of an operation had not been negligent. Lord Denning however summarized the duty as follows:

“It would be putting too high a burden on a medical man to say that he must read every article in the medical press…the medical man's duty is limited to taking reasonable steps to keep himself abreast to modern developments in technique…failure to read a particular article may well be excusable while disregard of a series of warnings in the medical press could perhaps be cogent evidence of negligence”.

AIDS is associated with a virus now known as the Human Immunodeficiency Virus (HIV). There are two main types of this HIV Virus, HIV-1 and HIV-2. HIV-1 is responsible for most of the cases of AIDS all over the world particularly in the USA and in Europe. HIV-2 is increasingly being reported from AIDS cases in West Africa.

The known routes of transmission of the HIV Virus are as follows:

INOCULATION OF BLOOD

- Transfusion of blood and blood products.
- Needle sharing among intravenous drug users.
- Needle prick, open wound and mucous membrane exposure in health-care workers.
- Injection with unsterilized needles.

SEXUAL

- Homosexual (male to male)
- Heterosexual (male to female and female to male)

PERINATAL

- Intrauterine
- Peripartum

There are putative routes but these have been investigated and it has been conclusively shown that they are NOT involved in the transmission of the AIDS virus. These are:

CLOSE PERSONAL CONTACT

- Household
- Workplace
- School
- Health-care workers without exposure to blood.

INSECTS

Mosquitoes and others: Not known to be a means of transmission.

The blood of a person who is infected with the HIV will test positive for antibodies to the virus. A person who is positive for HIV will develop the full disease within the period of 5years in about 20 – 30% of cases. These are the individuals that spread the disease and because the disease is 'silent' in these individuals, the control has not been very easy.

The disease that indicate AIDS are diseases due to the suppression of the immune defense mechanisms in the body. These include some fungal, protozoa, bacteria and viral infections that are not usually seen in 'normal' individuals; and some tumours.

The management of AIDS requires a combination of approaches, preventive therapeutic and supportive. A major emphasis is placed on prevention because there is presently no effective means of treating this condition. There is also presently no effective vaccine against the HIV. Prevention is therefore based on the traditional public health intervention methods.

The preventive measures include antibody testing to protect blood and organ recipients and education about the danger of sharing needles during intravenous drug use. There is also need to stress programmes that educate the public about safer sexual practices, including the roles of promiscuity and anal intercourse in facilitating transmission of the virus. It has been shown that the use of condoms decreases the risk of sexual transmission. There are controversies on the role of antibody testing as a screening device for detecting sub-clinical infection. Should patients be tested in hospital as a means of protecting health care workers? The risk of HIV transmission in the health care setting is extremely low, but it is not zero and there is controversy regarding the utility of knowing the HIV status of all patients. However, the emphasis is currently on the application of universal precautions within the hospital environment rather than on universal screening.

Treatment for the patients can be divided into two categories: (1) treatment aimed at the HIV infection and treatment aimed at the secondary infections and the malignant tumours associated with HIV infection. There are two key points that underline such therapies:

(1) Prompt diagnosis and early therapy are essential.
(2) Prolonged and indefinite therapy is usually required.

THE MEDICO-LEGAL ASPECTS:

SCREENING AND PROFESSIONAL SECRECY

One of the main medico-legal issues is screening for AIDS is the medico-legal concept of Professional Secrecy. Medical Practice is built on a relationship of trust and confidence in which the patient might disclose may intimate things which the doctor undertakes to regard as a professional secret. This relationship is imperative if a patient is not to be afraid to seek the advice of doctors and if doctors are to be free to ask whatever questions they believe to be necessary for the diagnosis and treatment of patients.

The rule of professional secrecy is embodied in the oldest code of medical practice – The Hippocratic oath. Hippocrates, who by common consent is the father of medicine, formulated an oath to be taken by all his

he relevant section of the oath reads, "Whatever in connection with my professional practice or not in connection with it that I may see or hear in the lives of men which ought not to be spoken abroad, I will not divulge as reckoning that all should be kept secret". This oath has since been modified, and all fresh medical graduates now swear to a Physician's Oath when being inducted into the medical profession, after passing the final examination in the medical school. The relevant section of the Physicians oath reads, "I will respect the secrets which are confided in me, even after the patient has died".

There is however no absolute privilege on the communication between a doctor and his patient and there are circumstances under which he may have to divulge the information.

These include:

a) When compelled by the law
   (1) In a Court of Law
   (2) On Statutory certificates – death certificates
   (3) Notifiable diseases
   (4) Miscellaneous
      i. Birth registrations
      ii. Treatment of arm robbers.
b) With the consent of the patient.
c) Where there is a public duty to disclose.
d) Where the interest of the doctor requires it.

AIDS is a notifiable disease and all cases should be reported to the Local Medical Officer of Health. For now, prevention is the mainstay of management, it is therefore appropriate that a lot of effort is directed at screening. It is now an accepted practice in medicine, that all blood should be screened before use, organs should also be screened before use for transplantation. However, the law requires that you get the consent of a blood donor before you screen his or her blood and the result of the screening, if positive, should be disclosed only to him and the medical officer of Health in his district. It is only a Court of Law that can order a doctor to disclose the result of a blood test against the wish of the patient.

Has the wife of an HIV positive man or the husband of an HIV positive woman the right to know the HIV status of the spouse? This question is very important in that heterosexual intercourse is one of the recognized means of transmission of AIDS. Husbands or wives may also abandon their spouse if they have AIDS or if they are HIV positive. There is only a moral right to disclose under these circumstances and it is only a Court of Law that can compel disclosure. The health care personnel can only counsel concerned individuals and hope that their decision will be guided by wise counsel.

