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GENERAL INFORMATION

Annals of Ibadan Postgraduate Medicine is published biannually by the Association of Resident Doctors, UCH chapter. It is normally published in the months of June and December.

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INFORMATION FOR AUTHORS

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The Annals of Ibadan Postgraduate Medicine (Journal of the Association of Resident Doctors, UCH Chapter) is published biannually.

The Editorial Board welcomes contributions in all fields of medicine including medical technology, as well as economic, social and ethical issues related to the practice of medicine especially in a developing country.

It is meant to meet the continuing educational needs of post-graduate doctors as well as stimulate research and academic pursuit.

TYPE OF ARTICLES

Reviews and Annotations: These are normally invited contributions. They are expected to be concise and exhaustive. Must not exceed 20 typed and double spaced pages References should not exceed 50.

Commentaries: They are invited editorial on any subject suggested by the Editor in chief which should not be more than 1,500 words and not more than 10 references.

Original Research Articles: This can be accepted as a man article or a short communication. A main article or a short communication should contain between 2,000 and 3,000 words. It usually presents the result of a large study (prospective or retrospective).

It must contain an abstract of not more than 200 words.

Short communications are reports of smaller studies. This should have not more than 6 references, one illustration and one Table.

Topical Issues: This is our novel article which deals with issues like:

- Medical ethics as it affects medical practice in Africa
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The requirements for authorship and for preparation of manuscripts submitted to the journal are in accordance with the uniform requirements for manuscripts submitted to Biomedical Journals (JAMA 1993; 269:2286; N Engl J. med 1991; 324:424-428; BMJ 1991; 302: 338-41; Ann Intern Med. 1997; 1126 36-47).

PREPARATION OF MANUSCRIPTS

- Manuscript will be considered for publication on the understanding that it has been submitted exclusively to the journal except for addresses and speeches.
- That it is not being considered for publication elsewhere at the time of submission.
- That the data submitted has not been published elsewhere.
- However a paper presented at a scientific meeting or conference will be considered if it has not been published in full in a proceeding or similar publication.
- Authors are free to submit manuscripts

rejected by other journals. In a similar way, they are free to submit articles rejected by this journal elsewhere.

- The editors would wish to be informed about any conflicts of interest in the submitted manuscripts and any previous reports that might be regarded as a duplication of some data.
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- Three copies or the manuscript (or a copy electronically) should be submitted to:

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ORDER OF ARRANGEMENT

- Arrange the article in this order. (1) Title page; (2) Abstract; (3) Text (4) Reference; (5) Tables and (6) Figures and Legends.
- Pages should be numbered in sequence beginning with the Title page as 1, abstract as 2 etc.
- Each section of the manuscript must start on a new page.
- All manuscript should be typed doubled spaced on a plain white A 4 (8"x 11") paper with a 25mm margin at the top, bottom and sides.

1. Title Page: This should contain

- Full title of the paper
- The name of each author, their highest academic qualification as well as their academic and medical titles.
- The name of the department(s) and institution (s) the work was carried out below the name of the last author listed.
- The name, address, e-mail address, telephone number and fax number of the author responsible for correspondence.
- Three to six key words.

2. Abstract:

This is required only for clinical studies and should not be more than 250 words. It should contain the background, objective, method, results and conclusions of the study. It should be structured.

3. Main Body of the Text

This should be divided into:

(i) Introduction
(ii) Materials and Method
(iii) Results
(iv) Discussion and
(v) Conclusion for original articles

Case reports should have:

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- Use of acronyms or abbreviations should be limited to units of measurement. All measurements should be in metric units (Metre, Kilogram, and litre) or their decimal multiples.
- Temperatures should be in degree Celsius, blood pressures in millimeters of mercury and haemoglobin in g/dl.
- Authors are advised to use the generic names of drugs unless where the Trade name is important to the article. Trade names should be designated by use of the symbol.
- The names of manufacturer, city and coutry,

of manufacture of specialized equipment, chemicals and pharmaceutical products cited in the text must be mentioned.

4. References

The journal follows the convention of the Vancouver reference list system. General arrangement, abbreviations and punctuation are uniform requirement for manuscripts submitted to biomedical journals.

- Follow index medians for periodicals
- All authors should be listed when they are four or less. However, list only the first three and add *et al* when five or more.
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- Number them in Arabic numerals (Tables 1, 2, etc in the order in which they are mentioned in the text.
- Each table should have a footnote which identifies the abbreviation used.

6. Figures and Figure Legends

- The Journal welcomes illustrations either as line drawings or glossy photographs.
- Photographs should be in black and white. Where a coloured photograph is submitted, the author(s) will be charged some money.
- Illustrations should be referred in text as e.g. Fig. 2 Each figure should bear a reference number correspondence to a similar one in the text.
- The illustration should be marked at the back with the name(s) of the authors and title of the paper.
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- The journal does not accept slides and computer generated graphics.
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- Any previously published figures must be accompanied by a written permission.

EDITORIAL STYLE

The journal follows the British conventions of spelling, punctuation and grammar. All submitted articles must have excellent design and correct methods of statistical analysis. The statistical methods must be appropriate to the study. Interpretation of data must be correct and accurate.

ETHICS

Studies and trial involving human beings must contain a statement that it was approved by the regional or institutional ethical committee.

It must also show that the human subjects gave their informed consent.

PEER REVIEW

We operate the peer review system. All submitted articles are first red by at least a member of the Editorial Board. Those potentially acceptable are then passed on to referees who are experts in the various fields concerned. We ask referees to comment on originality, scientific reliability and clinical relevance or usefulness. Those adjudged suitable are then submitted to statistician for statistical review.

Those that fall short may be rejected outright or sent back to authors for corrections. For

rejected articles, only one copy will be given to the author(s). Those that successfully pass through all the stages will be considered for publication. Two copies of revised manuscripts should be sent back to the Editor-in-Chief.

Copyright

On acceptance, the copyright of the paper will be vested in the Journal and Publisher.

Acknowledgement of Receipt

For every manuscript received by the Journal, an acknowledgement is dispatched immediately to the authors.

EDITORIAL

Infectious diseases remain a major health problem in the developing world. The scourge of economic and political quagmire and the attendant poverty, malnutrition and ignorance creates the enabling environment for microbes to thrive with splendour among the peoples of these nations. And no thanks to the ravaging HIV/AIDS pandemic that is worsening the situation and causing a re-emergence of hitherto curtailed infectious diseases even in the developed nations of the world. This edition and the next focus on aspects of different infectious diseases, especially those prevalent in resource-limited settings.

Dr. Shima Gyoh, in his lecture, sensitizes medical practitioners about malpractice and medico-legal issues especially in the context of increasing enlightenment of the public as regarding their rights and privileges in medico-legal matters and reminding us of the ethics of the medical profession.

To win a battle you must first thoroughly understand your enemy. Hence, Prof. F. Adu gives a detailed account of the molecular structure of the polio virus. Dr. A Fatiregun reviews the epidemiology of poliomyelitis and current worldwide efforts at eradicating the polio virus.

While a cure is yet to be found for HIV infection, currently available anti-retroviral drugs reach only 4-8% of persons needing it even though they have demonstrable clinical benefits Dr. Abdul G. Habib identifies areas of concern and suggests measures to ensure the success of Anti-retroviral Treatment Programmes in resource-limited countries especially Nigeria.

The ear, nose and throat are important gateways into the body, hence Dr. O.A. Lasisi reviews how HIV/AIDS manifests therein either by way of direct invasion, opportunistic infections, neoplasm or neurologic damage. Tuberculosis remains a topical disease especially because of its twin relationship with HIV. Dr. A.O. Kehinde, in this edition, reviews current ideas and development geared towards early and better diagnosis of tuberculosis.

The original article reports the frequencies of the lupus anticoagulant in a cohort of healthy pregnant and non-pregnant Nigerian adults and suggests a method for screening this protein in persons in whom the antiphospholipid syndrome is suspected.

Typhoid fever remains a major public health problem in developing countries. Factors responsible for the continuing rise in its incidence, prevalence morbidity and mortality are identified, and suggested solutions proffered in the review article by Dr. J.A. Otegbayo. Infertility remains a central issue in gynecological practice especially in sub-Saharan Africa and pelvic inflammatory disease is a major cause. Drs. Akin-Tunde Odukogbe and Bolarinwa Ola herein review the current concepts in the diagnosis and treatment of this sometimes silent but ravenous disease. Years ago, in some parts of Nigeria, the passage of blood in the urine by a male adolescent was equatted to the female menstruation and believed to signify male sexual maturity. Health education measures have since been instituted. Dr. O.G. Arinola, in his article, reviews the immunological status of Nigerian school children with urinary schistosomiasis.

The epidemiology of several cancers indicates the involvement of some infectious agents in their pathogenesis. Drs A.O. Oluwasola and A.O. Adeoye in this edition review this association between infectious agents and cancer and suggest preventive measures.

We also present in this edition a commentary by Dr. M. O. Obajimi *et al* in which an advocacy is made for standardizing breast ultrasonography in Nigeria given its affordability, availability and non-utilization of ionizing radiations. We welcome reactions to this from our esteemed readers.

This edition also features relevant web links on infectious diseases and other regular features. Certainly, this edition is not exhaustive on infectious diseases; we therefore look forward to publishing in the next edition articles on several other topics in infectious diseases.

Rufus Akinyemi
Editor-in-Chief

Original Article

The Lupus Anticoagulant in a Population of Healthy Nigerian Adults

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Key words: *Lupus anticoagulant, aPTT, KCT, antiphospholipid syndrome*

SUMMARY

Patients with the antiphospholipid syndrome are at a high risk of recurrent thrombosis and recurrent fetal loss. Infertility and a number of other clinical manifestations have also been attributed to this syndrome. There are many tests for detecting the presence of the lupus anticoagulant but the most sensitive remains controversial. In this study we have used a combination of activated partial thromboplastin time (aPTT) and Kaolin clotting time (KCT) to determine the presence of the antibody in 125 healthy individuals which included pregnant women. Six (4.8%) and four (3.2%) of the subjects had elevated aPTT and a KCT ratio ≥ 1.2 respectively. The tests showed a high prevalence of the lupus anticoagulant in the multiparous group than the other groups while there is paucity of the anticoagulant in the pregnant women who are not at risk. We suggest the use of both aPTT and KCT for the screening of patients in whom the antiphospholipid syndrome is suspected.

INTRODUCTION

The lupus anticoagulant (LA) is an immunoglobulin that binds phospholipid and hence inhibits coagulation tests. It is not only found in disease states but could be detected in healthy people[1]. The identification of this antibody is a routine procedure in developed countries but this is not yet so in developing countries and because of this, the diagnosis of the antiphospholipid syndrome is often based on clinical assessment.

The anticoagulant which was first described in association with systemic lupus erythematosus (SLE) [2] is sought for when a clinician suspects the presence of the inhibitor due to its recognized clinical features or an unexplained prolonged Activated Partial Thromboplastin Time (aPPT). There are various tests available for detecting the presence of the lupus anticoagulant but the most sensitive remains a controversy. The tests used are the aPPT [3], kaolin clotting time (KCT)[4], dilute Russell's viper venom time (RVVT)[5], and the platelet neutralization test (PNT)[6]. At least two of these tests must be performed when investigating a patient suspected of having the lupus anticoagulant [6]. Detection of anticardiolipin antibody using enzyme linked immunosorbent assay is another test which is sensitive to the presence of the anticoagulant but this may not be practicable in a developing country set up.

In this study the presence of the lupus anticoagulant was sought for in healthy individuals using the aPTT and the KCT.

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MATERIALS AND METHODS

The population studied included 125 healthy adults comprising 51 male and 74 female. Twenty-six of the females were nulliparous, 25 multiparous and 23 pregnant women with no history of habitual abortion, infertility or ecclampsia.

A free flowing venous blood was collected from each subject, 4.5mls of which was delivered into plastic tubes containing 0.5ml of 3.2% trisodium citrate. Platelet poor plasma was prepared by centrifugation of the collected blood at 2000g for 30 minutes. The plasma was processed within two hours of collection. Control plasma was obtained from 6-8 healthy volunteers.

KCT and aPTT were determined by standard methods with bovine brain as the source of phospholipids [7]. A graph was plotted for each

of the subjects and a KCT ratio determined thus:

$$\frac{\text{KCT (80\%N: 20\%test)}}{\text{KCT 100\%N}},$$

The lupus anticoagulant was taken to be present at a KCT ratio of ≥ 1.2 (8) the graph was interpreted as described by Laffan & Bradshaw [8]:

Pattern 1 - Classical lupus anticoagulant.

Pattern 2 - Coagulation factor deficiency as well as lupus anticoagulant.

Pattern 3 - Plasma containing the anticoagulant but also deficient in a cofactor necessary for its full inhibitory effect.

Pattern 4 - Absence of lupus anticoagulant.

RESULTS

The ages of the subjects ranged between 19 years and 42 years with a median of 25.5 years.The mean aPTT was 39.8 ± 5.5 seconds and the mean KCT was 82.1±20.4 seconds. Twenty seven (22 %) of the subjects studied had the pattern 1 graph while 54 (43%) and 26(21%) had the patterns 2 and 3 graphs, respectively, only 18(14%) had the Pattern 4 graph (Table I). Four (3.2%) of the population screened had a KCT ratio of ≥ 1.2 and thus could be interpreted as having the lupus anticoagulant; all these were males and had the pattern 2 graph. Table II shows the relationship between the PTTK and KCT of each group with the pattern of the graph obtained.

aPTT that was greater than 50 seconds (mean ± 2SD) was taken as abnormal. This was seen in 6(4.8%) of the subjects studied, this comprised 2(1.6%) of the males, 1(0.8%) pregnant woman and 3(2.4%) of the multiparous women. None of the nulliparous females had a value greater than 50 seconds.

DISCUSSION

The term lupus anticoagulant (LA) is a misnomer since it is associated with thromboembolic disorder

TABLE 1: Prevalence of the different LA graph patterns in the different groups.

Type of LA graph	Study population	Male	Pregnant female	Multiparous female	Nulliparous female
1	27(21.6%)	14(27%)	0	11(44%)	2(8%)
2	54(43.2%)	24(47%)	11(47%)	6(26%)	13(50%)
3	26(20.8%)	10(20%)	6(26%)	5(20%)	5(19%)
4	18(14.4%)	3(6%)	6(26%)	3(12%)	6(23%)

TABLE 2: The relationship between the mean PTTK and KCT of each group with the type of graph obtained.

Types of graph	Males		Pregnant Females		Multiparous Females		Nulliparous females	
	PTTK	KCT	PTTK	KCT	PTTK	KCT	PTTK	KCT
Type 1	38.1	80.1	-	-	42.0	81.5	40.0	93.0
Type 2	41.7	98.9	41.7	73.3	45.0	102.8	39.6	89.7
Type 3	36.7	67.6	36.0	74.8	39.6	75.5	36.5	59.5
Type 4	34.6	65.0	40.0	79.7	36.0	70.3	37.7	83.0

rather than a bleeding tendency. It is known to occur in a variety of conditions and particularly in obstetrics cases where adverse effects like early abortions and second or third trimester intrauterine deaths are common. Successful pregnancies do however occur in the presence of the lupus anticoagulant[6]. The prevalence of the anticoagulant among women with a history of two or more miscarriages varies between 5-50% in different series [9]; the prevalence in SLE may be as high as 65%. In this study of normal subjects, 21.6% had the classical lupus graph, the use of the KCT ratio however brought the prevalence down to 3.2%, which is similar to a prevalence of 2.3%, found in the sera of pregnant primiparous women in an antenatal clinic in West Indies [10]. The subjects studied are in the reproductive age group because this is the age group in whom the obstetric complications of the lupus anticoagulant are most likely to be encountered.

Inter-laboratory variations exist in detecting the antiphopholipid antibody particularly in the detection of the anticardiolipin antibody. In contrast, lupus anticoagulant results are more reproducible despite the fact that these tests are laborious[11]. The detection of the lupus anticoagulant will require the use of more than one test, with the aPTT as a screening procedure [12]. There is therefore the need for at least one other method in excluding the anticoagulant. No significant difference was found in specificity among aPTT, dRVVT, KCT and dilute aPTT but aPTT and dRVVT were significantly more specific than anticardiolipin antibodies [13]. Dilute aPTT was found to be more sensitive than dRVVT, KCT and aPTT. It is therefore recommended that the aPTT be used as a screening procedure for LA and the KCT, dRVVT or dilute aPTT be used for confirmation in laboratories that cannot afford procedures that are more sophisticated.

It is surprising that the pattern 1 graph that typifies the classical lupus anticoagulant was not recorded among the pregnant females; they also had the highest prevalence of the pattern 4 graph (No LA). More of the pregnant women however had the pattern 3 graph. The presence of more of the pattern 3 graph in the pregnant women compared to the other groups might explain why the lupus anticoagulant is implicated in many obstetrics conditions, since the cofactor which is necessary for the full inhibitory effect of the anticoagulant is low among them. The multiparous women on the other hand recorded the highest prevalence of the pattern 1 graph and a low prevalence of the pattern 4 graphs. The mean PTTK and KCT of this group are also higher than those of the other groups. This could be why 90% of cases of SLE are seen in women and usually in the childbearing age. The presence of the lupus anticoagulant (in its different forms) in 86% of the population in this study will explain its association with a variety of diseases. There is however, a need for further studies using these tests on patients who are at risk of having the lupus anticoagulant.

We conclude that a combination of the aPTT and the KCT ratio will suffice in confirming the diagnosis of the lupus anticoagulant in a developing country.

REFERENCES

1. Devine DV and Brigden ML. The antiphospholipid syndrome: when does the presence of antiphospholipid antibodies require therapy. PostgraduateMedicine.1996; 99: 105-108; 113-125.

2. Conley CL and Hartmann RD. A haemorrhagic disorder caused by circulating anticoagulant in patients with disseminated lupus erythematosus. J. Clin.Invest.1952; 31: 621-622.

3. Robert A. Two different incubation times for the activated Partial Thromboplastin Time (aPTT): a new criterion for diagnosis of lupusanticoagulant.Thrombosis and Haemostasis.1994; 71: 220 - 224.

4. Exner T, Rickard KA and Kronenberg H. A. Sensitive test demonstrating lupus Anticoagulant and its patterns.Br. J. Haematol.1978; 40:143 -151

5. Thiagaranjan P, Pengo V and Shapiro S. The use of the dilute Russell Viper Venom Time for the diagnosis of lupus anticoagulant. Blood.1986; 68: 869-874.

6. Thiagaranjan P and Shapiro S. Disorders of thrombus formation: lupus anticoagulants. Methods in Haematology 1983; 7: 121.

7. Kotila TR, Fatunade HB, Ajakaiye F *et al.* Bovine brain: a cheap source of Phospholipids reagent in the determination of PTTK. The Nigerian Postgraduate Medical Journal 1999; 6: 1-3

8. Laffan MA and Bradshaw AE. Investigation of a thrombotic tendency In Dacie JV and Lewis SM, Eds Practical Haematology 8th edn. Edinburgh, Churchill Livingstone 1994; 354.

9. Maclean MA, Cumming GP, McCall F *et al*. The prevalence of lupus anticoagulant and anticardiolipin antibodies in women with a history of first trimester miscarriages. Br.J.Obstet. Gynaecol.1994; 101:103-106.

10. Wharfe G, Fletcher H, Reid M. Lupus anticoagulant in Jaimacan primiparae and the clinical sig nificance in asymptomatic patients. West Indian Medical Journal 1999; 48(3) : 126 - 128.

11. Peaceman AM, Silver RK, MacGregor SN, *et al*. Interlaboratory variation in antiphospholip antibody testing. American Journal of Obstetrics and Gynaecology 1992; 166: 1780-1787.

12. Shokunbi WA, Inwood MJ. The lupus anticoagulant and the APTT: Derivation of the APTT correction ratio. The Nigerian Postgraduate Medical Journal 1999; 6: 33-36.

13. Ferro D, Saliola M, Quintarelli C *et al*. Methods for detecting lupus anticoagulants and their relation to thrombosis and miscarriage in patients with systemic lupus erythematosus. J. Clin. Path.1992; 45: 332 - 338.

Malpractice and Medico-Legal Issues

Dr Shima K Gyoh

Chairman, Medical and Dental Council of Nigeria(MDCN).

The Medical and Dental Council exists for the protection of the interest of the patient and for guiding the doctor to provide skilled, safe, appropriate and friendly health care for members of the public that need it. Although, the health care team consists of a variety of important professionals giving investigative, dispensary, curative and other ancilliary services for patient care; the doctor alone has the moral and legal liability and is often sued when any part of that health care goes seriously wrong. Although this may seem unfair, it is absolutely as it should be. People needing medical attention go to a particular health institution in order to see a particular doctor, perhaps because of his reputation. There always exists an unwritten contract between the doctor and his patient, and this contract is justifiable. It is up to the doctor to ensure that he has a good team of associate professionals working with him because he is legally liable for their errors.

As the public has become more and more enlightened, the doctor's involvement with the law has gone beyond the expert witness. He is now being increasingly subjected to public accountability for all aspects of the practice. Complaints often arise, and if they are not carefully managed, may go beyond the health institution to the law courts, or to the Medical and Dental Tribunal, or to both. While lawyers are expected to serve the interest of justice from the point of view of their clients, some endeavour desperately to serve that interest by capitalizing on any technical legal loophole, which now becomes the issue, while the real issues are relegated to the background. The client is served but justice is compromised from the point of view of society. While the Legal Assessor is there to limit such tendencies on legal aspect, medical professionals in the MDCN try to limit it on medical iissues.

If the MDCN were not there, the charge of professional misconduct would not be appreciated, and the mishaps resulting from them would be the offence for which the doctor would be charged. For example, if a patient died as a result of the mistakes of the doctor, he would have to face a charge of murder or manslaughter. Medicine would become a dangerous profession to practice. By creating the MDCN, it is now possible for doctors themselves to determine whether a particular colleague exercised sufficient skill and care that would be expected of a competent and caring professional. As they say, it takes a thief to catch a thief !

It is obvious that the aim of creating the MDCN is to produce a suitable environment to make the doctors and dentists self regulate thier profession. It is given sufficient powers to govern the profession and to enforce reasonable and acceptable standards of professional practice and etiquette.

The public needs to know whom among the people presenting themselves as doctors and dentists the MDCN is screened and found competent and safe. The list is published as the Register of doctors and dental surgeons. It should be authoritative, reliable and accessible to the employers of health professionals and to the general population. In the UK, the Register is produced annually. The MDCN has not yet achieved this ideal due to past mismanagement. The new management is going to change that picture within the near future. The Register is mentioned because the MDCN has authority only over registered practitioners. The offences committed by non-registered practitioners have to be sued in ordinary courts since it is a criminal offence to practice orthodox medicine without being qualified and registered practitioners.

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Being the text of a Lecture delivered at the monthly Oyo State Branch of the Nigerian Medical Association (NMA) Continuing Medical Education (CME) series held on Tuesday, May 31, 2005 and hosted by the Association of Resident Doctors, University College Hospital, Ibadan, Nigeria

Principles of Good Practice (Ethics)

The principles of good practice constitute an unwritten contract between clinicians and their patients, and form the basis on which the MDCN expects all registered doctors and dentist to practise. They are summarized as follows:

1. Make the care of your patient your first concern.
2. Treat every patient politely and considerably. While the doctor retains the right to choose his patients except in emergencies, all treatment must be conducted without discrimination.
3. Respect patients' dignity and privacy, and do not force treatment on an unwilling conscious patient.
4. Listen to the patients and respect their views.
5. Give patients information in the way they can understand.
6. If you get involved in biomedical research on human beings:
    a. The patient's informed consent is essential.
    b. It must not involve withholding effective treatment.
    c. Your research protocol must be approved by an Ethical Committee.
7. Respect the rights of patients to be fully involved in decisions about their care.
8. Use only scientifically sound methods, keeping your professional knowledge and skills up to date. Expose unsound practice and practitioners.
9. Recognize the limits of your professional competence, consult and/or refer to others when necessary.
10. Be honest and trustworthy, never certify what you have not verified, or assist other people by dishonest opinions and prescriptions.
11. Respect and protect the confidential information of patients. The widespread practice of sending entire case notes to the pharmacy for drugs or the pathology labouratory for blood investigations unnecessarily exposes the confidential information in the case notes. Appropriate forms exist for these services.
12. Make sure that your personal beliefs do not prejudice your patient's care.
13. Act quickly to protect patients from risk if you have a good reason to believe that you or your colleagues may not be fit to practice.
14. Avoid abusing your position as a doctor.
15. Work with colleagues in the way that best serves the patient's interests. Collaborate with persons or other professionals in the health team in rendering care, but ensure that:
    a. The professionals are competent in their fields.
    b. They are recognized by their professionals bodies.
    c. You do not delegate to anyone procedures that are the exclusive responsibility of medically qualified clinicians.
    d. You retain the absolute authority and take full responsibility for whatever happens to the patient.

Right and Responsibilities

- Only a registered practitioner may practice.
- Other members of the health team must perform under the permission and supervision of a doctor or dentist.
- When an MDCN- registered practitioner is not available, others perform according to standing orders prepared by the supervising doctor or dentist of the institution. If they perform outside the framework of the standing orders, then they become liable for the error.

Professional Misconduct (Infamous Conduct)

This is a general term describing a clinician's avoidable act of omission or commission against the principles of good practice, with consequences detrimental to the patient. The act may be deliberate, with some ulterior motive, or more commonly, due to negligence or carelessness. The term more or less covers all offences for which clinicians may be charged before their professional disciplinary tribunal.

Malpractice

A definition can be composed from informatiothe

MDCN pamphlet on "Rules of Professional Conduct" thus: *Malpractice is failure, in the practice of medicine or dentistry, to exercise the skill, decorum and standards adjudged appropriate and acceptable to the generality of the registered members of the profession and recognized by the MDCN*.

The skills and correct method of practice in medicine and dentistry are learned by apprenticeship over 5 to 10 years *after graduation*. This is why the residency programme exists. Graduation from a medical or dental college is only an indication that the new graduate has attained sufficient theoretical knowledge to start training to be a clinician. Only consultants are fully trained. All other professionals are not supposed to work on their own. One of the most dangerous aspects of clinical training is to be a self-taught practitioner. Unfortunately, our system promotes being self-taught, for it is the new graduates that are sent to work in remote rural areas where they have no senior colleagues or even a library to consult. In order to solve unfamiliar problems, they often invent methods that are not in accordance with the safer established standard practice in the profession. We should remember that scientific medicine is built on knowledge and skills acquired and improved over the centuries, and passed from one generation to another. Many of these skills and attitudes cannot be found in textbooks.

The greatest weapon against malpractice is to be thorough and pay attention to detail. Take a complete history, do a complete examination and base your provisional diagnosis on the evidence before you. Avoid diagnosis by guesswork and inspiration. The MDCN has now insisted that every doctor must own personal basic diagnostic equipment, which they should always use during clerking.

A concerned practitioner, who devotes one hundred percent attention to his or her clinical responsibilities would hardly get involved in malpractice. The temptation to quickly get away or tally in order to meet other engagements elsewhere may cause an otherwise skilled practitioner to take regrettable decisions. Needless to say, the temptation to make more money by choosing the more expensive or invasive procedure is malpractice.

Negligence

Our guidelines give a list of what is usually considered to be negligence:

1. Fails to give prompt attention to a patient.
2. Manifests incompetence in clinical assessment of patient.
3. Wrong diagnosis in the presence of obvious clinical presentation.
4. Fails to advise a patient on the risks attendant on a particular course of management or operation.
5. Makes glaring mistakes.
6. By action or omission causes other members of the health team under his supervision to act to the detriment of the patient.

Self-Advertisement

Direct and indirect self-advertisement aimed at attracting patients is forbidden, whether done by the doctor or through an agent. Other forbidden actions are:

(i.) Press announcement of dramatic breakthroughs in treatment.

(ii.) Professional touting.

(iii.) Sign boards that are advertorial rather than informative in nature.

Other factors

Practitioners can be charged with infamous conduct in a professional respect under the following circumstances:

a. Improper termination of a pregnancy, which is criminal abortion under the Nigerian law.
b. Conviction in a court of law for certain offences that the MDCN considers to be incompatible with the status of a medical or dental practitioner.
c. Attending to patients while under the influence of alcohol or drugs. Alcoholism and drug abuse are offences.

Conclusion

People who have a true vocation to be doctors derive much pleasure from practicing their

profession, and they thrive under the hard work and have no problem with the regulations. They may occasionally fall into temptation and get into trouble, perhaps through tiredness and overwork, but they admit their mistakes and appear sorry rather than resort to lies and mobilize their resources and friends for a cover-up. They have a much easier time with the Medical and Dental Tribunal. The profession of medicine may appear glamorous, but it demands your soul, and people with a vocation gladly give it.

The greatest weapon against malpractice is to be thorough and pay attention to detail. You are a medical detective, trying to discover the crime committed by disease. Take a complete history, do a complete examination, and base your diagnosis on the evidence before you.Avoid diagnosis by guesswork and inspiration. If you are too tired or not well enough to do this, pass the patient to a sympathetic colleague.

If you ever accidentally get into trouble and are great enough to see your fault, admit it. No one is above making mistakes; the public and the MDCN know that. You will do much better than you fear. Denial and lies send the wrong signals to everyone. Above all, remain understanding and tender to the injured family. They may be bitter, angry and even hostile, especially after the loss of a human life, but you should remain cool and comforting to them. Clinicians should always try to understand things from patients' point of view.

REFERENCES

1. Rules of Professional Conduct for Medical and Dental Practitioners.MDCN. 1995.

2. Code of Medical Ethics in Nigeria MDCN; Revised Edition. 2004.

3. Good Medical Practice. General Medical Council of the UK. 2004.

Epidemiology and Control of Poliomyelitis

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SUMMARY

The World Health Assembly (WHA) declared that the World Health Organization (WHO) was committed to the global eradication of poliomyelitis. As with smallpox, eradication involves the additional criterion of the elimination of indigenous transmission of wild virus. This article reviews the epidemiology of poliomyelitis, strategies for polio eradication and the progress made so far. Threats to eradication objectives are identified and changes in polio eradication initiative deadline are outlined.

INTRODUCTION

Drawing from the successful smallpox initiative, the World Health Assembly (WHA) resolved to eradicate polio from the world by the year 2000[1]. As was the case with smallpox virus, poliovirus causes acute non- persistent infections, humans are the only reservoir, virus survival in the environment is limited, and immunization with vaccine interrupts virus transmission. Collectively, these factors make polio virus a candidate for eradication [2].

The smallpox eradication effort led by the World Health Organization (WHO) in the 1960s and 1970s offers a clear example of the financial and humanitarian benefits that accrue to the world community after total eradication of a disease. Since the last case of smallpox was detected in 1977, billions of dollars have been saved in vaccine procurement. More importantly, thousands of deaths and millions of cases of a disabling disease are averted each year. The global eradication of polio is expected to offer similar benefits to humankind. Worldwide, an estimated $1.7 billion is expected to be saved each year[3].

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The goal of global eradication of wild polio virus was defined as: no cases of clinical poliomyelitis associated with wild poliovirus, and no wild poliovirus found worldwide despite intensive efforts to do so. The primary strategies for achieving this goal are two folds. One is the administration of polio vaccine in the manner most effective to interrupt transmission of wild poliovirus. This includes attaining high routine immunization coverage with at least three doses of oral polio vaccine, conducting national im munization days (NIDs) and "mopping-up" immu nization when polio is reduced to focal transmission. The other strategy is the implementation of action-oriented surveillance for all possible cases of poliomyelitis. This includes case investigation and isolation of virus from stool specimens[4].

Polio is a disease that does not respect national borders or continental boundaries, and in that sense is truly a problem of global concern requiring large-scale international cooperation. The progress to date has been marked by cooperation and coordination among countries and regions of the world. Also the efforts of polio endemic countries have been encouraged and supported by an effective coalition of partners including WHO, Rotary International, and United Nation Children Fund (UNICEF) and the governments of Australia, Canada, Denmark, Finland, Germany, Japan, Norway, Sweden, the United Kingdom, the United States etc. The participation of Rotary International represents the largest contribution ever by a private sector organization to a public health initiative[2].

As at the time the goal to global eradication of poliomyelitis was established in 1998, wild polio virus (WPV) was endemic in more than 125 countries on five continents paralyzing more than 350,000 children per annum. Only 1,170 confirmed cases of polio were reported in 2004 representing a greater than 99% reduction in poliovirus. Today, only 6 countries in the world remain endemic and these include Nigeria, India, Pakistan, Niger, Afghanistan

and Egypt [5]. Experience in the Americas, where polio has been eliminated since August 1991, demonstrates that the recommended strategies are effective and the global eradication of polio is feasible [2].