Should an HIV positive woman discover that she is pregnant and should she request an abortion on medical grounds? In countries where abortion is legalized, the pregnancy would probably be terminated. In countries where abortion is illegal, the woman can go to court and seek permission to go to a country where she could legally have the pregnancy terminated.

TREATMENT AND MEDICAL NEGLIGENCE: THE AIDS PATIENT

The law allows a doctor to choose his patient except in emergencies where the doctor is obliged to apply measures to preserve the life of the patient before referring the patient to another hospital. A patient also has the right to change his own doctor. The proprietor of a private hospital may elect not to admit AIDS patients to his hospital. It is however the duty of the Government to provide hospitals that should have adequate facilities to manage AIDS cases.

MEDICAL NEGLIGENCE:

Negligence is a common law concept, for a person to be held negligent in law, three conditions must be fulfilled.

(1) He must owe a duty to another person.
(2) He must have committed a breach of that duty.
(3) As a result the person to whom the duty was owed most have suffered a loss. Translating this into the terms of medical practice:
   i. The person must be the doctor's patient.
   ii. The doctor must have done something which is not acceptable in medical practices or omitted to do what is the accepted practice.
   iii. As a result the patient must have suffered a loss.

WHEN IS DUTY OWED?

The moment a doctor or a hospital undertakes to treat a patient, the patient is entitled to proper care. As I mentioned earlier, patients can choose their doctors and doctors can also choose their patients, but in emergencies, the patient is entitled to a reasonable level of care to ensure that he survives to see another doctor.

It therefore follows that if a known AIDS patient is rushed to any hospital in an emergency, the doctor and the hospital staff cannot reject him. Should he be turned back in a bad state and should he die before getting to another hospital the doctor and the hospital are liable in law.

STANDARD OF DUTY:

No doctor is expected to be perfect. The law expects every doctor to have the standard of an ordinary competent practitioner of his grade or the specialty to which the doctor belongs. The standard expected of a registrar is different from that expect of a specialist consultant. The law expects doctors to be abreast of current knowledge in the profession so that the patient can rightly benefit from the advances in the medical sciences.

It will amount to a breach of duty if a doctor gives a patient blood that has not been screened for AIDS. Should that patient become HIV positive than the doctor and the hospital are liable? The Federal Ministry of Health had directed that no patient should receive blood that has not been screened for antibodies to the HIV virus. It is no defense for the doctor to claim ignorance of this practice or for the hospital authorities to claim that there are no necessary materials to screen blood before transfusion.

STERILIZATION OF INSTRUMENTS AND NEEDLES:

It is now known that AIDS can be transmitted in hospitals and other health care centres by equipments that have punctured the skin such as needles and instruments used in surgical operations. These instruments should be sterilized by autoclave before reuse or safely discarded. The current teaching now is that whenever possible, disposable needles and equipments should be used. It would amount to a breach of duty in law if a person contacts AIDS through the use if unsterilized equipments.

AIDS AS A PROFESSIONAL HAZARD:

As I have mentioned earlier on in this paper, there is the risk of transmission of HIV to health care workers. Available data suggests that the risk is very low but it is not non-existent. One report noted that the infection occurred in 3 of 351 health-care workers who had needle stick exposures to the blood of HIV-infected individuals (Curran et al., 1988). In this same report there were 3 cases of HIV infection apparently following exposure of skin lesions or mucous membranes to infected blood. Another report found that out of 2,200 persons who were injured while working with blood or other materials contaminated with HIV, 16 ultimately became seropositive for HIV infection (Barnes DM 1988). The conclusion from all of these is that great care should be taken within the health-care setting to protect against transmissions of this type. AIDS is therefore an occupational hazard and a health-care staff is entitled to compensation if he contacts AIDS in a health-care setting. It is the duty of the employers to ensure that the staff are not unduly exposed to contacting AIDS.

TREATMENT

It is the duty of Health-care authorities to ensure that there are adequate facilities for the treatment of AIDS in government hospitals. One of the problems with the management of AIDS is the cost of the drugs. Some of which have to be taken for prolonged periods of time. Our hospitals are now used to the 'OS syndrome' (OUT OF STUCK). Patients are made to buy even the needles that are used to administer injections. Are the hospital authorities covered in law to adopt this rather peculiar Nigerian attitude to health care delivery? It will be a difficult position to justify in law because it will be strange to a legal system that operates within the ambits of an international penal system. This is why concerned individuals are clamouring for an all embracing National Health Insurance Scheme that covers all Nigerians and not only workers in a formal civil service sectors as its currently being largely practiced.

COMPENSATIONS:

An action for negligence involves a civil process and the patient is not asking for the punishment of the offending doctor but for the recovery of monetary compensations from him for not exercising proper care in treatment. I always tell my colleagues that it is the right of the patient to be compensated for the damages. This is why all doctors are enjoined to be insured and there are Insurance Companies in Nigeria that indemnify doctors for malpractice suites. All the Federal Government Teaching Hospitals now require their doctors to have an insurance cover but I don't know if this practice has extended to State and Local Government Level.

The insurance scheme is to ensure that the patients are compensated for the damages and that the doctors are not liquidated for not being able to pay the compensations.

There is the concept of vicarious liability in law and this is prominent in cases of Medical negligence. It simply implies that the authorities that own the hospital are equally liable for whatever happens in their hospital. It therefore follows that when a doctor is being sued for negligence, the hospital authorities are jointly sued with the doctor. This is why the hospital authorities should insist that all doctors in their employment are covered for malpractice by an insurance policy with a reputable company.