Epidemiology of Poliomyelitis

The words *polio* (grey) and *myelon* (marrow) are derived from the Greek. It is the effect of the poliomyelitis virus on the spinal cord that leads to the classic manifestation; paralysis[6]. The Polio virus is a member of the enterovirus subgroup family picornaviridae. They are transient inhabitants of the gastro-intestinal tract (GIT) and stable at acid pH like other enteroviruses. They are small, ether-sensitive with RNA genome. There are 3 serotypes, P1 P2, and P3. P1 most typically causes outbreaks, and is the most likely serotype to cause paralysis. P2 is the easiest to eradicate followed by P3. They are all rapidly inactivated by heat, formaldehyde, chlorine, and UV light [8].

Poliovirus infects only human beings and there is no animal reservoir. The virus does not survive long in the environment outside the human body and there is no long-term carrier state. Person-to-person spread via faeco-oral route is the most important route of transmission. Oral-oral route may also account for some cases. Two peaks of transmission, Feb to May (low transmission period) and August to November (high transmission period) in Africa are recognized, while transmission peaks in winter in the temperate countries. Cases are most infectious from 7 to 10 days before and after the onset of symptoms[6, 7].

The portal of entry is the mouth. Primary replication occurs in the pharynx and GIT. The virus invades local lymphoid tissue, enters the blood stream and may infect cells of the CNS. Replication in motor neurons of the anterior horn cells and brain stem results in cell destruction and causes the typical manifestation of poliomyelitis. The virus is usually present in the throat and in the stools before the onset of illness. One week after onset, there is little virus in the throat, but the virus continues to be excreted in the stools for several weeks[6].

The incubation period is commonly 6 to 20 days with a range from 3 to 35 days[8]. Up to 95% of all polio infections are sub clinical without symptoms. An estimated ratio of asymptomatic to paralytic illness is usually 200:1. Notwithstanding, infected asymptomatic persons shed virus in the stool, and are able to transmit the virus to others. About 4 to 8% of infections are non-septic without clinical or laboratory evidence of central nervous system (CNS) invasion. This type of infection is described as abortive poliomyelitis. The symptoms observed range form upper respiratory tract infection (sore throat, fever), gastro intestinal disturbances (nausea, vomiting, abdominal pain, constipation and rarely diarrhoea), to influenza - like illness. In 1 to 2% of infections, non-paralytic aseptic meningitis occurs usually following non-septic illness with stiffness of the neck, back and legs. Typically, these symptoms last 2 to 10 days followed by complete recovery. Less than 2% of all polio infections result in flaccid paralysis. Paralytic symptoms generally begin 1 to 10 days after prodromal symptoms and progress for 2 to 3 days. The prodrome may be biphasic, especially in children with initial minor symptoms separated by a 1 to 7 day period from more major symptoms. Additional prodromal signs and symptoms can include loss of superficial reflexes, initially increased deep tendon reflexes and severe muscle aches and spasms in the limbs or back. The illness progresses to flaccid paralysis with diminished deep tendon reflexes, reaches a plateau without change for days to weeks then strength begins to return. The paralysis is asymmetrical with no sensory losses or changes in cognition. Many affected persons recover completely and in most cases, muscle function returns to some degree. Patients with weakness or paralysis 12 months after onset will usually be left with permanent residuals[6, 7, 8]

There are 3 clinical types of paralytic polio. Spinal polio is most common and accounts for 79.5% of paralytic cases characterized by asymmetric paralysis that most often involves the legs. Bulbar polio accounts for 2% of cases and leads to weakness of muscles innervated by cranial nerves. Bulbospinal polio accounts for 19% of cases and is a combination of bulbar and spinal paralysis. The

case fatality ratio (CFR) for paralytic polio is 2 to 5% in children and up to 30% in adults depending on age. It increases to between 25% and 75% with bulbar involvement [9].

Protective immunity against poliovirus infection develops following immunization or natural infection. Immunity to one poliovirus type does not protect against infection with other poliovirus types. Immunity following natural infection or administration of live oral polio vaccine (OPV) is believed to be lifelong. The duration of protective antibodies after administration of inactivated polio vaccine (IP) is unknown. Infants born to mothers with high antibody levels against poliovirus are protected for the first several weeks of life [10].

The differential diagnosis of acute flaccid paralysis include paralytic poliomyelitis, Guillain-Barre syndrome and transverse myelitis; less common aetiologies are injection neuritis, encephalitis, meningitis and tumors [4]. Distinguishing characteristics of paralytic polio are asymmetric flaccid paralysis, fever at onset, rapid progression of paralysis, residual paralysis after 60 days, and preservation of sensory nerve function.

Definitive diagnosis of poliomyelitis is by viral isolation. Polio virus may be recovered from stool or pharynx. Isolation of virus from the cerebrospinal fluid (CSF) is diagnostic but rarely accomplished. Oligonucleotide mapping or genomic sequencing is required to differentiate wild like or vaccine-like virus[11]. Neutralizing antibodies appear early in the serum and may be at high levels. CSF shows an increased number of WBC (10 to 200 cells / mm^3) and mildly elevated protein (40 to 50 mg / 100 mls) [6].

Mass immunization with polio vaccine is the sole effective means of preventing poliomyelitis. Killed and live - attenuated vaccines are available and are both safe and effective when used correctly. High standards of personal and environmental hygiene especially sanitary disposal of sewage and provision of adequate and safe water supply are other proven primary preventive measures. These, in combination with community health education constitute the primary preventive package for control of poliomyelitis. There is no specific treatment for polio. Good nursing care, from the beginning of illness can minimize or prevent crippling. Physiotherapy initiated in the affected limb on time is of vital importance. It helps the weakened muscles to regain strength, as is likely the child may have to be put on metal calipers [6, 7, 8].

Srategies For Polio Eradication

Polio transmission has been interrupted in the regions of the Americas, the Western Pacific, and Europe to date. The eradication of Polio in countries of these regions has demonstrated the effectiveness of the polio eradication strategies. Attaining and sustaining high routine coverage of more than 80% with at least 4 doses of oral polio vaccine given at birth, 6, 10 and 14 weeks thereafter respectively is one strategy known to effectively interrupt transmission. However, the infrastructure as well as the financial commitment to achieving this, are lacking in most polio endemic countries. Hence the need for supplementary immunization activities, conceived to improve coverage on a short term, and serve as basis to strengthened routine immunization. Conduct of national immunization days and sub -national or mop - up immunizations are such supplementary immunization activities [4].

During national immunization days (NIDs), doses of OPV are given to all children in a defined age group, usually 0-59 months of age, in as short a period of time as possible (preferably 1-2 days), regardless of their immunization status. The doses of OPV administered during NIDs are considered extra doses, which supplement and do not replace the doses received during routine immunization services. The planning and execution of NIDs is a major public health event receiving much publicity and involving many participants in the public and private sectors. The logistic, coordination, and social mobilization of NIDs are carefully planned well in advance for excellent implementation. By giving oral polio vaccine at the same time to all children over a short period of time in a large geographic area, transmission of poliovirus is interrupted. To be effective, NIDs must achieve high coverage with

OPV. Therefore, special efforts are necessary to reach children who are often missed by the routine immunization programme. For those already immunized, NIDs boost both serum and intestinal immunity against poliovirus.

Mop - up immunization is conducted when polio has been reduced from an endemic disease (i.e. occurring throughout the country) to a disease that occurs only in focal areas. It is usually implemented during the low season of polio transmission. Exception occurs in countries where polio virus is thought to have been eliminated or almost eliminated; mop - up immunization might be conducted immediately after a case is confirmed as polio, regardless of the season [4].

Acute flaccid paralysis (AFP) surveillance is another important strategy in polio eradication. Its purpose is to detect reliably areas where poliovirus transmission is occurring or likely to occur; and to allow supplementary immunization to be focused where it is needed. As the number of polio cases approaches zero, the ability to detect and respond rapidly to every case of AFP becomes critical. To ensure that every case of polio is detected intensive surveillance for AFP has to be conducted.

AFP surveillance allows programme managers to monitor progress and to determine whether strategies are implemented effectively. Certifying a country as polio-free requires that there are no reports of new cases of poliomyelitis caused by wild poliovirus. It also requires evidence that a country can detect a case of paralytic polio should it occur. As an indicator of a country's ability to detect polio, at least 1 case of AFP per 100,000 children <15 years of age should be detected, even in the absence of polio. The AFP rate in children < 15 years of age is an indicator of the sensitivity of the surveillance system[12].

Isolation and identification of poliovirus from the faeces is the best current method to confirm the diagnosis of poliomyelitis. WHO, in collaboration with several other institutions, has developed a global network of laboratories to provide this service. Molecular techniques are available to characterize fully the poliovirus. Maintaining a reference bank of the molecular structure of known viruses allows the geographic origin of new isolates to be traced. When necessary to determine whether the virus was im ported or indigenous. The laboratory will also determine whether isolated viruses are wild or vaccine-like. The global laboratory network is a 3-tiered system. Each tier provides different services, all of which are essential and must be coordinated. The network also coordinates the flow of specimens, reagents and information between different levels of laboratories and between laboratories and programmes. The laboratory network will play a key role in certification of polio eradication by verifying the absence of wild poliovirus circulation. In addition to AFP surveillance, this may include stool surveys of healthy children in high-risk area and environmental surveillance. The laboratory network can perform potency tests on polio vaccine if circumstances indicate possible failure. In selected situations, a laboratory might participate in epidemiologic sero-surveys if knowledge of the antibody status of the population or a given cohort is important [13].

AFP surveillance consists of: detecting, reporting and investigating suspected cases, collecting data from reporting sites, analyzing data and using them for action, reporting findings and lastly providing feedback (information) to all levels and interested parties. To have a sensitive and responsive surveillance system of suspected polio, immediate notification of AFP in children aged <15 years of age is required. When no case of AFP is detected, reporting units should still send a monthly/ weekly report indicating zero cases. This is called "zero reporting". To improve completeness, timeliness and sensitivity of AFP surveillance for instance in Nigeria, WHO has designated persons in all the 36 states and Abuja who make weekly visits to sites likely to have cases of acute polio, such as major hospitals and rehabilitation centres. Visits are made particularly to paediatric and neurology wards to inquire about cases of AFP, including Guillain-Barre syndrome. A search of all inpatient and outpatient medical records is also conducted for review of preliminary and final diagnoses. For the purpose of surveillance, any sudden weakness in any of the limbs in a child less than 15 years, occurring within two months of detection or report is considered an AFP

Progress in Global Eradication of Poliomyelitis

Five years after the year 2000, the date initially proposed for the global eradication of polio has been elusive though considerable progress has been made. A major tactical revision in the initiative was introduced in 2003, leading to a revised time frame for certification of eradication now in 2008. In the new agenda, poliovirus transmission is expected to be stopped by the middle of 2005, achieve certification standard surveillance in all countries by the end of 2005 and finish supplementary immunization by the end of 2006 [14].

The eradication of Poliomyelitis as with smallpox, involves the additional criterion of the elimination of indigenous transmission of wild virus. However, poliomyelitis is inherently more difficult to eradicate than smallpox. Among the epidemiologic characteristics in which the two diseases differ are the asymptomatic illness that is characteristic of most polio infections and the ability of the poliovirus to spread by enteric transmission, both of which make the identification and containment of cases more difficult. In contrast, smallpox was clinically obvious and eradication was quite easy to confirm. Differences between the vaccines are also important. Smallpox vaccine is heat stable, one dose is required for protection lasting several years, and vaccination leaves a readily visible scar. Trivalent OPV looses substantial potency after one day at 37^{o}C and multiple doses are required for full protection. Another difference is that properly administered smallpox vaccine has been a highly effective immunogen, whereas sero-conversion rates after one to four doses of OPV have been suboptimal in developing countries[2]. Confirming that poliovirus has stopped being transmitted will therefore require far more sophisticated test and facilities.

In spite of these and other differences, the eradication of smallpox provides a model for success. Substantial progress had been made in global polio eradication with NIDs and AFP surveillance, but Nigeria currently poses the highest risk to the achievement of the global goal. With a case load of 792 cases in 2004 alone, Nigeria had the highest number of polio cases anywhere in the world, and this accounted for 63% of the global wild polio case count and 84% of the cases in Africa. The number is more than 2 times compared to 2003 case total case count [5].

Poliovirus from the northern part of the country is re-infecting previously polio free areas within and outside Nigeria. Exportation of virus from Nigeria had been reported in Republic of Benin, Burkina Faso, Cameroon, Chad, Ghana, Niger, Togo, and more recently Saudi Arabia, Ethiopia and Yemen.

Many states in southern Nigeria were polio free from mid - 2001 to mid - 2003, demonstrating that transmission can be stopped in the country with high quality immunization campaigns. However, since the OPV safety issue emerged in 2003 and with subsequent stoppage of NIDs for some part of 2003 coupled with poor routine immunization coverage, viruses spread to all southern states with the exception of Ekiti, Edo, Ebonyi, Abia, Rivers, and Akwa-Ibom states. To make matters worse, indigenous virus was found in Oyo state.

CONCLUSION

The greatest threat to a polio free world include a failure to reach all children with immunization in the endemic nations especially in Nigeria, India and Pakistan combined with ongoing insecurity in some countries with re-established transmission particularly Cote-d'Ivoire and Sudan. Also gaps in subnational surveillance of the disease particularly in West, Central and Horn of Africa coupled with low immunization rates in these countries are other challenges the polio eradication initiative faces. WHO estimates that US$75 million and US$200 million will be needed for the later half of 2005 and all of 2006 for PEI activities respectively. These funds are still being sourced.

REFERENCES

1. World Health Assembly. Global eradication of Poliomyelitis by the year 2000. Geneva World Health Organization, 1988: resolution WHA 11.28.

2. Cochi SL, Hull HF, Sutter RW, Wilfert CM, Kartz SL. Commentary: the unfolding story of global poliomyelitis eradication. Journal of Infectious

Diseases 1997; 175 Suppl 1: S51-53.
edition Edinburgh Kent 1990; 36-38.

3. Bart JK, Foulds J and Patriarca P. The global eradication of poliomyelitis: benefit-cost analysis. Bull WHO 1996; 74:35-45.

4. World Health Organization. Field guide for supplementary activities aimed at achieving polio eradication, 1996 revision. Global programme for vaccine and immunization WHO, Geneva 1997.

5. World Health organization. Global polio eradication initiative 2004 annual report.

6. Centre for Disease Control. Poliomyelitis in epidemiology and prevention of Vaccine-Preventable Diseases. The Pink Book .8th edition 2005; 89-100.

7. Park K. Parks textbook of Preventive and Social Medicine. Sixteenth edition m/s Banarsidas Bhanot Publishers India 2000; 151-157.

8. Lucas AO and Gilles HM. A new short text book of Preventive Medicine for the tropics. Third

9. Horstmann DM. Clinical aspects of acute poliomyelitis. American Journal of Medicine 1949; 6: 592 - 605.

10. Krugman RD, Hardy GE and Sellers C. Antibody persistence after primary immunization with trivalent oral poliovirus vaccine. Pediatrics 1977; 60: 80-82.

11. Kew OM, Mulders MN, Lipskaya GY, da Silva EE and Pallansch MA. Molecular epidemiology of Polioviruses. Seminars in Virology 1981; 6: 401-414.

12. Birmingham ME, Linkins RW, Hull BP and Hull HF. Poliomyelitis surveillance-the compass for eradication. J Infec Dis 1997; 175: S146-S150.

13. Nathanson N. Epidemiologic aspects of poliomyelitis eradication. Rev infection Dis 1984; 6 (suppl 2): S308-S312.

14. World Health Organization. Global polio eradication initiative strategic plan 2004-2008. WHO Geneva 2003.

Immunological Aspects of Urinary Schistosomiasis in Ibadan, Southwestern Nigeria

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SUMMARY

Humans infected with Schistosoma parasite demonstrate substantial immune responses against both the intravascular adult worms and the schistosoma eggs retained in the tissue. However, no immunologically mediated adverse effect on the adult worms has been described. Also, the strong cellular responses directed to the eggs are modulated during the course of chronic infection. Thus continued exposure of the host to worm and egg antigens usually lead to regulation of the engendered responses and maintenance of a stable chronic host-parasite relationship.This review aims at providing background information on the immunological status of Nigerian school children (especially in Ibadan) with urinary schistosomiasis.

History and Epidemiology

Schistosomiasis, also known as bilharziasis (after Theodor Bilhaz), is widespread with a relatively low mortality rate but a high morbidity rate, causing severe debilitating illness in millions of people [1].

Urinary schistosomiasis (caused by *Schistosoma haematobium*) was first discovered in soldiers of Napoleon stationed in Egypt between 1779 and 1891 who suffered severe haematuria [1]. In Nigeria, urinary schistosomiasis is known to have existed from time immemorial and might have been brought to the country by the migrating Fulani people when they travelled westwards from the Nile Basin [2]. The early record of urinary schistosomiasis in Nigeria is that of German explorer who, in 1881, published the occurrence of endemic haematuria in Bonny Province [2].

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A study carried out in the Department of Pathology, University College Hospital, (UCH), Ibadan, Nigeria between 1958 and 1963 revealed a relatively low incidence of pathological lesions due to schistosomiasis in Ibadan [3]. This must be accepted with caution because as at then, the incidence of *Schistosoma haematobium* ova in the urine of patients in UCH was only 3.1% [3].

According to W.H.O. report [1], Nigeria is one of the countries most seriously affected by urinary schistosomiasis and the disease is hyperendemic over large areas. Record survey in Ibadan showed that the infection is common among school children (above 5 years of age) especially males [4]. One of the reservoirs of urinary Schistosomiasis and its *Bulinus* snail intermediate host in Ibadan is an abandoned fish pond along Parliament Road, State Secretariat, Ibadan [5].

Immuology

Immune responses to an immunogen comprise cellular, humoral or innate immunity, but those that are evoked during *S. haematobium* infection are discussed below.

There is a dearth of information about immune responses to *Schistosoma haematobium* infection in Ibadan because earlier studies were concentrated on epidemiology and pathology. There is no sudden immunologic crisis leading to parasite elimination, but immunity develops gradually taking several years to become pronounced. In the early stage of infection, immunity is partial, nevertheless of vital importance in limiting the infection.

Innate Immunity

Innate immunity, which protects the body at all times from invasion by a vast majority of micro-organisms, may be natural, constitutional or genetic immunity. The skin is an example of innate immunological factor, which is known to protect against the invasion of cercaria.

The larva stage of *Schistosoma haematobium* that infect humans is the free-swimming, fork-tailed cercaria. Cercaria are attracted to the host by L-arginine and warmth [5]. Certain long chain poly-unsaturated free fatty acids percieved by argentophilic papillae of cercaria triggers its skin penetration and transformation to schistosomules. This transitional change must be accomplished within 10-15 minutes otherwise the cercaria will die off [5]. The implication of this is that the degree of infection tolerated by each host and skin susceptibility to lytic enzymes of the cercaria depend on the age of the host and the characteristics of the epidermal/dermal barrier of the skin. Thus, older hosts with enzyme-resistant polymerised skin are less susceptible to *Schistosoma* infection than very young host [5].

Involvement of genetic factors in the resistance to schistosomiasis is yet to be carried out in Nigeria. Genetic studies in Brazilians have shown that two distinct genetic loci control human susceptibility to schistosomiasis [26]. An interesting question to be answered is whether *Schistosoma* parasite has had any influence on the evolution of the mammalian im-mune system. The outcome will support the concept that infectious disease is the driving force for the polymophism observed in the major histocompatibility complex (MHC).

Immunoglobulin and Autoimmunity

The level and specificity of immunoglobulin in urinary schistosomiasis is controversial. This is due to variation in duration of infection, geographical origin of the host, intensity of infection and age of the patient [7]. Serum hypergammaglobulinaemia, hypoprotein-aemia and selective proteinuria are features of subjects with urinary schistosomiasis in Ibadan [8] as found in other environments [9].

Polyclonal B-cell activation found to be responsible for hypergammaglobulinaemia in urinary schistosomiasis could have arisen from the direct effect of *S. haematobium* on B-lymphocytes. Similarly, elevated levels of IgG1, IgA and IgE in urinary schistosomiasis are associated with Th2 responses [10]. It is reasonable to propose that cytokines produced by Th2 subset of CD4+ cells play a crucial role in the induction of hypergammaglobulinemia. This hypothesis is supported by the well-known dependence of polyclonal IgE responses on IL-4 as well as a data suggesting a requirement for IL-6 in the induction of hypergammaglobulineamia [10].

The functional role of IgM and IgG4 in schistosomiasis was elucidated. IgM in urinary schistosomiasis acts as a blocking antibody while IgG4 controls antigen recognition by IgE and consequently regulates anaphylactic reaction and IgE mediated immunity [11]. Immunological pathways involving IgE have been shown to damage and protect against developing schistosomule but the slow build-up of protective IgE and early production of IgG4 blocking antibody are responsible for delaying the development of protective immunity against urinary schistosomiasis [13].

Levels of different classes of immunoglobulins vary at stages of urinary schistosomiasis. Serum IgA and IgM were found to be elevated at acute stage of urinary schistosomiasis [12], therefore suggesting the diagnostic use of these immunoglobulin classes.

Several protozoan infections are associated with extensive development of autoantibodies and, in a few documented instances, autoreactive T-cells. A data has implicated the involvement of *S. haematobium* parasite in the production of rheumatoid factor [24]. Nevertheless, an aetiological role of these autoantibodies in pathology (e.g. glomerulonephritis, anaemia) has not been directly established.

Complement Factors

The serum concentration of C3 is inconsistent (reduced or raised or normal) in patients with schistosomiasis [13]. In this environment (Ibadan), C3c was raised while C4 was reduced in children with urinary schistosomiasis [8]. The components of schistosomule glycocalyx have the ability to activate complement pathways to generate chemoattractants that promote adherence of phagocytic cells [14]. Despite the activation of complement system on the surface of schistosomule, it is not damaged or killed. How schistosomule survives complement activation is a mystery but may be associated with the existence of newly formed double

outer membrane. Warren [15] pointed out that as young worms develop and migrate to organs of the body, there are changes not only in their surface topography and morphology but also in their antigenicity.

Immune complexes due to *Schistosoma* antigens have been related to the amount of complement components or products in the serum of the host. It has been known that adult *Schistosoma* releases antigenic materials into the circulation of mammalian hosts [15]. Such antigens have been detected in serum and urine but these circulating antigen decrease with treatment and age of schistosomiasis patients [15]. Free *Schistosoma* antigens are present only in massive infections but in the more moderate infection, which is normally found in nature, circulating antigens immediately combine with antibody forming complexes [16].

Clinical observations have shown that serum level of schistosomal antigen closely parallel the level of circulating immune complexes. The deposition of such immune complexes in basement membrane induces glomerular diseases [15,16].

T Lymphocyte - Mediated Pathology

Patients with urinary schistosomiasis develop a complex array of both humoral and cellular immune responses to soluble cercaria, worm and egg antigens, but only the egg antigens are important in the pathogenesis of granuloma disease [17].

Granulomas are localized cellular reactions against materials that are retained in tissues often for prolonged periods of time. They are complex inflammatory responses often classified as either "foreign body", or "hypersensitivity"-type granulomas. The former is primarily composed of macrophages and fibroblasts without an immunogenic nidus, while the latter occur in response to antigens and usually require T-cell sensitization. Most of the granulomatous pathology to schistosome egg belongs to the second category. These focal reactions represent the host's attempt to wall-off, contain, and perhaps destroy schistosome ova deposited in tissues (e.g. liver, intestine, bladder). Nevertheless, as lesions, which stimulate extensive tissue fibrosis, they are at the same time harmful to the host and are the primary cause of schistosomal disease [19,20].

The focal tissue destruction occurring in schistosomiasis, is followed by fibrosis, a wound-healing process in which fibroblasts are brought into the lesions and collagen is produced, resulting in scarring and obstruction of blood and/or lymphatic vessels. These events are clearly triggered by the inflammatory response to the parasite or its eggs and are dependent, at least in part, on T lymphocytes. In the case of schistosomiasis, the progressive fibrosis responsible for portal hypertension is thought to result primarily from egg granuloma formation [25]; while the two processes appear to be linked, they can be regulated differentially.

In human schistosomiasis, Th1 cells produce high level of IFN and IL-2 at the pre-acute and acute stages of infection but production subsequently diminishes at chronic stage when IL-4 and IL-5 are, predominant [18]. A study in Nigeria (Ibadan) showed that immune responses controlled by Th2 cytokines predominate during urinary schistosomiasis though Th1- mediated immune responses are present. The implication is that diseases such as tuberculosis and leprosy that are resolved by Th 1 cytokines may be aggravated, while severe malaria and trichuriasis may be effectively controlled in subjects with urinary schistosomiasis [19]. This requires further investigation.

Mechanism of schistosomular killing by eosinophils and neutrophils

Complement components in the presence of antibodies are activated on the surface of schistosomula to attract eosinophils, which adhere via C3-C3 receptor interaction [20]. Following adherence eosinophils begin to flatten against the parasite surface so as to form an exact template of the surface topography. The eosinophil granules that contain hydrolytic enzymes in addition to major basic protein move towards the basal region of the cell fuse together to form vacuoles connecting with basal plasma membrane and release of vacuolar contents onto the surface of the parasite [20]. Hydrolytic enzymes released by eosinophils are peroxidase, beta-glucuronidase, phospholipase-B, ribonuclease, aryl sulphatase and cathepsin, plus major basic protein from the granule crystalloid [21]. Freeze fracture studies have shown that the outer bilayer of the

double outer membrane is damaged first and becomes locally separated from the inner bilayer that is attacked by eosinophil secretions [21]. Tegumental vacuolation follows and as a result of permeability changes in the remaining membrane, small lesions are formed through which eosinophil migrates [21]. After this, eosinophils flatten as they move between the tegument and the underlying muscle layers [20,21]. In this way, eosinophils strip the tegument away from the body of the worm.

A study showed that neutrophils are responsible for less damage of schistosomule when compared with the damage caused by eosinophils. This may account for the association of eosinophilia with urinary schistosomiasis [22]. Though a neutrophil possesses more Fc receptors than an eosinophil the antibody mediated adherence of neutrophil to schistosomular surface is not permanent and does not result in significant damage and killing [23]. Neutrophil damages schistosomula by both direct physical means using pseudopodia, and enzyme action of the vacuoles. Neutrophils extrude enzymes (beta-glucuronidase, lactic dehydrogenase, myeloperodixase, and certain vasoactive amines) along the free border of the cells. After which, the adherent neutrophils push pseudopia processes into the tegument resulting in the death of the parasite [23].

Proposed Further Studies and Vaccine Strategies

Future work should relate rates of re-infection to age, sex, hormone levels, humoral and cellular immune responses, host genetics, and the incidence of other infections.

An effective vaccine against *Schistosoma* would be a valuable control tool and the high levels of protection elicited in rodents and primates by radiation-attenuated cercariae provide proof of principle. A major obstacle to vaccine development is the difficulty of identifying the antigens that mediate protection. The technologies collectively called proteomics, including 2D electrophoresis, liquid chromatography and mass spectrometry, now permit any protein to be identified provided there is extensive DNA data, and preferably a genome sequence. Applied to soluble (cytosolic) proteins from schistosomes, proteomics reveals the great similarity in composition between life cycle stages, with several WHO vaccine candidates amongst the most abundant constituents. The proteomic approach has been successfully applied to identify the secretions used by cercaria to penetrate host skin, the gut secretions of adult worms and the proteins exposed on the tegument surface. Soluble proteins can also be separated by 2D electrophoresis before western blotting to identify the full range of antigenic targets present in a parasite preparation. The next step is to discover which target proteins represent the weak points in the worm's defences [27]. The vaccine study may be difficult to achieve in our environments because of compounding problems.

CONCLUSION

(i) Certain functions of immune system (especially cell mediated immunity) in Nigerians with urinary schistosomiasis are adequate, this may account for the absence of severe malaria and viral infections in them.

(ii) Based on immunological classification, urinary schistosomiasis in Nigerians is an acute stage disease.

REFERENCES

1. W.H.O. World Health Report, 2001.

2. Cowper S.G. Bilharziasis (Schistosomiasis) in Nigeria. Trop. Geogr. Med. 1972; 25:105-108.

3. Edington G.M. and Gilles H.M. Pathology in the tropics. Edward Arnold , London.1969

4. Arinola O.G. Prevalence and severity of urinary schistosomiasis in Ibadan, Nigeria. East Afr. Med. J. 1995; 74(5): 64-67.

5. Smithers S.R. Recent advances in the immunity of schistosomiasis. Br. Med. Bull. 1972; 28: 49-54.

6. Dessaint J.P., Capron M, Bout D and Capron A . Quantitative determination of specific IgE antibody to schistosome antigens and serum. Clin. Exp. Immunol.1975; 20: 427-436.

7. El-Missiry, Fawzy A.G., Abdalla M.A, Farrag A.M and Rakha M. Cellular and humoral immunological changes in chronic renal failure associated with schistosomiasis. J. Egypt. Soc. Parasitol.

8. Arinola O.G and Salimonu L.S. Humoral immunity in Nigerians with *S.haematobium* infec tion. W.Afr. J.Med. 1999; 18(4):275-280
9. Butterworth A.E. Studies on human schistosomiasis; Chemotherapy, immunity and morbidity. Ann. Parasitol., Hum. Comp. 1990; 65 Suppl. 1:53-57.
10. Arinola O.G. and Salimonu L.S. *S .haematobium* infections affects the efficacy of certain vaccines. Science Focus. 2004; 5: 116-118.
11. Hagan P., Chandiwana S, Ndhlovu P, Woolhouse M.,and Dessaint A.The epidemiology, immunology and morbidity of *S. haematobium* infections in diverse communities in Zimbabwe. Trop Med. Geog. 46: 227-232.
12. Hagan P. and Abath F.C Recent advances in immunity of human schistosomiasis. Mem. Inst. Oswaldo Cruz. 1992; 87 Suppl. 4: 95-98.
13. Hussein M.M., Ahmed M.M., Fayed M. . Intestinal schistosomiasis. J. Egypt Soc. Parasitol.1993; 23: 769-773.
14. Warren K.S. The secret of immunopathogenesis of schistosomiasis: *in vivo* models. Immunol. Rev. 1982; 61: 189-213.
15. Santoro F. Praza A. Silva A.E.andCapron A. Correlation between circulating antigens detected by RIPEGA and C1q-binding immune complexes in human schistosomiasis. Amer. J. Trop. Med. Hyg. 1981; 30(5): 1020-1025.
16. Arinola O.G. Acute phase proteins, soluble circulating immune complexes and enhanc ing substance to inhibition of leucocyte migration in sera of urinary schistosomiasis subjects. Trop. J. Med. Res. 2001; 5(2): 1-7.
17. Ogunba E. O., Maddison S.E, and Tsang V.C.W., Slemenda S.B. (1982). Reactivity of frac tionated egg antigens of *S. mansoni* with sera of patients with *S. haematobium.* Afr. J. Med. Med. Scs. 2001; 11: 67-73.
18. Pearce E.J. Casper P, Grych J.M., Lewis production accompanies induction of Th2 responses by a parasitic helminth. J. Exp. Med. 1991; 173: 159-166.
19. Arinola O.G and Salimonu L.S. *S. haematobium* stimulates predominantly Th2 medi ated immune responses in some Nigerian children. Science Focus. 2003; 4: 14-17.
20. Ramalho-Pinto F.J., McLaren D.J., and Smither S.M. Cell mediated killing of schistosomula by eosinophil in vitro. J. Exp. Med. 1978; 147: 147-156.
21. Gleich G.J., Loegering D.A., Kupper F, Bajaj S.P., and Mann K.G. Physiological and bio logical properties of the major basic protein from eosinophil granules. J. Of Exp. Med. 1974; 10: 313-332.
22. Arinola O.G. and Salimonu L.S. Anthro pometric parameters and haematological parameters in relation to severity of urinary schistosomiasis among Nigerian primary school children. J. Sc. Engr. Tech. 1999; 6(3): 1977-1986.
23. Vadas M.S., David F.R., Butterworth A.E., Pisa N.T. and Siongok T.A. A new method of the purification of human eosinophils and neutrophils and a comparison of the ability of these cells to damage schistosomula. J. Immunol. 1979; 122: 1228-1236.
24. Arinola O.G. and Salimonu L.S. Rheuma toid factor in sera of Nigerian school children with urinary schistosomiasis. Afr. J. Med. Med. Scs. 2000; 29: 329-330.
25. Wyler D.J. Schistosomes, fibroblasts and growth factors: how a worm causes liver scarring. New Biol. 1991; 3: 734-740.
26. Dessein A. J. Marquet S., Henri S., Eldin N., El-Wali M.A., Hillaire D, Rodrigues V., Prata A., Ali Q.M., Gharib B, deReggi M., Magzoub M.M.A, Saeed O.K., Abdelhameed A.A. and Abel L. Infection and diseases in human schistosomiasis are under distinct major gene control. Microbes and Infections. 1999; 1(7): 561-568.
27. Full Contents of International Journal for Parasitology 30, April 2000. Thematic Issue on Parasite Genomes.