CONCLUSION

The threats of HIV/AIDS to health are obvious. But the medico-legal aspects appear to have been overlooked and neglected. Enlightenment on these aspects should be given their pride of place especially now that most patients are getting increasingly aware of their rights. This will help to prevent unnecessary litigations. It should be noted however that doctors also have their own rights and which ought to be protected. In view of the possibility of a small percentage of HIV positive patients being in their 'window period' it is advisable and indeed safer for doctors to always assume their patient to be HIV positive and adopt the universal precaution guidelines. There is need to have clear cut hospital policies on the ways HIV/AIDS patients should be managed and a breach should attract stiff penalties. A reorientation is imperative to sensitive doctors towards developing patients-friendly disposition to patients who are living positively with HIV/AIDS. The relevant bodies and other stake holders in the control, care and management of HIV positive patients needs to step up enlightenment campaigns on the need to accept victims without any form of discrimination. A pragmatic prosecution of the foregoing proposals will make health care delivery and the entire citizenry the better for it.

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FAMILIAL HYPEREKPLEXIA: A CASE REPORT AND REVIEW OF THE LITERATURE

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ABSTRACT:
Familial Hyperekplexia is a rare but important condition with variable inheritance. It is important to recognize this potentially fatal condition and institute treatment promptly. We are reporting the clinical course and the management of a female neonate born in our unit, with family history of Familial Hyperekplexia.

Key words: Hyperekplexia, Familial Hyperekplexia (FH), Neonatal, Hypertonia, Apnea

CASE REPORT

A baby girl was born to a 31-year-old Para two, gravida one mother at 37 weeks and 5 days of gestation by Spontaneous Vertex Delivery, following induction of labor for decelerations on cardiotocograph. APGAR scores were nine at one and five minutes. Her mother had been diagnosed with hyperekplexia in childhood, carrying a mutation in GLRA 1 gene which was reported "likely to be inherited in an autosomal dominant pattern". This baby's birth weight, occipito-frontal circumference and length were 2,400 grams (9^{th} - 25^{th}centile), 32cm (2^{nd} -9^{th}centile) and 47cm (9^{th} centile), respectively. Routine Newborn Examination at 7 hours of age was normal, apart from a history of vomiting after feeds. Subsequent review at 19 hours of age due to the maternal family history of Hyperekplexia revealed "normal cry, global hypertonia, increased neck retraction and increased startle on glabellar and nose taps". Examination of other systems were normal. The baby was on the hypoglycemic protocol in view of low birth weight and remained normoglycemic. Investigations done in view of hypertonia and increased startle response showed no evidence of sepsis, electrolyte or metabolic abnormalities.

Her mother had a spontaneous abortion at 9 weeks' gestation in a previous pregnancy. During the current pregnancy, she had experienced periodic per vagina bleeding, a "black out" and urinary tract infections at 13, 19 and 15 weeks respectively. Foetal scans were normal. Maternal routine antenatal serology tests were negative for Hepatitis B surface antigen-HBsAg, Syphilis and HIV. She was a teetotaler, nonsmoker and not a known psychoactive substance user. The baby's older male sibling and maternal uncle were reported to be carriers of the hyperekplexia gene, but asymptomatic. The baby's father was asthmatic while the maternal grandmother had Type 2 Diabetes Mellitus. Both parents were unrelated Caucasians with no history of metabolic disorders.

Baby developed likely physiological jaundice on the second day of life which was treated with phototherapy for two days. Both mother and Baby's blood groups were O-Positive and Baby was direct Coombs test negative. In view of persistent hypertonia, Clonazepam was commenced on the fourth day of life and was discharged home on the thirteenth day of life to be followed up at the Neonatal Clinic.

In early infancy, baby had repeated outpatient visits and admissions to the Hospital. She was seen at 4 and 6 weeks of age for suspected Otitis media and Bronchiolitis. At 7 weeks of age, she was admitted for repeated episodes of "choking, gagging during feeds vomiting and raspy breathing" consequent to which she was started on Gaviscon® and Ranitidine® for gastro-esophageal reflux with the subsequent addition of Domperidone at 7 months of age. At 9 weeks of age she was readmitted following poor feeding with vomiting, an episode of floppiness, repeated abnormal movements (jerking of extremities, tonic posturing), deviation of gaze to the right and tachycardia. Investigations and monitoring were unremarkable and a retrospective assessment of Hyperekplexic Crisis was made following an initial assessment of seizures. She remained apparently well until 10 months of age when she had varicella which she tolerated without sequelae. Subsequent follow-up showed decreasing hypertonia but transient increase in frequency of startles at 15 months of age following an unrelated accidental fracture of her left ankle. She was discharged and transferred to the Neurological Unit at 21 months of age for follow-up.

Literature Review

Hyperekplexia (HR) is a condition in which there is an exaggerated startle reflex causing apnea, frequent falls and injury.[1-3] It can be classified based on severity (minor and major)[3,4], and mode of inheritance (familial/hereditary and sporadic).[3,4] In the minor form of HR startle reflexes are exaggerated from normal while the major type presents with generalized muscular rigidity in the neonatal period.[3,4]

Familial Hyperekplexia (FH)- Online Mendelian Inheritance in Man (OMIM) 149400 (Synonyms: Familial Startle Disease, Startle Disease, Familial Startle Reaction, Stiffman Syndrome, Congenital Stiffman Syndrome, Congenital Kok Disease and Stiff Baby Syndrome) was first described in 1958.[5-10] It is a rare, heritable, none epileptic, severe paroxysmal neuromuscular disorder characterized by marked hypertonia and exaggerated responses or startle reflexes to unexpected tactile, auditory and visual stimuli.[4,7,11,12] Its pathognom is a non-habituating, generalized flexor spasm to a glabellar tap.[3,8] gated chloride channels that cause post synaptic hyper-polarization and synaptic inhibition in the brain stem and spinal cord.[8] The disruption of the function of these inhibitory glycinergic receptors increases the general level of excitability of motor neurons, thus accounting for hyperekplexia.[6] Familial Hyperekplexia is caused by mutations in the genes for pre and post synaptic glycine receptors in the brain, brain stem and spinal cord.[5,14,15] The mutations may cause loss of function of glycine receptors, reduced glycine receptor clustering at synapses or reduced glycine release from presynaptic terminals[15]. Human glycine receptors are made of 3 alpha-α and 2 beta-β subunits.[10,13,16,17] Four types of alpha units-α_1-α_4 and one beta subunit have been identified[10,13,17]. Mutations of the gene coding for the α_1 subunit in 5q33-35 are more common, accounting for 30% of cases with most mutations found in exons 6 and 7. Mutations of the β subunit have also been described.[7,8,18,19]