Typhoid Fever: The Challenges of Medical Management

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Keywords: *Typhoid, medical management, challenges*

INTRODUCTION

Salmonella enterica serotype typhi is the aetiological agent of typhoid fever, a multisystemic disease with protean manifestations and initial lesions in the bowel. Typhoid fever still remains a major public health problem in developing countries even in the twenty first century[1,2]. This was also the case in America and Europe three centuries ago, until measures for sanitary disposal and supply of potable water were put in place. Unacceptable morbidity and mortality are still recorded in developing countries in spite of availability of several drugs over the years for the treatment of typhoid fever. There is enough evidence to show that the prevalence of typhoid fever in any community is an index of communal hygiene and effectiveness of sanitary disposal.

In Nigeria, as in other developing countries of the world, studies have estimated over 33 million cases and 500,000 deaths due to typhoid fever per year [3]. Several factors are responsible for the failure of public health measures to tame the tide of the continuing rise in the incidence, prevalence, morbidity and mortality of typhoid fever. The objective of this review is to highlight the challenges in medical management of typhoid fever and to proffer solutions.

The major challenges to the management of typhoid fever are diverse and formidable; especially so in economically disadvantaged continents such as Central and South America, Middle-East, South-East Asia and Africa. These challenges are similar and interactive in all countries listed. This review will focus on the under listed factors:

1. Poor environmental sanitation
2. Potable water
3. Health education
4. Confounding disease
5. Personal and communal hygiene
6. Laboratory facilities
7. Drug resistance
8. Fake and counterfeit drugs

Poor Sanitation

Adequate sanitation is the safe management of human excreta and includes both "hardware" (sanitation technologies, such as toilets and hygienic latrines) and "software" (hygiene promotion, such as hand washing with soap). The World Health Organization stated in the year 2000, that 40% (2.4billion) of the world's population lacked access to basic sanitation [4].

One of the major public health concerns in cities in developing economies are slums with overcrowding at its worst. Poor urban planning without regard for waste disposal and drainage facilities. All these tend to encourage transmission of infectious diseases. An international workshop in1986 identified ingestion of foods or water contaminated by acutely infected persons or chronic typhoid carriers as the most common form of transmission of the disease[5]. As a result of poor sanitation, typhoid fever is very common in communities where contaminated water and food is common.

Potable Water

Availability and potability of drinkable water is still a luxury in most developing nations of the world. The WHO estimated that 1.2 billion of the world's population lack access to potable water [5]. At the peak of the dry season, especially in developing countries, water is often sourced from various doubtful places most of which are contaminated by human waste. This no doubt accounts for the rise in the incidence of typhoid fever, which has been docu-

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mented in such communities during this period of the year [2,6].

Health Education

Knowledge is limited about many infectious diseases in developing countries as many diseases are still attributed to spiritual attacks by the common folks. Also, as a result of illiteracy, half-measures are often taken by self- medicating, in order to avoid the unaffordable cost of modern healthcare in a situation where there is no health insurance cover. This often leads to mismanagement with unsubstantiated remedies and misplaced spiritual intervention. As a consequence of this, patients with typhoid fever often present late and so with complications. Olubuyide in 1992 documented delay in seeking medical care, misdiagnosis, and inappropriate therapy as the factors that may contribute to mortality from typhoid fever among Nigerians [7]. Occasionally, inadequate pre-medication before seeking medical care often changes the expected clinical picture of the disease, thus also leading to misdiagnosis.

Confounding Diseases

Typhoid fever, as a multisystematic disease has been dubbed the great mimicker especially in the tropical and subtropical environment, where several other confounding infections and infestations present with febrile illness. Many of these febrile illnesses such as malaria, viral hepatitis and liver abscess, often present in a similar way as typhoid fever or even co-exist with typhoid fever. This often leads to delay or misdiagnosis and subsequent increased incidence of complications and mortality [8,9,10.11].

Personal and Communal Hygiene

Poor personal and communal hygiene is a common occurrence in less developed nations of the world especially among the illiterate population. Lack of public sanitation as a result of ineffective health policies leads to reckless deposition of wastes and use of bush paths and riverbanks as refuse dumps and defecation points. During the early rainy season, faecal matter from some carriers of typhoid fever are washed into rivers and brooks. Unsuspecting members of the community use it for various domestic purposes including drinking, cooking, etc.

Laboratory Facilities

It is very difficult to isolate Salmonella typhi from urine and stool specimens in most developing countries. This is often due to lack of culture media, expertise and sometimes previous exposure to inadequate doses of antibiotics.

Another major problems relating to the laboratory is the abuse of the Widal's test. Some clinicians will not treat or suspect the disease unless the test is positive, while others treat with a positive result even in low titres for an endemic zone of typhoid fever or in the absence of clinical symptoms and signs. Ohanu *et al* showed that malaria could interfere with serological diagnosis of typhoid fever leading to overdiagnosis [12]. Typhoid fever in most developing countries is thus a disease of over- and under diagnosis. It would be wise to carry out studies of baseline value of typhoid agglutinins for every locality as has been done in some areas to know the diagnostic utility of the Widal's test. Advances in diagnosis of typhoid fever with the use of enzyme-linked immunosorbent assay [13] is still beyond the reach of most developing nations.

Drug Resistance

Resistance to chloramphenicol developed two years after its discovery in 1948; this phenomenon has since become a major challenge to contend with in the management of typhoid fever. Resistance has since been noticed with virtually all drugs including trimethoprim and ampicillin [14]. Recent studies have shown resistance and reduced susceptibility to ceftriazone and the quinolones [15, 16], however, quinolones are still regarded as the best and first-line drugs in the management of typhoid fever.

Fake and Counterfeit

In 2001, the National Agency for Food and Drug Administration (NAFDAC) in Nigeria, reported 50% of the drug in circulation in Nigeria to be fake. The problem of counterfeit and fake drugs no doubt has compounded the problem of management of typhoid fever, with a great potential for increased morbidity and mortality.

Suggested Solutions to Challenges in Mangement

It appears quite obvious that the solutions to medical management of typhoid fever will be along the line of the identified problems noted above. Improvement in personal and communal hygiene, effective waste disposal system and provision of potable water will no doubt go a long way in reducing the incidence of typhoid fever. Effective treatment of index cases, health education both for the populace and physicians are other important measures. Determination of drug sensitivity patterns and aggressive policy will be quite helpful. The difficulty in diagnosis could also be overcome by making laboratory facilities such as culture media available. Parry et al recently suggested the use of conjugate Vi vaccine as part of the Expanded Programme of Immunization[17]. The cost-effectiveness of this latter measure may however be negative for resource – poor countries, where preventive measures by way of improved sanitation and provision of potable water would be more beneficial. Above all, resources should be made available, accessible and affordable to the common man; National Health Insurance appears to be the answer to this as well as economic empowerment of the people in emerging economies like Nigeria.

REFERENCES

1. Lin FY, Vo AH, Phan VB, Nguyen TT, Bryla D, Tran CT, Ha BK *et al* .The epidemiology of typhoid fever in the Dong Thap Province, Mekong Delta region of Vietnam. Am .J. Trop. Med. Hyg. 2000; 62: 644-648.

2. Otegbayo JA, Daramola OO, Onyegbutulem HC, Balogun WF and Oguntoye OO. Retrospective analysis of typhoid fever in a tropical tertiary health facility.Trop Gastroenterol. 2003; 23:9-12.

3. Institute of Medicine, New vaccine development: establishing priorities, 1986 Washington DC. National Academy Press.

4. WHO and UNICEF. Global assessment of water supply and sanitation.2000.

5. Edelman R and Levine MM. Summary of an international workshop on typhoid fever. Rev Infect Dis. 1986; 8: 329-349.

6. Luby SP, Faizan MK, Fisher-Hoch SP, Syed A, Mintz ED, Bhutta ZA *et al*. Risk factors for typhoid fever in an endemic setting, Karachi, Pakistan. Epidemiol Infect. 1998; 120: 129-138.

7. Olubuyide I.O. Factors that may contribute to death from typhoid infection among Nigerians. West Afri J Med. 1992; 11:112-115.

8. Ammah A, Nkuo-Akenji T, Ndip R and Deas JE. An update on concurrent malaria and typhoid fever in Cameroon. Trans R Soc Trop Med Hyg. 1999; 93: 127-129.

9. Khan M, Coovadia Y and Sturm AW. Typhoid fever complicated by acute renal failure and hepatitis: case reports and review. Am J Gastroenterol. 1998; 93: 1001-1003.

10. Wilairatana P. Acute viral hepatitis A: a cause of jaundice in typhoid fever. Southeast Asian J Trop Med Public Health 1996; 27: 406-407.

11. Giorgio A, Tarantino L and De Stefano G. Hepatic abscess caused by Salmonella typhi: diagnosis and management by percutaneous echo guided needle aspiration. Ital. J. Gastroenterol. 1996; 28: 31-33.

12. Ohanu ME, Mbah AU, Okonkwo PO and Nwagbo FS. Interference by malaria in the diagnosis of typhoid using Widal's test alone. West Afr J Med. 2003; 22: 250-252.

13. Jesudason MV, Sridharan G, Arulsevan R, Babu PG John TJ. Diagnosis of typhoid fever by the detection of anti-LPS and anti-flagellin antibodies by ELISA. Indian J Med Res. 1998; 107: 204-207.

14. Mirza SH, Beeching NJ, Hart CA. Multi-drug resistant typhoid: a global problem. J Med Microbiol. 1996; 44: 317-319.

15. Saha SK, Talukder SY Islam M and Saha S. A highly ceftriaxone- resistant Salmonella typhi in Bangladesh. Pediatr Infect Dis J 1999; 18: 387.

16. Brown JC, Shanahan PM, Jesudason MV, Thomson CJ and Amyes SG. Mutations responsible for reduced susceptibility to 4-quinolones in clinical isolates of multi-resistant Salmonella typhi in India. J Antimicrob Chemother. 1996; 27: 891-900.

17. Parry CM, Hien TT, Dougan g, White NJ and Farrar JJ. Typhoid fever. N Engl J Med 2002 Nov 28; 347(22); 1770-1782.

The Virology of the Polio Virus

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INTRODUCTION

The poliovirus is the aetiological agent of the disease poliomyelitis- a disease that has been known from time immemorial to paralyse and cripple children as well as adult, rich and poor, literate and illiterate. The disease is characterized by acute flaccid paralysis of any of or rarely both of the limbs. The fatal form may involve the medulla and brain stem where the virus causes bulbar poliomyelitis [1].

The poliovirus had been responsible for many epidemics since the 18th century. Epidemic poliomyelitis as a modern disease occurred in Europe in the mid 1800s and in North America in the 1890s [2].

Since then, there had been some landmarks in the study of the virus. In 1905, Landsteiner and Popper [3] transmitted the virus to monkeys by the intracerebral inoculation of the human brain tissue homogenates. Enders [4] cultured the virus in non-neural tissue, thereby eliminating animals for pathogenic studies. This simple discovery marked the beginning of significant progress in the study of the structure, epidemiology, control and prevention of poliomyelitis. This study eventually led to the discovery of the three serotypes and the successful development of vaccines from the virus [5,6]. The most important development in the fight against the poliovirus and in the history of poliomyelitis was the introduction of polio vaccines by Salk and Sabin [7,8].

In 1981, poliovirus became the first RNA virus genome to be molecularly cloned and sequenced. Recent development has included the cloning and sequencing of several strains of the three types of poliovirus [9,10,11,12]. These techniques have made it possible to determine the precise viral coat amino acids that induce antibody techniques. The poliovirus came to limelight and became a virus of global health importance when the World Health Assembly (WHA) in 1979, following the successful eradication of small pox, decided to target the virus for eradication [13]. Since then tremendous data, information and knowledge have been accumulated on the biology, structure and molecular structure of the virus.

This review article looks into some of the properties and recent knowledge of the poliovirus.

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The Structure and Biology of the Poliovirus

The poliovirus is a sub-microscopic intracellular, obligate, non-enveloped icosahedral- shaped virus of diameter between 27-30nm. It is a human enterovirus belonging to the viral family Picornaviridae. The picornaviruses are the smallest of the RNA viruses.

The virus exists in three well-defined serotypes- types 1,2, and 3 and infects cells via a specific receptor – PVR: CD-155. The receptor is a protein which is part of the immunoglobulin super family and is present on the extracellular and intramembranous regions of cells of human origin. This property accounts for the reason why man is the only host for the virus [14].

The RNA genome of the poliovirus consist of a single messenger active strand which is polyadenylated at the 3' terminal and carries a small protein called Vpg at its 5' untranslated (ntr) region. The RNA encodes a large polyprotein which is cleaved into three precursor proteins-the capsid proteins P1 and two non-capsid proteins- the morphorgenic proteins P2 and the protease and replicase P3. These precursor proteins are cleaved into 4,3 and 4 end products [14] (Fig. 1).

The poliovirus contains 4 polypeptides chains: VP1, VP2, VP3 and VP4. The fifth protein, the

Fig.1: Poliovirus RNA and posttranslational processing of the poliovirus polyprotein

VPO, is the precursor which is cleaved intoVP4+VP2 during viral maturation. One of the functions of these viral sub-units is the determination of the host range tissue tropism i.e. disease pathology and antigenecity of the virus [14].

Antigenic Characteristics of Poliovirus

The polio virus consist of three antibody defined types tagged serotypes 1, 2, and 3 [15]. Although, these three serotypes share some antigens, they are however characterized by marked intertypic differences [16].

The viral neutralizing epitopes are located on the three external structural capsid proteins – VP1, VP2, and VP3. Within a serotype, antigenic differences may occur between different isolates [16]. The virus type is actually defined by the capsid encoding sequences that are highly conserved. The non-capsid and non-coding sequences are not highly conserved and may recombine with other enteroviruses in the community. Immunological cross reactivity between serotypes 1 and 2 is easily demonstrated while cross reactivity between 2 and 3 may be detected but hardly between 1 and 3. The serological relationship between 1 and 2 can be epidemiologically demonstrated because presence of type 2 specific antibodies confers significant protection against type 1 infection [17].

Type 2 is more immunologically broad and that may be responsible for the fact that it is the first serotype to disappear during vaccination campaigns. The type 2 polioviruses were last seen in the world in 2002.

Genetic Differences Between the Polioviruses

Polioviruses, like other RNA viruses, have error-prone virus encoded RNA polymerase enzyme, which lacks proof reading activities. This results in rapid accumulation of mutations upon replication [18]

Epidemiologically, there are two categories of the poliovirus(WPV) which are also known as non- Sabin-like (NSL) and the Vaccine virus also known as Sabin –like (SL). These two categories are common to all the 3 serotypes. These two types of viruses are detected by intratypic differentiation tests
(ITD) which are based on one antigenic method, the polyclonal or monoclonal ELISA[19] and one molecular method which can enter the polymerase chain reaction (PCR) or RNA probe hybridization technique [20,21]. From this concondant non Sabin like ITD results are classified as wild, concordant Sabin-like as vaccine virus while any discordant results or sabin-like isolates lacking the two ITD tests are subjected to sequencing analysis of the major viral capsid surface protein, the VP1 [22].

In the sequence analysis, isolates with <1% difference from sabin-like virus are classified as sabin-like while isolates showing between 1%-15% difference in sequence analysis of the VP1 amino acids are classified as vaccine-derived poliovirus (VDPV).

Between the P1 wild prototype and the P1 sabin are 55 nucleotide changes. A change at position 480 of the amino acid sequence is responsible for the neurovirulence between the P1 wild and the Sabin1. There are 23 nucleotide changes between

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the P2 wild and the P2 Sabin while the neurovirulence is determined by a change in position 481 and one other in the VP1. Only 11 nucleotide changes differentiate the wild P3 from its P3 sabin counterpart while the amino acid determining the neurovirulence is situated at position 472. The wild polioviruses irrespective of their serotypes consists of many genotypes, they are of high genetic diversity. They are highly transmissible and are usually highly neurovirulent. In contrast, the vaccine viruses originate from one original strain, are of low genetic diversity, low transmissibility and of very

The oral polio vaccine (OPV) being a live-attenuated viruses vaccine behaves like the wild as regards evolution. The vaccine viruses may and usually do back mutate quite often during replication in human vaccinees [23]. When such vaccine virus strains back mutate and reacquire neurovirulence and transmissibility, the resultant virus is virtually wild-like [24]. Such OPV virus strains therefore cause paralytic poliomyelitis in susceptible vaccinees, although infrequently. This is called vaccine-associated paralytic poliomyelitis (VAPP). This is normal and occurs only very rarely. The chance of developing poliomyelitis without vaccination far much overweighs the possibility of developing a VAPP following vaccination. The option still remains therefore that vaccination is the best approach of preventing poliomyelitis.

The Polio Molecular Clock

Polioviruses are among the most rapidly evolving viruses known. The rapid evolution permits the pattern of poliovirus transmission to be followed with precision [25, 26]. Several factors combine to determine the overall rate of virus evolution. These include the replication error rates, the virus population size and growth rate, the frequency of genetic bottlenecks, the intensity of selective forces and the mechanism for genetic exchange [27]. Error rates for the poliovirus replicase have been estimated to be $10^{-4 \text{ to } 10-5}$ per site per replication [28,29,30]. Nucleotide substitutions(90% of which in the coding region are synonymous codons) accumulate at overall rate of 10^{-2} substitutions per site per year and at $3x10^{-2}$ substitutions per year at synonymous sites [25, 31, 32, 33, and 34].

Evolution rates are similar across serotypes and between wild and vaccine-derived polioviruses. Interestingly the bottlenecks driving the rapid evolution of polioviruses appear also to occur during replication in the human intestine in addition to that which happens during person-to person transmission [35, 36]. Many poliovirus clinical isolates are recombinants [25, 35, 36]. Heterotrophic recombinants are frequently isolated from vaccinees given trivalent OPV [35, 37]. All wild polioviruses probably have a recent history of recombination because frequent genetic exchange with other species C enteroviruses and vaccine derived polioviruses appear to be typical of circulating polioviruses [25,38]. Crossover is most common in the non-capsid region, less common in the 5` nontraslated region and very rare nontranslated within the capsid region [39].Molecular clock data have been used to estimate the dates of the common ancestors to wild [25,26] and vaccine derived [34] polioviruses.For example it was possible to determine the date of receipt of an OPV dose that
eventually gave rise to a type 2 vaccine derived poliovirus in a vaccinated Nigerian child that developed acute flaccid paralysis following vaccination with the OPV [40].

Circulating Vaccine-derived Poliovirus (cVDPV)

In recent times, another definition of poliovirus came into recognition.This is the circulating vaccine-derived poliovirus (cVDPV). These are revertant excreted recipient poliovirus vaccine strain OPV derived from the strain as a result of accumulating quantitative genetic change especially in the VPI capsid region. These viruses are usually related to the OPV strains from which they are derived but with significant genetic changes >1% difference. They are characterized by evidence of circulation and sustained person-to-person transmission and recombination with species C enteroviruses and other non-polio enteroviruses NPEV. cVDPVs behave very

much like the wild type virus. They multiply very well at supra optimal temperature of 39.5° C. cVDVs outbreaks usually occur where the corresponding

Fig. 2: Dendrogram summarizing sequence relatedness among 17 type 2 polioviruses across the interval of nucleotides 3295-3444(VPI/2A region)

Fig. 3: Nigeria: Comparison of monthly WPV cases, 2003-16th April, 2005

serotypes have earlier been eradicated or eliminated. Factors favouring the appearance of cVDPVs include major gap in OPV coverage i.e. low vaccine coverage and other general environmental conditions favouring poliovirus spread.

Over the past 5 years there have been localized outbreaks of cVDPV in Hispaniola [24], the Philippines, [41] Madagascar, [42] and Nigeria[40]. Retrospective studies have also confirmed occurrences of cVDPV in Belarus, Poland and Egypt [43]. The appearance of cVDPV is posing a great threat to the polio eradication programme. Immunization managers must ensure in all countries that high polio vaccination coverage is maintained.

Virological SurveIllance of Poliovirus

Efficient surveillance tools for wild polio and cVDPV are well developed. A global network of highly competent poliovirus laboratories has been established by WHO to apply these tools in tracking the virus and in guiding immunization campaigns [44]

Standard methods for poliovirus isolation in cultured cells [45] have been developed by use of recombinant murine cells expressing the poliovirus receptor [46]. Sero differentiation of the three poliovirus serotypes has been extended through the development of cross-absorbed antisera that distinguish OPV-derived strains from wild polio virus isolates. The most definite method is however based upon the sequence differences among polioviruses genomes [47]. Sets of highly specific nucleic acid probes [20] and polymerase chain reaction (PCR) primers [21] have been developed for routine identification of poliovirus isolates. By far the most powerful approach is comparative genomic sequencing [47] Sequence relationships can be efficiently summarized in the form of dendograms(Fig 2). With the application of genomic sequencing and molecular epidemiological approaches, it is now possible to determine the source of imported viruses, follow the pathway of virus transmission, monitor the progress of control activities, identify reservoirs sustaining virus transmission and develop molecular reagents for rapid detection of wild poliovirus.

Wild Poliovirus in Nigeria

Nigeria remains one of the six countries of the world where the wild poliovirus is still endemic. The virus is still very much in circulation especially in the northern band of states where routine immunization and mass immunization is still not efficient enough to stop the transmission of the virus. Last year alone, Nigeria topped the list of countries of the world in reporting the largest number of wild poliovirus with a total of 867 [48]. In 2005, Nigeria accounts for 35% of the global wild poliovirus case count and 92% of the cases in Africa since the beginning of 2005. Between January 2nd and 16th April 2005, a total of 157 wild poliovirus cases have been reported from 18 states of the federation (Fig 3). Of the 18 infected states, 7 states of the North Western Zone account for 68% of the total case count. 78% of the wild poliovirus cases are children below 3 years of age and 71% have received less than 3 doses of OPV. Nigeria has not only remained the main reser voir of the wild poliovirus, poliovirus originating from Nigeria have been imported to many countries of the world like Ghana, Burkina Faso, Chad, Sudan, Ethiopia, Saudi Arabia, Malawi, Indonesia and lately Yemen.

REFERENCES

1. Howe HA and Wilson JL. Poliomyelitis: In Rivwers, T.M. Horsfall, FL eds Viral and Ricketssia disease of man. 3rd ed. Philadephia: Lippincott. 1957; 432- 478.

2. Nathanson N and Martin JR. The epidemiology of poliomyelitis: enigmas surrounding its appearance, epidemiology and disappearance. Am. J Epidemiol. 1979; 110:672-692.

3. Landsteiner K. and Popper E. Ubertrangung der poliomyelitis acuta auf aften. Z. Immunitatsforsch. 1909; 2: 377-390.

4. Enders JF, Weller TH and Robbins FC Cultivation of Lansing strain of poliomyelitis virus in culture of various human tissues. Science 1949; 109: 85-87

5. Bodian D. Poliomyelitis: Pathologic Anatomy. International poliomyelitis congressed Poliomyelitis: Papers and discussions presented at the 1st International poliomyelitis

conference .Philadephia: J.B. Lippincott, 1949; 62-84.

6. Kessel JF and Pait CF. Differentiation of three groups of poliomyelitis virus. Proc Soc. Biol. Med. 1949; 70:315-316.

7. Salk J.and Salk D. Control of influenza and poliomyelitis with killed virus vaccine. Science 1977; 195: 834 - 837.

8. Sabin AB and Bougler LR. History of Sabin attenuated poliovirus oral live vaccine strains. J. Biol. Stand 1973; 115-118.

9. Raccaniello VR, Baltimore D Molecular cloning of poliovirus DNA and determination of the complete sequence of the viral genome. Proc. Natl Acad. Sci. USA 1981; 78: 4487-4891.

10. Nomoto A, Omata T, Toyoda H, Kuye S, Horie H, Kataoka Y *et al*. Complete nucleotide sequence of the attenuated poliovirus sabin 1 strain genome.Proc. Natl. Acad.Sci USA 1982; 79: 5793-5797.

11. La Monica L, Mariam C, and Raccaniello N. Mapping sequences required for mouse neurovirulence of polio virustype2 Lasing. J.Virol. 1986; 56: 55.

12. Pevear DC, Oh CK, Cunninghan LL, Callenoff M and Jubelt B. Localization of the genomic regions specific for the attenuated mouse adapted poliovirus type 2 strain.North Holland Publishing Co. 1990; 93-112.

13. World Health Assembly. Global eradication of poliomyelitis by the year 2000. 1988 WHA resolution No 41.28.

14. Rolland RR. Piconaviridae and their replication. In: Field Virology 2nd ed. Edited BNFields,DM Knipe, *et al*. Raven Press NY . 1990 507-605.

15. Minor PD, Ferguson M, Evans DMA and Almond Jwand Icenogle JP Antigenic structure of poliomyelitis virus of serotypes 1, 2 and 3.J Gen Virol 1986; 67, 1283-1291.

16. Melnick JR. Enterovirus: poliovirus, coxsackieviruses and new enteroviruses. In: Field Virology. (ed) NY. Raven Press 1992; 549-605

17. Davies BD, Dulbecco R, Eisan AN Gimbery HS Wood WD and Mc Carthy M. Microbiology 1975; Herpes C.Row. Maryland.

18. Holland JJ, de la Torre JC, and Stemhawer DA. RNA virus population as quasispecies. Current topic in Microbiology and Immunology 1992; 176:1-20.

19. van der Avoort HG, Hull BP, Hovi T.Pallansch, M. Kew OM, Crainic R, Wood DJ *et al*. Comparative study of five methods for intratypic differentiation of poliovirus.J Clin Microbiol. 1995; 33:2562-2566.

20. De L, Nottay B, Yang CF, Holloway BP, Pallansch MA, Kew OM. Identification of vaccine derived poliovirus by hybridization with specific RNA probes. J.Clin Microbiol. 1995; 33: 562-571.

21. Yang CF, De L, Holloway BP, Pallansch MA and Kew OM. Detection and identification of vaccine related poliovirus by polemerase chain reaction. Virus Res. 1991; 20:159 -179.

22. CDC. Outbreak of poliomyelitis –Domini can Republic and Haiti. 2000-2001. MMWR 2001; 50: 147-148.

23. Minor PD. The molecular biology of po-lio vaccines. J Gen. Virol. 1992; 73:3065-3077.

24. Kew OM, Morris-Glassgow O. Lander-verde U, Berns M, Shaw C, Garrib, JA, Blackman E, Freeman CJ, *et al*. Outbreak of poliomyelitis in Hispaniola associated with type 1 vaccine derived poliovirus . Science. 2002; 296:356-359.

25. Liu HM, Zheng DP, Zhang LB, Oberste S, Pallansch M, and Kew OM. Molecular evolution of a type 1 wild vaccine poliovirus recombinant during widespread circulation in China.. J Virol 2002; 74:11153-11161.

26. Shulman LM, Hansher R, Yang SJ, Yang CF, Manor J *et a*l. Resolution of the pathways of poliovirus type 1 transmission during an outbreak. J Clin. Microbiol. 2000; 38: 945-952.

27. Domingo E and Holland JJ .RNA virus mutations and fitness for survival. Annu. Rev. Microbiol. 1997; 51:151-178.

28. de la Torre JC, Giachette C, Semlar BL and Holland JJ. High frequency of single-base transitions and extreme frequency of precise multiple-base reversion mutatuions in poliovirus. Proc. Natl. Acad. Sci USA 1992; 89: 2531-2535.

29. Drake JW. Rates of spontaneous muta tions among RNA viruses. Proc Natl Acad Sci. USA 1993; 90: 4171- 4175

30. Wimmer, Ehellen CU.,and Cao X. Ge netics of poliovirus . Annu. Rev. Genet. 1993; 27: 353 - 436.

31. Bellmunt A, May G, Zell R, Pring-Ak erblom P, Verhagen W and Heim A. Evolution of poliovirus type 1 during 5.5 years of prolonged enteral replication in an immunodeficient patient. Virology 1999; 265: 178 -184.

32. Gavrillin GV, Cherkasova EA, Lip askaya GY, Kew OM, and Agol VI.(2000)Evolution of circulating wild poliovirus and of vaccine derived poliovirus in an immunodeficient patient: a unifying model. J. Virol. 1999; 74: 7381-7390.

33. Kew OM, Mulders MN and Lipaskaya, GY. Moleculaar epidemiology of poliovirus. Semin Virol. 1995; 6: 401-406.

34. Martin J, Dunn G, Hull R, Patel V, and Minor PD. Evolution of the Sabin strain of type 1. 2000

35. Cammack NJ, Phillips A, Dunn G, Patel V, and Minor PD. Interttypic genomic re-arrangements of poliovirus strains in vaccines. Virology. 1989; 167: 507-514.

36. Kinnunem LA, Huovilainen A, Poyry T and Hovi T. Rapid molecular evolution of wild type 3 poliovirus during infection in individual hosts. J. Gen Virol. 1990; 71:317-324.

37. Georgescu M, Delpeyroux F, Tardiy-Panit M, Balanant J, Combiescu AA, Guillot S and Crainic R. High diversity of poliovirus strain s isolated from the central nervous system from patients with vaccine associated paralytic poliomyelitis. J.Virol. 1994; 68: 8089-8101.

38. Kew OM, Pallansch MA, Nottay BK, Rico-Hesse R, De L and Yang CF. Genomic relatiuonship among wild polioviruses from different regions of the world.In.M.A. Brintonand F.X. Heinz (ed) New aspects of positive strand RNA viruses. American Society for Microbiology, Washington DC. 357-365.

39. Georgescu MM, Delpeyroux F and Crainic R. Tripartite genome organiszation of natural type 2 vaccine/nonvaccine recombinant poliovirus. J Gen Virol 1995; 76: 2343-2348.

40. Adu FD, Iber J, Bukbuk D, Gumede N, Yang SJ, Jaume J, Sule F, Yang CF, Burns C, Pallansch M, Harry T and Kew OM. Isola tion of a type 2 vaccine derived poliovirus from a Nigerian child. J. Clin Microbiol (In press).

41. Thorley B, Paladin F, and Shimizu H Poliomyelitis due to vaccine derived polioviruses in the Phillipines. Presented at the XII Interna tional Congress of Virology, Paris, 27th- 1 Aug. 2002.

42. CDC. Public Health Dispatch: Polio-myelitis-Madagascar. 2002 MMWR 51: 622.

43. Yang CF, Naguib T, Yang S.J., Nasr E, Jorba J. *et al*. Circulation of endemic type 2 vaccine derived poliovirus in Egypt from 1983-1993. J. Virol. 17; 15: 8366- 8377.

44. Hull HF,Ward NA, Hull BP, Milstein JB, and Quadros C. Paralytic poliomyelitis: seasoned strategies, disappearing disease. Lancet 1994; 343: 1331-1333.

45. WHO Manual for the virological investigation of poliomyelitis (WHO/EPI/CDS POLIO 90.) 1992; Geneva.

46. Hovi T and Stenvik M. Selective isolation of poliovirus in recombinant murine cell line expressing the human poliovirus receptor gene. J.Clin Microbiol 1994; 32:1366-1368.

47. Rico-Hesse R., Pallansch MA., Nottay BK and Kew OM. Geographic distribution of wild poliovirus type 1 genotypes . Virology 1995; 160: 311-322.

48. WHO Nigeria: Geographic distribution of wild poliovirus cases. WHO Bulletin of vaccine preventable diseases. 2004; Vol. 3. No. 4.WHO Nigeria / EPI Office WHO, Abuja.