Familial Hyperekplexia may be inherited in an autosomal dominant or autosomal recessive manner.[3,20] The autosomal dominant type is more common, with almost complete penetrance and variable expressivity.[3,20,21] Six missense mutations- P250T, Q266H, R271L, R271Q, K276E and Y279L - are inherited in an autosomal dominant manner.[7] Four- I244N, del Exon 1-6 α_1 subunit gene and compound mutations in the R252H and R392H inherited from both parental alleles are inherited in an autosomal recessive manner.[7] Other novel mutations resulting in Familial Hyperekplexia have also been described.[22-24] Sporadic forms of Hyperekplexia have been described in association with brainstem or extrapyramidal diseases[25], paraneoplastic disorders[25], encephalitis[25], brainstem hemorrhage[25], sarcoidosis[25], Chiari malformation[25] and multiple sclerosis.[25] The mechanism/s by which these conditions cause Hyperekplexia are unknown.[25]

Symptoms of Familial Hyperekplexia usually occur shortly after birth and invariably within the first week of life with generalized hypertonia-attenuating during sleep, myoclonus, trismus and apnea.[3,4,17,25] Antenatal presentation may occur with abnormal uterine movements or prenatal startle responses.[3,5,17,25,26]. Onset of symptoms in later life have been reported.[2-4] Diagnosis is easily made in a neonate with Hyperekplexia and a family history of

Hyperekplexia. However, this should not preclude a proper diagnostic evaluation, since Familial Hyperekplexia can present in association with other common neonatal causes of jitteriness, apnea and seizures.[3,9,27,28] Differentials in the neonatal period are hypoglycemia which may co-exist with Familial hyperekplexia[9], Tetanus[3,25], Stiff-Man Syndrome[1,28], Myoclonic Seizures[3], Disordered GABAergic motor inhibition of motor cortex, brainstem and spinal cord[1], Phenothiazine Toxicity[3], Paroxysmal Extreme Pain Disorder[9] and Crisponi Syndrome.[9] In adults, differentials include Giles de La Tourette[3], Swartz Jampel Syndrome[3], Isaacs Mertens[3], Reticular Reflex Myoclonus[3,25] and other obscure pathologies like Jumping Frenchman of Maine[3], Miryachit-in Siberia[3] and Latah in Malaysia and Indonesia.[3]

Hypertonia usually resolves spontaneously by the third year of life while excessive startle reflexes persist into adulthood, manifesting as falls unassociated with loss of consciousness.[4,8,22] Electroencephalograph and nerve conduction velocities are usually normal,[3] while electromyography shows almost permanent muscular activity with periods of quietness.[3] No characteristic Computed Tomography findings have been reported.[3] Studies using Magnetic Resonance Spectroscopic Imaging have reported normal or reduced relative N-acetyl aspartate(NAA) to Creatinine(Cr) and Choline-Cho ratio (NAA/Cr+Cho) ratio in frontal, central and parietal lobes of affected persons.[4,29] Reported associated findings and complications of FH include facial dysmorphism[22], central apnea[3,11], nocturnal/diurnal/hypnagogic myoclonus[3,28], sinus node paucity with bradycardia[30], complete heart block[31], SIDS[3,11], umbilical and inguinal hernia[3,28], hip dysplasia[18,28], pyelectasis[18,28], developmental delay[4,22,28] intellectual disability[1], status epilepticus[32], hesitating gait[1,22], space phobia[1,22] and startle induced falls.[4,5,13,2,33].

Hyperekplexia is a rare illness with varying degrees of severity.[3] Familial Hyperekplexia presents in the neonatal period and may lead to death, following apnea, cardiac arrhythmias or cardiac arrest. It has also been implicated in near miss Sudden Infant Death Syndrome and Sudden Infant Death Syndrome,[30,34-38] with two case series reports documenting 20% mortality.[37,39] Because of its rarity, large treatment trials are not feasible; hence therapeutic measures are empiric.[36] Clonazepam, a benzodiazepine with potent 5-hydroxytryptamine agonist properties, is considered to be the drug of choice for the treatment of hypertonia and apneic episodes in FH.[3,28,40-42] It considerably reduces or abolishes the occurrence and severity of generalized hypertonia and severe apneas in hyperekplexia with consequent reduction in morbidity and mortality.[21,27,38] It is presumed to act by potentiating another inhibitory postsynaptic receptor of the Type A GABA.[3,28,40-42] Other medications that have been used in the treatment of FH with varying results are Carbamazepine, Vigabantrin, Valproic Acid, Alcohol, Phenobarbitone, Chlordiazepoxide, Diazepam, Phenytoin and Piracetam.[3,28,41] The Vigevano maneuver; forced flexion of the head and legs towards the trunk, can also be employed to abort severe episodes of apnea associated with hypertonia.[3,40]

Discussion.

Hyperekplexia is a rare disease that may mimic other common neonatal conditions.[1,3,4,7,9,11,12,25,28] The age and manner of presentation of our neonate was typical[3,4,17,25] and a diagnosis was easily made, based on maternal history with typical physical findings on examination, along with negative sepsis and metabolic screens ruling out alternative diagnosis. However, it should be noted that the mother was diagnosed in childhood, implying a delay in maternal diagnosis which is consistent with a case report.[4,28]

The apparent lack of symptoms in an older male sibling and male maternal uncle carrying the gene is curious, since reports indicated that the proband had a "likely autosomal dominant" inherited type of Familial Hyperekplexia that "usually has complete penetration". This might be attributed to inheriting an incompletely penetrant gene,[36] variable expressivity[24,28] or modification of expressivity by genes on the Y chromosome. If the sibling has a less expressed form his symptoms may be delayed or remain subclinical.

The response to clonazepam[3,28,40-42] and subsequent reduction in hypertonia is characteristic and follows the natural course of FH.[3,4,17,25] The clinical diagnosis of gastro-oesophageal reflux in this patient is unusual,

Hyperekplexia. It also shows the difficulty of distinguishing provoked hyperekplexia from gastro-oesophageal reflux.

Though the baby had an evaluation for Developmental Dysplasia of the Hip-DDH at discharge as part of the normal pre-discharge "baby check", the authors are of the opinion that babies with HR should also be evaluated for hernia[3,28], pyelectasis[18,28] which are also known associations of FH, in addition to DDH.

The aim of this report is to raise awareness among clinicians of this rare, but potentially mortal disease, with a high likelihood of misdiagnosis, but which, when considered as a differential, can be easily diagnosed and managed. We also recommend that a differential of hyperekplexia be entertained in babies with unexplained hypertonia.

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Competing interests: None.

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REPORT OF WORLD ORAL HEALTH DAY 2017

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INTRODUCTION:

World Oral Health Day is celebrated globally every year on 20 March and is organized by FDI (World Dental Federation). World Oral Health Day was launched in 2013 to raise awareness of the importance of good oral health and its significance in safeguarding general health and well-being. This was done through an international awareness campaign created and launched by FDI, adapted and promoted locally by national dental associations in over 140 countries worldwide.

The World Oral Health day 2017 was celebrated in Bayelsa state by the Nigerian Dental Association in collaboration with the Nigerian Medical Association Bayelsa State chapter on the 20th of March, 2017 with the theme *"Live mouth smart"*.

The activities spanned from the 18th to the 23rd of March 2017 and included talk shows on radio and television, road walk and oral health campaign as well as free dental check-up and treatment in three centers:

1. The Federal Medical Centre Yenagoa
2. The Dental Centre, Niger Delta University Teaching Hospital Okolobiri
3. The Dental Clinic, Diete Koki Memorial Hospital Yenagoa

The oral health campaign took place in Ogboloma, Okolobiri, Obunagha and finally ended in Tombia market in Etegwe all in Yenagoa local government area.

The talk shows took place in Royal FM 95.5 Agudama- Epie Yenagoa, on Saturday 18th of March 2017 while the television program took place in the Nigerian Television Authority Yenagoa on the 23rd of March 2017.

Brief history of the world oral health day celebration

WOHD was officially launched in 2007 and was originally celebrated on 12 September, the birth date of FDI founder Dr Charles Godon. However, the campaign was not fully activated until 2013, when further to a decision by FDI's General Assembly (governing body) in September 2012 the date was changed[1] to 20th March 2017.

. The main reason for this change is to avoid conflict with FDI's World Dental Congress which took place during the same period.

The new date of was chosen to reflect that:

- Seniors must have a total of 20 natural teeth at the end of their life to be considered healthy
- Children should possess 20 baby teeth
- Healthy adults must have a total of 32 teeth and 0 dental cavities

  Expressed on a numerical basis this can be translated as 3 / 20 hence March 20

Previous campaign themes:

- 2013: *Healthy Teeth for a Healthy Life*
- 2014: *Celebrating Healthy Smiles*
- 2015: *Smile for Life*
- 2016: *Healthy mouth, Healthy body*.

World Health Day is one of eight official Global Health campaigns marked by WHO, along with World Tuberculosis Day, World Immunization Week, World Malaria Day, World No Tobacco Day, World AIDS Day, World Blood Donor Day, and World Hepatitis Day.[2]

Aim of the program

The main aim is to raise awareness of oral health issues so that governments, health associations and the general public can work together to achieve healthier mouths, and happier lives.

Secondarily to reduce tooth decay and to raise awareness to better oral health seeking behavior

To celebrate the benefits of a healthy mouth and to promote worldwide awareness of the issues around oral health as well as the importance of looking after oral hygiene to everyone old and young[3].

Staff:
A total number of 9 dental surgeons and 7 dental therapists, 10 dental surgery assistants and 3 dental technologists took part in the program.

Patients seen:
One hundred and sixty nine patients were treated during this program comprising 89 (52.6%) men and 80 (47.3%) women. While the figure appears large, it is pertinent to note that the patients were spread over a couple of days due to the small number of Dental Surgeons and Therapists as well as the availability of dental chairs
The mean age of the men was 36.8 ± 11.39 years, and that of the women was 33.8 ± 14.7 years. About 50% of those treated had their teeth extracted as a result of Dental caries and Periodontal diseases while 77 (49.5%) had scaling and polishing done.
Only 8 (4.7%) of the patients; 5 men and 3 women had restorative treatment done.
During the interactions in the communities, we discovered that a lot of them were ignorant of the causes of oral diseases for instance; they still believe that dental caries was caused by worms.
They were also not aware of the various treatment options available to them as most of them felt that every carious tooth must be extracted.
The other major problem was lack of adequate resources.
Currently, facilities for proper oral health care are only available in two out of the eight local government areas of Bayelsa state and even these facilities need to be upgraded
It is hoped that, the government of Bayelsa state should as a matter of urgency, open up more, well equipped dental centres in all the local government areas as well as renovate and equip the old ones with modern equipment

Conclusion
The World Oral Health Day 2017 has come and gone. It is hoped that the government will rise up to its responsibilities of making oral health care affordable and readily accessible to the people of Bayelsa state.