Commentary

BI-RADS Lexicon: An Urgent Call for the Standardization of Breast Ultrasound in Nigeria

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SUMMARY

Ultrasound technology and its ability to demonstrate breast anatomy and pathology has changed dramatically and rapidly in the last decade, sonography is now utilized to characterize and manage palpable and mammographic abnormalities.It is also useful in evaluating nipple discharge and mammary implants. Breast ultrasound (BUS) is an invaluable tool for assessing the extent of malignant disease and regional lymph nodes is also available for evaluation of the breast after breast cancer treatment. All of the above have encouraged the development of BI-RADS ultrasound to further improve and standardize Breast Sonography. This Lexicon is being presented to radiologists, breast surgeons, breast oncologists, breast pathologists, and breast sonographers.

INTRODUCTION

Imaging plays an important role in the management of breast diseases. However, imaging of the radiologically dense breasts represents a diagnostic challenge for interpreting radiologists. Breast cancer especially non-calcified breast cancer is also more likely to be missed in dense breasts than in radiologically fatty breast [1]. In addition to the decreased visibility of the lesions secondary to the increased density of the breast tissue there is probably an independent increased risk of malignancy in dense breasts. For these reasons, new diagnostic modalities have been introduced to the armamentarium of investigation protocols in order to improve the chances of visualization of breast malignancies. These include MRI, CT, Digital Mammography, Colour Doppler and Ultrasound of the Breast. Mammography though remains the most sensitive method for detecting pre-clinical breast carcinoma, its limited specificity results in the need to biopsy many lesions to determine whether they are benign or malignant [2, 3].

In the United States and Europe, imaging the breast with MRI and digital mammography is common practice. In the majority of the Sub- Saharan countries, the absence of these state- of- the art imaging modalities makes Breast Ultrasound (BUS) an attractive alternative diagnostic tool, now that some studies suggest a future role for Sonography in breast screening [4]. Ultrasonography does not utilize ionizing radiation, it is affordable, readily available, repeatable and sensitive.

The characterization of mammographic lesions into categories was developed by the American College of Radiology (ACR) for reporting and data analysis within the United States of America [5]. It is referred to as Breast Imaging Reporting and Data System (BI-RADS) categories. The growing use of ultrasonography worldwide created this need for a standardized method for lesion characterization, description and reporting [6].

In addition, it was hoped that this would enable easy entry of data into databases for future analysis. Finally, assignment of an ACR BI-RADS category was intended to standardize management decision based on final BI-RADS assessment. This Lexicon though not perfect has been successfully used in mammography.

It is believed that with minor modifications the Lexicon can be used directly for BUS and there

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is every reason to expect that sonographic BI-RADS categorization will be as successful as mammography has been. The general role of BUS is to make a more specific diagnosis than could be made with clinical and mammographic findings. Other more specific goals are preventing unnecessary negative biopsies, preventing unnecessary short-interval follow-up, guiding interventional procedures, improving clinical skills, finding cancer that was missed or underclassified by mammography and staging cancers by determining the extent of the malignant disease [7, 8].

Based on the success of BI-RADS with mammography, the development of a lexicon for breast ultrasound became a necessity. Infact, it is now a high priority. Though breast sonography is in its infancy in Nigeria it is pertinent to standardize this imaging technique in order to meet International standards and enhance shared terminology among referring physicians, radiologists and patients which will in turn give better understanding for diagnosis and management implications [9].

Furthermore, this lexicon will provide a basis for validation of outcomes across multiple centers, as studies in Nigeria can be adequately compared or correlated with other centers in America and Europe. There is therefore an urgent need to adopt this Lexicon, Breast Imaging Reporting and Data System (BI-RADS) Ultrasound.

It is against this background that this communication is being presented to acquaint radiologists in Nigeria with the current trend in breast sonography and reporting.

Technique of Breast Ultrasound (BUS)

Indications for breast sonography include the following: the initial evaluation of palpable abnormalities in women under 30 years, initial identification and characterization of palpable and non palpable abnormalities, guidance of interventional procedures and evaluation of problems associated with breast implants[4, 5]. The growing use of ultrasonography world-wide created the need for a standardized method for lesion characterization, description and reporting [6], especially now that studies suggest future roles for sonography in breast screening [7].

The use of this ultrasound lexicon is predicated on an excellent sonographic technique using a linear transducer whose center frequency ranges between 7-12 MHz. The patient is scanned supine in the contra-lateral posterior oblique position. The patient is asked to position her ipsilateral arm above her head and her ipsilateral hand behind her head. This positioning in combination with a variable degree of compression of the breast with the transducer, accomplishes two important things. Firstly, it thins the area of the breast being scanned to the greatest degree possible, ensuring that the transducer used for breast ultrasound (BUS) will adequately penetrate to the chest wall. Secondly, it pulls the normally conically shaped tissue planes of the breast into a horizontal orientation that is nearly parallel to the transducer surface perpendicular to the ultrasound beam. This positioning technique minimizes the amount of image degradation.

Scanning Planes

Longitudinal and transverse scan planes may be sufficient for a generalized scan, however the demonstration of normal ductal anatomy requires scanning in the radial scan planes because the normal mammary ducts are normally orientated radially away from the nipple.

Lesion Localization

The method used has three desriptors: a clock face-localisation, similar to that of the American College of Radiology (ACR) Lexicon; a description of how far from the nipple the lesion lies and a description of the depth of the lesion. This is achieved using a descriptor with five components namely, the breast side (right or left), the clock-face location, the distance from the nipple, the depth of the lesion and the scan plane orientation descriptor. Several previous studies[10, 11, 12] have shown that these multiple features must be analyzed to achieve as great specificity as possible in sonographic characterization.

Axillary Lymphadenopathy

In whole breast ultrasound, the study is not completed until a look is taken at the axilla. In sonomammography the normal node measures about 1cm. It is also bean shaped with an echogenic hilum and a hypoechoic cortex giving the usual cortico-medullary differentiation.

Doppler Studies

Power ultrasound and Colour Doppler ultrasound depicts the location of blood vessels when planning a percutaneous breast biopsy. Description of the vascularity of the lesion is however not a reliable predictor of benignity or malignancy [12, 13, 14].

Sonographic Features

The primary sonographic features of a lesion include the shape, orientation margins, matrix echogenicity and attenuation (Table 1). These features should be described and applied in a consistent fashion. In addition, secondary association findings including architectural distortion, retraction or angulation of Cooper's ligaments, dilated ducts, calcifications and changes in the skin, subcutaneous fat and pectoral muscle should also be recorded. These sonographic features of masses have been enumerated previously [10, 11, 12].

The most appropriate descriptor for each category of characteristics should be applied when describing a lesion. Documentation should be performed in accordance with the American College of Radiology standards.

When a solid lesion is present, careful analysis of its contour, margins matrix and attenuation may help in its classification. Starvos *et al* [10] proposed three categories of solid lesions that could be classified as BI-RADS Category 3 (probably benign). They are masses with intense and uniform hyperechogenicity relative to fat, masses with ellipsoid shape and a smooth margin and masses with two or three gentle lobulations and also a thin smooth margin. Each of these masses has an individual negative predictive value for malignancy of 98.8% - 100% [10].

Margin

For solid masses, irregularity of shape and margin dominate other features suggesting malignancy with a Positive Predictive Value(PPV) of malignancy of 86% - 93%[10,11]. The lesions with the other features of lower specificity are classified as BI-RADS category 4 or 5, Biopsy is recommended to confirm diagnosis.

Orientation

If the long axis of a mass is not parallel to the skin, synonymously termed taller than it is wide; the likelihood of malignancy is 62-81%[10,11], it is commonly seen in cancers < 1cm in size[10]. Most fibroadenomas and some cancers are oriented with their long axis parallel to the skin (wider than tall)[15].

Echotexture/Echopatter

This is defined relative to the fibroglandular tissue of the breast hypoechoic masses have lower echoes to the fibroglandular tissue while isoechoic masses have echoes equal to the fibroglandular tissue. Echopattern appears to be less helpful in differentiating benign from malignant solid masses[15], as most masses are usually hypoechoic.

Posterior Acoustic Features

Acoustic attenuation or shadowing is suspicious for malignancy. As many as 21% of benign lesions will show shadowing. Similarly, acoustic enhancement while common in benign lesions may be present in up to 42% of cancers.

Vascularity

The description of the vascularity of the lesion is not a required standard as no reliable distinction has yet been made between benign and malignant lesions on this basis[13, 14]. The vascularity of the lesion is normally described as either the same, increased or decreased when compared to that of the surrounding parenchyma.

The BI-RADS ultrasound descriptors are illustrated in Table 1. In referring to this table, it is important to re-emphasize the fact that the greatest specificity is achieved by the evaluation of multiple features of the mass rather than any single attribute.

Final Assessment

As with mammography, a BI-RADS final assessment and recommendation should be specified (Table 2). When BUS is performed alone or as an adjunct to mammography, one final assessment and

Table 1:

Table2: BI-RADS; ULTRASOUND Final Assessment Categories

Categories/Codes	Assessment	Recommendations
0	Incomplete	Needs additional imaging evaluation
1	Negative	No lesion found
2	Benign find	No malignant features
3	Probably benign finding	Low probability of malignancy e.g. fibroadenoma
4.	Suspicious abnormality	Intermediate probability of malignancy
5.	Highly suggestive of malignancy	High probability of malignancy (appropriate action should be taken including tissue biopsy)
6.	Known Cancer	Biopsy proven malignancy definitive therapy (appropriate action should be taken).

management recommendation should be specified as illustrated in fig. 1.

Fig. 1: Mass lesion. Breast ultrasound. **Shape;** spherical, **Orientaion:** round,(Does not have one axis longer than the other) and therefore classified as non paralle. **Margin;** circumscribed, distinct and smooth. **Echogenicity:** homogenous and hypoechoic. Note the shadow enhanchment posterioly consistent with a typical cyst. **Final assessment** BI-RADS 2. A benign finding with no malignant feature.

This final assessment and management should be based on the most suspicious features present. In like manner, when there are many different ultrasound findings or lesions in the same breast, the summary BI-RADS category for the entire breast should always be the highest BI-RADS category in that breast. In other words, if there is a palpable lump caused by sonographically normal-appearing fibrous tissue (BI-RADS 1), two simple cysts (BI-RADS 2) and one nodule caused by a probably benign solid nodule (BI-RADS 3), the BI-RADS category for the entire study should be BI-RADS 3.

REFERENCES

1. Marla R. Hersh. Imaging the Dense Breast Appl Radiol 33(1): 22 –26, 2004.

2. Rosenberg AL, Schwartz GF, Feig SA, *et*

al Clinically occult breast lesions: Localization and significance. Radiology 1987; 162: 167 – 170

3. Bassett LW, Liu TH, Giuliano AE *et al:* The prevalence of carcinoma in palpable vs. impalpable mammographically detected lesions.AJR AMJ Roentgenol 1991; 157: 21 – 24

4. ACR Standard for the Performance of Breast Ultrasound Examination. ACR Standards, VA American College of Radiology, 2000; 389 - 392

5. Merritt CRB: The Breast Nodule in Ultrasound: A practical Approach to Clinical Problems (Ch 52) in Bluth EI, Arger P, Benson et al (eds). A practical Approach to Clinical Problems. New York, Theme, 2000.

6. Baker JA Kornguth PJ, 500 MS *et al.* Sonography of solid breast lesions. Observer variability of lesion description and assessment. AJR AMJ Roentgenol 1999; 172: 1621 – 1625.

7. Rotten D. Marc Levaillant, J., Lefloch, J.P., Constancis E. and Andre J.M.: Mass screening for breast cancer with sonomammography; a prospective study.European Journal of Obstetrics and Gynaecology and Reproductive Biology, 1988; 28; 257 – 267.

8. American College of Radiology (ACR): Breast Imaging Reporting and Data System (BI-RADS™) (ed 3) Reston, VA, American College of Radiology, 1998

9. Mandelson, EB. Berg. N. A., Merritt CRB. Towards a Standardized Breast Ultrasound Lexicon

BI-RADS: Ultrasound Seminars in Roentgenology, 2001; vol. xxxvi, 3: 217 – 225

10. Starvos AT, Thickmen D, Rapp CL *et al*: Solid breast nodules; Use of Sonography to distinguish between benign and malignant lesions. Radiology 1995; 196: 123 – 134.

11. High definition imaging: The role of Ultrasound in the diagnosis of breast cancer; Contribution

of US as an adjunct to Mammography. Radiology 1999; 213: 413 – 422.

12. Cole-Beuglet C, Soriano RZ, Kurtz AB *et al:* Ultrasound analysis of 104 primary breast carcinomas classified according to histopathologic type. Radiology1983; 147: 191 – 196.

13. Mc Nicholas MM, Mercer PM, Miller JC *et al:* All colour Doppler Sonography in the evaluation of palpable breast masses. AJR AMJ Roentgenol IU: 1993; 765 – 771.

14. Congrove D.O, Kedar RP, Bamper JC *et al*: Breast diseases: Colour Doppler in differential diagnosis. Radiology 1993; 189: 99 – 104.

15. Skagne P, Engedal K: Analysis of Sonographic features in the differentiation of fibroadenoma and invasive ductal carcinoma. AJR AMJ Roentgenol 170: 109 – 114, 1998

Management of Human Immunodeficiency Virus (HIV) Infection in Adults in Resource-Limited Countries: Challenges and Prospects in Nigeria.

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SUMMARY

Nigeria has an HIV seroprevalence of 5.0% with an estimated 3.5 million infected persons. By June 2005, an estimated 28 – 48,000 or 4 – 8% of those requiring Anti-Retroviral Treatment (ART) receive it through various means and support. It is targeted that 350,000 and 1 million persons will be on ART by 2006 and 2009 respectively. Clinical studies on ART have demonstrated virological, immunological and survival benefits comparable to those reported in the developed world. Situation analyses and audits in the country have shown promising and comparable findings to results elsewhere. They have also identified areas of potential concern – rational use of ART, adherence and monitoring. As ART scale up is ongoing there is need for continued technical support, laboratory standardization, commodities management / supply and training of health care workers. Simple guidelines and algorithms for ART, care and monitoring to facilitate rapid scale-up should be developed for use in tertiary and non-tertiary facilities in the country. Preventive and ART services should be fully linked. With considerable funding from many sources there is need for good governance, accountability, coordination and continuous provision of resources with cogent targets and objectives in the scale up as we seek to improve survival, quality of life and productivity of patients in Nigeria.

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INTRODUCTION

Human Immunodeficiency Virus (HIV) infection, the cause of Acquired Immune Deficiency Syndrome (AIDS) is an important cause of morbidity and mortality in much of sub-Saharan Africa. Nigeria currently has an estimated 3.5 million People Living With HIV/AIDS (PLWHAs) and a seroprevalence level of 5.0%. The epidemic has grown beyond the high-risk groups to the general population.

In resource-limited settings most interventions for HIV/AIDS are focused on prevention but in the past few years debate has persisted over the introduction and the degree of emphasis appropriate to the different components of HIV care. Since early 2002 the Nigerian Government has commenced Anti-Retroviral Treatment (ART) in 25 health facilities across the country [1]. This was boosted by the World Health Organization's (WHO) parallel initiative in late 2003 to scale up ART delivery through various sponsors to meet the "3 by 5" target of 3 million people receiving treatment by the end of 2005. By June 2005 the estimated number of people receiving ART in sub-Saharan Africa was 500, 000 or 11% of patients needing ART [2].

This review focuses on management of HIV infection in resource poor settings with particular reference to Nigeria. It highlights the problems and prospects of improving and scaling up HIV care in the country.

Anti-Retroviral Treatment (ART) in Adults

Concerns about the expansion of ART have revolved around the practical challenges of implementing treatment programmes, the high cost of drugs, limited capacity for monitoring and the potential development of drug resistance as a consequence

of poor compliance coupled with negligible improvements in survival. Proponents of ART scale up have invoked human rights arguments, challenged the relevance of cost-effectiveness analyses, expect stigma reduction, improved survival, quality of life and economic productivity and increased uptake of voluntary testing with widespread ART use. However, clinical studies of ART in resource-poor settings have demonstrated virological, immunological and survival benefits comparable to those reported in the developed world [3].