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CASE REPORT: HYPERTROPHIC CARDIOMYOPATHY WITH A SOLITARY KIDNEY IN A 35-YEAR-OLD NIGERIAN MAN.

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ABSTRACT

Background: Hypertrophic cardiomyopathy (HCM) is a genetic disease with an autosomal dominant inheritance. It is characterized by hypertrophy of the interventricular septum, apex or left ventricular free wall either in isolation or combined. The disease is often asymptomatic and discovery may be incidental such as during routine medical checkups or may present for the first time with sudden death especially in young people. A congenitally absent kidney occurs in one out of ten persons and increases the risk of compromise of renal function and development of hypertension.

Method: The case records of the index patient and literature review on both conditions were utilized.

Result: Mr. O. N., a young Nigerian male was deported from a Scandinavian nation back to Nigeria following completion of a seven year jail term for a drug trafficking offence. He was told his heart had stopped on several occasions, for which an echocardiogram was done and revealed abnormalities that would put him at risk for sudden death. Following a comprehensive medical review, he was also told he had just one kidney and would need regular checkups of its function. At presentation, cardiovascular system examination revealed a heaving cardiac apex despite no evidence of hypertension. Echocardiography revealed features of hypertrophic cardiomyopathy. A renal ultrasound scan confirmed an absent right kidney.

Conclusion: HCM is rarely diagnosed in our environment partly due to the poor medical seeking behavior of the populace and scarce availability of echocardiography services. A congenitally absent kidney is also relatively rare. This patient presented with two medical conditions which incidentally would usually go unrecognized in this environment unless on the event of sudden cardiac death in the case of HCM or complication of renal impairment and hypertension if single kidney is compromised. Resultant left ventricular hypertrophy, as a complication of hypertension, could mask the diagnosis of HCM or make it more difficult to recognize.

KEY WORDS: young man, hypertrophic cardiomyopathy, solitary kidney

INTRODUCTION

Hypertrophic cardiomyopathy (HCM) is transmitted as a Mendelian trait with an autosomal dominant pattern of inheritance[1]. It is defined by inappropriate hypertrophy which may involve the interventricular septum, apex or left ventricular free wall either in isolation or in combination, with typically a non-dilated chamber and no known cause, such as hypertension or aortic stenosis[2-4]. The disease is many instances is asymptomatic and first presentation may be sudden death especially in the young[4].

Prevalence has been put at 0.02 - 0.2% in the general population[5,6]. The diagnosis of HCM is made clinically by cardiac imaging using a 2-dimensional echocardiography[2].

Screening of family members for HCM should begin by age 12 and should be carried out every 12–18 months with two-dimensional echocardiography and 12-lead ECG, as well as history taking and physical examination unless the diagnosis is established or excluded by genetic testing[7]. Renal agenesis is a medical condition in which one (unilateral) or both (bilateral) fetal kidneys fail to develop. Unilateral renal agenesis affects approximately 1 in 1000 live births[8]. Most individuals with unilateral renal agenesis lead normal lives with no specific treatment necessary but may be at an increased risk for hypertension, nephrolithiasis, kidney infections, and/or renal failure[9]. The contralateral kidney is usually larger due to compensatory hypertrophy. Unilateral renal agenesis may be an isolated congenital malformation but may be associated with other chromosomal abnormalities and non-chromosomal syndromes[10]. Genitourinary anomalies are most frequent associated abnormalities[11]. Combination of HCM and renal agenesis is rarely reported[12] and an extensive literature search on google did not reveal any genetic links between the two conditions although other cardiovascular abnormalities have been documented in genetic syndromes associated with renal agenesis[13,14].

CASE REPORT

O.N, a 35-year-old Nigerian man presented at the medical out-patient clinic following deportation from a Scandinavian nation back to Nigeria after completion of a seven year jail term for a drug trafficking offence. He was told he had a heart condition that would put him at risk for sudden death. He was told his heart had stopped on several occasions and an echocardiogram had revealed abnormalities. He was also told he had just one kidney and would need regular checkups of its function. He thus presented for a medical checkup with a complaint of occasional palpitations. He had no history of dyspnoea, orthopnea, cough, leg swelling or angina pectoris. On examination, he was not ill looking, not in any obvious respiratory or painful distress, not pale, acyanosed, anicteric, afebrile with no dependent oedema. Examination of the cardiovascular system revealed a normal pulse rate of 80/minute and blood pressure was 120/80mmHg. His jugular venous pulsation was not visibly elevated and apex beat was located at the fifth intercostal space, mid-clavicular line, forceful. The heart sounds were S_1 and S_2 only. An apical holosystolic murmur, grade 3, was present. On respiratory examination the trachea was found to be central, and chest expansion was equal on both sides. Percussion notes were resonant bilaterally, with vesicular breath sounds. Abdominal examination revealed normal findings as did central nervous system examination.

Chest radiograph posterio-anterior view (Fig 1) showed a normal sized heart with no aortic unfolding. Lung fields were clear. Thoracic cage was normal. Standard 12-lead ECG (Fig 2) showed sinus rhythm with rate of 78beats/minute, poor R wave progression in precordial leads with deep S waves in right precordial leads and diminished left precordial R waves. T waves were inverted in inferior leads (II, III, and aVF) and leads V_2-V_6. Echocardiography (Figs 3a&b) showed normal left ventricular (LV) systolic function (ejection fraction 78%), grade 2 diastolic dysfunction, no resting wall motion abnormalities, LV septal wall (IVS) thickness of 17.8 mm, LV Posterior Wall (LVPWD) thickness of 13.9mm with IVS/LVPWD of 1.7, left ventricular cavity size of 40.5mm in end-diastole and systolic anterior motion of the anterior mitral valve leaflet.

He also had moderate mitral regurgitation.

An abdominal ultrasound scan (Fig 4) showed the right kidney was absent while the left kidney was moderately enlarged with intact corticomedullary differentiation and normal parenchymal echotexture. However the exact dimensions of the kidneys were not stated by the sonographer and the patient could not be reached for a repeat of the ultrasound scan. No abnormalities were noted in other organs. Fasting blood sugar was 4.0mmol/L. Lipid profile, electrolytes, urea and creatinine were normal. He was placed on a beta blocker and counselled on need for checkup visits including need for regular assessment of his renal function. He was also counselled on the need for screening of all first degree relatives for HCM using echocardiography. Ultrasound was also recommended for all his first-degree relatives.

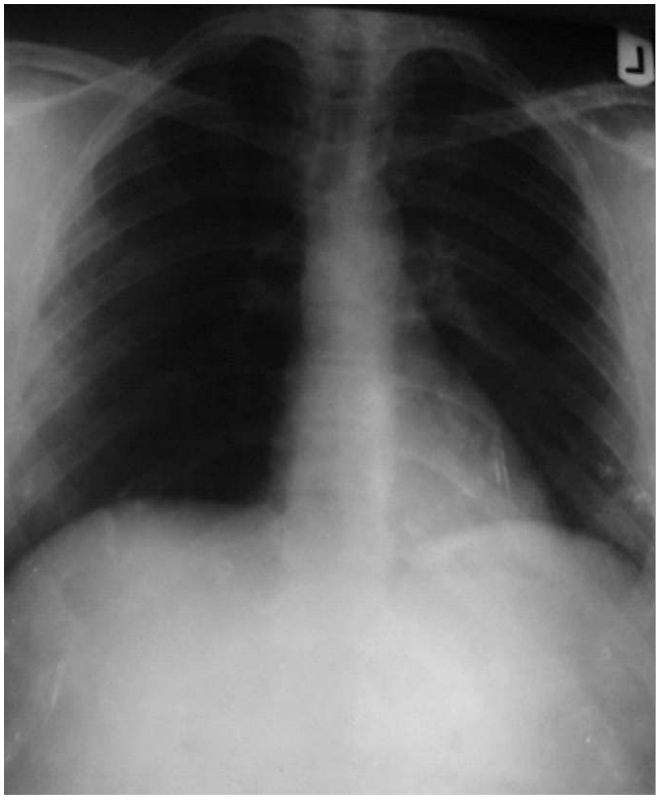

Fig 1: Postero-anterior chest radiograph shows normal heart size, clear lung fields and normal thoracic cage.
(Note: linear opacity overlying cardiac apex is an artifact)

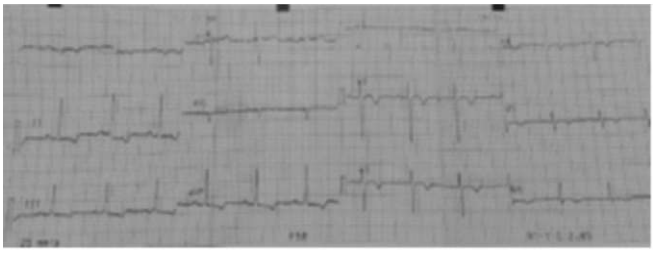

Fig 2: ECG showing poor R wave progression in precordial leads with deep S waves in right precordial leads and diminished left precordial R waves,
also T wave inversion in leads II, III, aVF, V2-V6

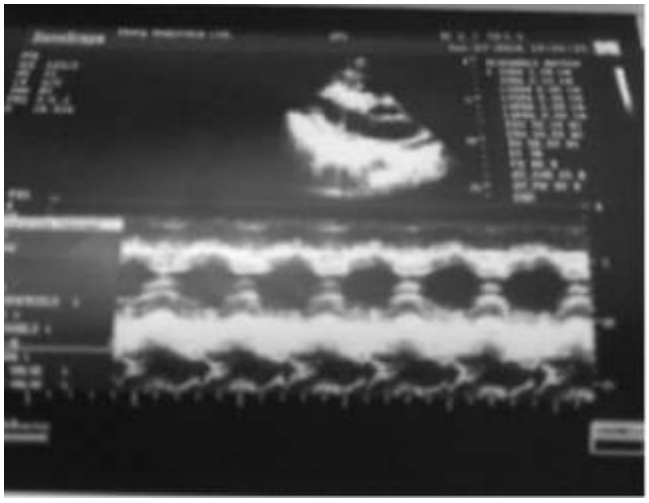

FIG 3a: M-mode echocardiogram showing disproportionate thickness of interventricular septum 17.8mm, Left Ventricular Posterior Wall (LVPWD) thickness of 13.9mm with IVS/LVPWD of 1.7

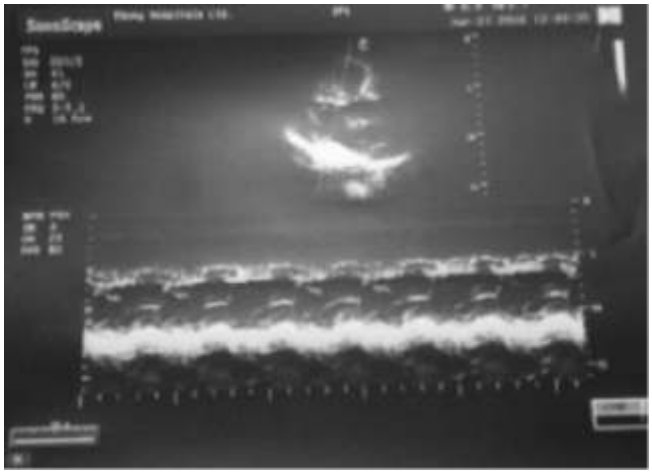

FIG 3b. M-mode echocardiography of the patient across the mitral valve showing Systolic Anterior Motion (SAM) of the anterior mitral valve leaflet.

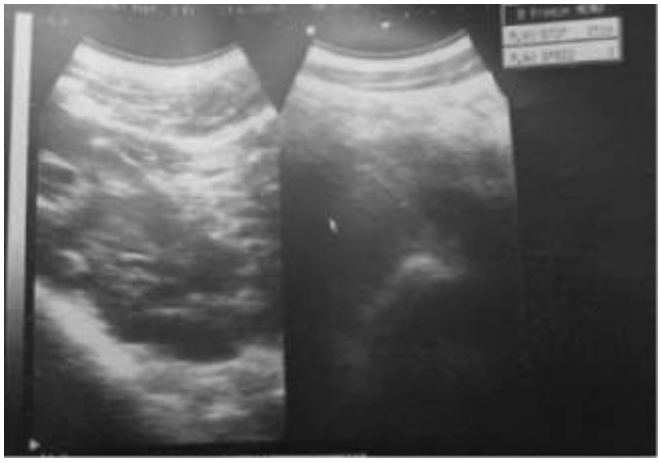

Fig 4: Ultrasound photograph of the abdomen showing non-visualization of right kidney (arrow indicates absence of kidney in the right renal fossa) with compensatory hypertrophy of the left kidney.

DISCUSSION

There are few reports on hypertrophic cardiomyopathy in Nigeria. In a study of cardiomyopathies involving 315,150 children ≤13 years in Southwestern Nigeria, hypertrophic cardiomyopathy (HCM) accounted for 16.13% of cases with a male to female ratio of 1:1.5[15] while in an echocardiography study by Mbakwem et al[16] of adults with cardiac diseases, only 1.9% of the 714 subjects studied met the criteria for a diagnosis of HCM. Most cases are asymptomatic but some cases report dyspnoea, chest pain and palpitations[3]. The initial clinical suspicion of HCM may be on account of finding of a heaving / forceful LV apical impulse in the absence of hypertension and the recognition of a heart murmur on examination as was the case in the index patient[17]. HCM is the most common cause of cardiac sudden death (SCD) in young people[1,4]. The 12-lead ECG is abnormal in 90 to 95 percent of patients with HCM and in 75 percent of asymptomatic relatives[3,18,19]. ECGs show a wide variety of abnormal patterns including increased voltages consistent with LV hypertrophy, ST-T changes with marked T wave inversion in the lateral precordial leads, left atrial enlargement, deep and narrow Q waves, with reduced R wave amplitudes in lateral precordial leads[18]. The index patient had poor R wave progression in precordial leads, diminished left precordial R waves and T waves were inverted in inferior leads (II, III, and aVF) and leads V_2-V_6. The clinical diagnosis of HCM is conventionally made with cardiac imaging, most commonly with 2-dimensional echocardiography[2,3,15,16]. A finding of left ventricular wall thickness on 2-dimensional echocardiography greater than 15mm in any myocardial segment not attributable to hypertension, aortic stenosis or any other cause of volume or pressure overload, is sufficient to make diagnosis[19] of HCM in adults. HCM is characterized by a small left ventricular cavity size (of <45mm in end-diastole)[19]. The index patient met the echocardiography criterion for HCM. Negative inotropic medication, such as β-blockers or non-dihydropyridine calcium channel blockers have some therapeutic benefits such as antiarrhythmic effects and improvement of symptoms of heart failure, by slowing heart rate and reducing the force of LV contraction (thus augmenting ventricular filling and relaxation) and by decreasing myocardial oxygen consumption[2,17] An implantable cardioverter defibrillator (ICD) is the mainstay therapy for sudden cardiac death (SCD) prevention and is indicated when a patient has a history of ventricular fibrillation (VF) or hemodynamically unstable ventricular tachycardia (VT)[2]. However, there is poor knowledge and practice of cardiopulmonary resuscitation in our environment in the event of a cardiac arrest[20,21].

The index patient also had congenital absence of the right kidney. Renal agenesis is a congenital anomaly in which there is absence of fetal kidney on one or both sides[22]. Patients are usually asymptomatic if only one kidney is absent. It may be found incidentally when the abdomen is imaged for other reasons. More often than not, the left kidney is affected and occurrence is more in males than females[23]. The aetiology is often unknown, it may be multi-factorial and an early vascular insult to the developing ureteric bud has been proposed as a possible cause[24]. Patients with unilateral renal agenesis may have associated

urological anomalies[10]. Patients with a solitary kidney are advised to have a screening micturating cystourethrography to rule out coexisting anomalies. The index patient did not do this test. Complications of unilateral renal agenesis may include development of secondary hypertension and clinical features of renal failure[9]. For 'uncomplicated cases', life-long follow-up of blood pressure, serum creatinine and urinary protein checks every year or two is advised. Also advisable is dietary advice to normalize an increased body mass index[25]. Sonography is a non-invasive modality and is an ideal tool for long term follow up when assessing the status of the solitary kidney. The biological children and other first degree relatives of persons with congenital solitary kidney have significantly increased risk for renal disease. Ultrasound is therefore recommended for them[26]. The index patient was advised on the need for regular serum electrolytes, urea and creatinine checks and follow up abdominal ultrasound scans. He was also advised on the need for ultrasound scans for his first degree relatives.

CONCLUSION:

HCM is rarely diagnosed in our environment partly due to the poor medical seeking behavior of the populace and scarce availability of echocardiography services. Unilateral renal agenesis is also relatively rare. This patient presented with two medical conditions which incidentally would usually go unrecognized in this environment unless in the event of sudden cardiac death in the case of HCM; or complication of secondary hypertension and or renal impairment if the single kidney is compromised. Hypertensive heart disease as a consequence of hypertension, with resultant left ventricular hypertrophy could mask the diagnosis of HCM or make it more difficult to recognize.

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