The Nigerian Government commenced using a combination of generic forms at subsidized cost targeting 10,000 adults and 5000 children. By 2004, 14,000 adults were on ART in the 25 centres in 19 out of 36 states and the Federal Capital, Abuja [4]. By June 2005, WHO estimated that the total number of people receiving ART in Nigeria was 28,000 – 48,000 or 4 – 8% of patients needing ART [2].Reassuringly a recent trial in Cameroon of a fixed-dose generic Highly Active Anti-Retroviral Therapy (HAART) regimen similar to the combination used by the Nigerian Government (nevirapine, stavudine, lamivudine) found 80% of patients had undetectable viral load at 24 weeks even though 92% of participants had AIDS at the beginning.

The probability of surviving and being free of new AIDS-defining events was 85% [5]. Studies have shown median increase in CD4 cell counts ranging from 75 – 245/μL, reductions in viral loads ranging from 1.6 – 3.3 log copies/ml for treatment naïve patients on HAART [5 – 10]. These benefits are associated with increases in median survival gains. In Brazil dramatic improvements with median additional survival gains of 40 months was noted for those diagnosed in 1996 when HAART was introduced compared to those not on ARV managed earlier [11].

Lessons from ART Clinical Audits (Table 1; Figure 1)

An ongoing unpublished audit of patients (n = 274) on the Nigerian Government sponsored ART in Kano found that a fifth of patients were lost to follow up six months [12]. Reasons for loss to follow up were unknown but likely due to mortality, relocation, cost of ART laboratory monitoring tests, voluntary ART stoppage and debilitating inter-current illnesses with poor support. However, the median follow-up is similar to the 6 – 20 months found in five African countries although the onset of the ART in Kano spans longer than in these studies [5 – 10]. Information on adherence, monitoring test results including CD4 cell counts and adverse drug reactions was lacking or incomplete. Similar findings were broadly noted in an assessment of a pilot ART programme in Uganda [10]. Independent indicators of initiating ART in HIV infected patients are significant symptoms, CD4 cell count of < 350/cmm, (or, if not available, lymphocyte count below 1200 per cmm with symptomatic disease) or high viral load [13]. However, only 4 of the 25 national centres initiated ART based on viral load testing [1]. Low cost, low technology assays to measure and monitor HIV load such as the Cavidi RT assay are being explored for use in resource-limited countries. In few patients (4%) ART was started without CD4 cell counts. Given the relatively high proportion of persons with high CD4 cell counts who were started on ART, the limited use of co-trimoxazole prophylaxis and under recognition of adverse drug reactions (ADR) from the audit indicates the need for continued education of health care givers about ART. The modular training initiative should be used to rationalize use of ARVs in patient management practices. To facilitate this, the WHO has released guidelines on simplified algorithms for treatment and monitoring to facilitate rapid scale-up of ART in resource-limited settings [2, 13].

The median CD4 cell count gains on initiating ART (Table 1) is higher than figures cited in studies which used flow cytometry [5 – 10]. It is reassuring but not easily explained, though manual coulter or dynabeads methods of counting CD4 cells are laborious, more prone to inaccuracy at higher cell counts and has poor correlation (r = 0.45) with values obtained by flow cytometry [14]. However, several groups have found good correlation between CD4 cell counts measured by coulter (manually) or by dynabeads with flow cytometry (r = 0.90 – 0.93) [14 – 17]. Figure 1 shows the two year progression of CD4 cell counts in patients on ART. Flow cytometry was started 3 – 4 months ago at

Table1: Findings in 274 HIV infected patients on ART* in a clinical audit in Kano.

Parameter	**Value or proportion (%)** (N = 274)
Follow-up (mths) median [range]	17.5 [1 – 38]
Patients with follow-up < 6mths	54 / 274 (19.7%)
Pre-therapy #CD4 cells/cmm median [inter-quartile range] *(n = 263)*	219 [131 – 320]
patients with pre-therapy #CD4 cells/cmm = 500/cmm	41 / 263 (15.6%)
#CD4 cells/cmm gain at ~24 wks over pre-therapy values median [inter-quartile range] *(n = 101)*	+ 348 [221 – 602]
Proportion with inter-current illness(es)	122 / 241 (50.6%)
Proportion with adverse drug reaction (ADR)	12 / 246 (4.9%)
Proportion on co-trimoxazole prophylaxis	46 / 268 (17.2%)

** 95.1% of patients were on nevirapine, stavudine, lamivudine combination. This combination is charged at N1000 per month's course. In the 38mths of the program there was a 3mths period when drug supply was erratic.*
 # CD4 cell counts was done using Manual / microscopic CD4 cell count (Coulter) and Dynabeads (Dynal) according to availability. Patients were charged N3000 per test.

Fig 1:

President's Emergency Plan For AIDS Relief / AIDS Care and Treatment in Nigeria (PEPFAR / ACTION) sites free of charge. It should be used widely in state or zonal centres. Taken together, this means whichever method is used there is need for continued technical support, quality control and quality assurance programmes in laboratories.

Monitoring

The total lymphocyte count is an imperfect predictor of CD4 cell counts. In a study of 2777 HIV seropositive persons in South Africa, the overall correlation between CD4 cell and total lymphocyte count was only modest (r = 0.70) [18]. In Nigeria a study of 32 adults with HIV infection who commenced ART found only a very weak correlation between the parameters (r = 0.25) [19]. However,

given the laboratory infrastructural deficiencies especially in non-tertiary health facilities total lymphocyte count can be used as a surrogate marker for absolute CD4 cell counts [13]. Our experience from preliminary analyses suggests simple measurements like changes in weight and haematocrit fairly mirrors CD4 cell changes. The combination of a modified WHO clinical staging system for HIV infection with haematocrit was demonstrated to predict CD4 cell counts of < 200
cells/cmm in Brazilian patients [20]. Their potential in conjunction with clinical staging, performance status and total lymphocyte count for monitoring patients on ART should be explored for use in non-tertiary health facilities. In tertiary PEPFAR/ACTION sites CD4 counts and laboratory monitoring tests are now offered free and should be used.

Adherence

Adherence is an important determinant of survival and is challenging in resource-poor settings where ARVs may be used without appropriate counselling or monitoring tools [21]. However, reports of adherence levels above 90% in Senegal and South Africa are encouraging [22, 23]. The Federal Government and PEPFAR charge N1000 per month for ART in adults but drug costs are important determinants of non-adherence with a study in Botswana estimating that adherence would rise from
54% to 74% if drugs were provided free [24]. It is hoped drugs will eventually be free. Sub-optimal adherence to ART is likely to result in the transmission of drug resistant virus strains within the community [21]. Despite the imperfections cited earlier several explanations can be adduced for failure of a sustained CD4 cell rise in Figure 1, though possibility of drug resistance reaffirms the need for rational ARV use, provision of second line and salvage alternatives as well as the need for resistance surveillance.

A study in Uganda found higher rates of resistance with poor adherence and dual therapy (especially to lamivudine) than in those who received HAART [10]. Other factors that affect adherence should be studied locally. Directly Observed Therapy Short course (DOTS) has been suggested as method for delivering ART and improving adherence, although it has limited success for tuberculosis in much of Africa with success rate of 75 – 79% in Nigeria [25, 26]. Home-based care and DOT should be considered in certain circumstances. Patient-focused, provider-focused and regimen-focused interventions should be studied and explored to improve adherence to ART in the country.

Management of Opportunistic Infections

In Nigeria, HIV is an important cause of mortality in hospitalized patients admitted to adult medical wards. For instance at AKTH in Kano, 30 – 40% of HIV infected patients die from poorly recognized or managed inter-current illnesses (unpublished) [27]. Common causes of death in hospitalized HIV infected adults in sub-Saharan Africa (Cote d'Ivoire, Zaire) include tuberculosis (38 – 41%), bacterial pneumonia (30 – 34%), cytomegalovirus (13 – 18%), cryptococcosis (3 – 19%), bacteraemia (16%), kaposi sarcoma (9 – 16%), cerebral toxoplasmosis (11 – 15%), non-specific enteritis (10%), etc [28, 29]. In Zaria, Nigeria, tuberculosis and acute bacterial infections accounted for 29% and 20% respectively in HIV infected hospitalized adults [30]. Given that HIV infection *per se* rarely kills, the capacity of health facilities to recognize, diagnose and manage opportunistic infections should be strengthened in addition to ART provision.

Faced with limited resources, the best framework for decision making is one that benefits the individual HIV infected patient and other people including those not infected with HIV. The clearest example of a high priority public intervention against opportunistic infection is probably the diagnosis, treatment and prevention of tuberculosis. Thus, in such settings essential packages for care should be provided. Essential drugs list for HIV/AIDS should be formulated for use especially in non-tertiary settings in the country. Such a list should contain – antituberculosis drugs, cotrimoxazole, ketoconazole (or fluconazole), metronidazole, broad-spectrum antibiotic (e.g. ampicillin), nystatin, gentian violet, hydrocortisone cream, codeine, paracetamol, aspirin, chlorpromazine, diazepam, multivitamin, calamine lotion, etc [31]. This should not be confused

with the Essential Medicine List for Nigeria which

was updated in 2003 and consists of 8 ARVs: didanosine, lamivudine, stavudine, zidovudine, efavirenz, nevirapine, indinavir, nelfinavir and fixed dose combination of lamivudine, stavudine and nevirapine. With the widespread limitations to diagnose opportunistic infections aetiologically, care approach should be syndromic as recommended by WHO and adopted in many sub-Saharan African countries notably Botswana [13, 32].

Rather than addressing tertiary settings solely, national guidelines should include management protocols for common syndromes and presentations [32], like the ones developed in Kano. These should incorporate limited number of laboratory tests.

Linking Preventive Programmes to ART

It has been shown that even with widespread use of ART the probability of epidemic eradication is high (0.85) only if risky sexual behaviors decrease [33]. Epidemiological analyses and modeling suggest that if the successes achieved in some countries in prevention of transmission can be expanded to a global scale by 2005, about 29 million new infections could be prevented by 2010 [34]. It is therefore necessary to strengthen linkages between ART and prevention programmes: Voluntary Counseling and Testing (VCT), Sexually Transmitted Diseases (STD) programmes, Tuberculosis (TB) services, Prevention of Mother-To-Child Transmission-Plus (PMTCT-Plus), etc. A large randomized trial in Kenya, Tanzania and Trinidad demonstrated 32% reduction ($p < 0.0001$) in such risky behaviors- the proportion reporting unprotected sex with a non-primary partner in VCT group compared with the control group affirming the potential role of VCT in reducing transmission [35]. Two large intervention trials in Mwanza, Tanzania and Rakai, Uganda on syndromic and mass management of STDs as a prevention tool for HIV infection found discrepant results [36, 37]. The intervention in Tanzania reduced HIV incidence by an estimated 42% while it showed little impact in Uganda [36, 37]. Possible explanations for these findings include maturity of the epidemic and the high rate of genital herpes in Uganda, as well as differences in the intervention strategy [38].

However, as STDs are important biological co-factors in the transmission of HIV, STD clinics provide important entry points into ART programmes and the two should be strongly linked within the country. The PMTCT-Plus aims to provide lifetime treatment to mothers and to prevent neonatal transmission [39]. This has been reflected in the recently revised national guidelines. Not only linkage of services is strongly desirable but integration of ART with these aspects of care and prevention should be mandatory wherever possible.

Conclusion, Scaling-up ART and Support

Nigeria has an on-going generalized epidemic and inevitably care will have to be scaled up considerably. It is targeted that 350,000 and 1 million persons will be on ART by 2006 and 2009 respectively (PEPFAR/ACTION). Several organizations including PEPFAR, Global Fund for Tuberculosis, AIDS & Malaria, WHO '3 by 5', World Bank, AIDS Prevention In Nigeria (APIN), Federal Ministry of Health, National Action Committee on AIDS (NACA) etc provide funding and support for these programmes and the ART scale up. Their initiatives are managed in the country by US Centres for Disease Control (CDC), US Agency for International Development (USAID) and others through tertiary institutions like Institute of Human Virology (IHV), University of Maryland, Harvard School of Public Health and Non-Governmental Organizations like Family Health International / Global HIV/AIDS Initiative in Nigeria.

The scale-up calls for appropriate achievable objectives which among others should: strengthen procurement and supply management systems ensuring continuous availability of commodities, diagnostics, drugs and supplies; ensure that health facilities are adequately equipped and personnel possess the knowledge and skills to deliver ART; strengthen systems for monitoring, evaluation and operational research; strengthen the involvement of communities in supporting the provision of ART; develop mechanisms to facilitate access to ART for the poor and vulnerable groups. There should be good management, coordination, accountability and provision of resources in the scale up as we seek to improve the survival, quality of life and productivity of PLWHA in Nigeria.

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REFERENCES

1. Federal Ministry of Health (2003). Situation of Anti-Retroviral drug use in Nigeria. November 2003.

2. World Health Organisation (WHO). Progress on global access to HIV antiretroviral therapy; An update on "3 by 5". WHO, June 2005.

3. Hogan DR and Salomon JA. Prevention and treatment of HIV/AIDS in resource-limited settings. Bulletin of the World Health Organization 2005; 83: 135 – 143.

4. Idoko J. Nigerian ART Program: Scaling up 2005 (unpublished).

5. Laurent C, Kouanfack C, Koulla-Shiro S, Nkoue N, Bourgeois A, Calmy A, *et al.* Effectiveness and safety of a generic fixed-dose combination of nevirapine, stavudine, and lamivudine in HIV-1 infected adults in Cameroon: open-labe multicentre trial. Lancet 2004; 364: 29 – 34.

6. Coetzee D, Hildebrand K, Boulle A, Maartens G, Louis F, Labatala V, *et al.* Outcomes after two years of providing antiretroviral treatment in Khayelitsha, South Africa. AIDS 2004; 18: 887 – 895.

7. Djomand G, Roels T, Ellerbrock T, Hanson D, Diomande F, Monga B, *et al.* Virologic and immunologic outcomes and programmatic challenges of an antiretroviral treatment pilot project in Abidjan, Cote d'Ivoire. AIDS 2003; 17 suppl 3: S5 – 15.

8. Landman R, Schiemann R, Thiam S, Vray M, Canestri A, Mboup S, *et al.* Once-a-day highly active antiretroviral therapy in treatment-naïve HIV-1 infected adults in Senegal. AIDS 2003; 17: 1017 – 22.

9. aurent C, Diakhate N, Gueye NF, Toure MA, Sow PS, Faye MA, *et al.* The Senegalese government's highly active antiretroviral therapy initiative: an 18-month follow-up study. AIDS 2002; 16: 1363 – 1370.

10. Weidle PJ, Malamba S, Mwebaze R, Sozi C, Rukundo G, Downing R, *et al.* Assessment of a pilot antiretroviral drug therapy programme in Uganda: patient's response, survival, and drug resistance. Lancet 2002; 360: 34 – 40.

11. Marins JR, Jamal LF, Chen SY, *et al.* Dramatic improvement in survival among adult Brazilian AIDS patients. AIDS 2003; 17: 1675 – 82.

12. Habib AG, Babashani M, Nwokedi EE, Kuliya-Gwarzo A, *et al.* A clinical audit of ART use in management of HIV infection in Kano, Nigeria (in preparation).

13. World Health Organization (WHO). Scaling up anti-retroviral therapy in resource-limited settings: treatment guidelines for a public health approach. WHO, Geneva, 2004.

14. Didier JM, Kazatchkine MD, Demouchy C, et al. Comparative assessment of five alternative methods for CD4 T lymphocyte enumeration for implementation in developing countries. J Acquir Immune Defic Syndr 2001; 26: 193 – 195.

15. Ferreira OC Jr, Suleiman G, Brites C, *et al.* A rapid and reliable assay to enumerate CD4 T lymphocytes in whole blood. J Acquir Immune Defic Syndr 1994; 7: 1224 – 1227.

16. Carella AV, Moss MW, Provost V and Quinn TC. A manual bead assay for the determination of absolute CD4 and CD8 lymphocyte counts in HIV infected individuals. Clin Diagn Lab Immunol 1995;
2: 623 – 625.

17. Lyamuya EF, Kagoma C, Mbena EC, *et al.* Evaluation of the FACScount, TRAx CD4, and Dynabeads methods for CD4 lymphocyte determination. J Immunol Methods 1996; 195: 103 – 12.

18. van der Ryst E, Kotze M, Joubert G, *et al.* Correlation among total lymphocyte count, absolute CD4 count and CD4 percentage in a group of HIV-1 infected South African patients. J Acquir Immune Defic Syndr Hum Retrovirol 1998; 19: 238 – 244.

19. Akanmu AS, Akinsete I, Eshofonie AO, Davies AO, Okany CC. Absolute lymphocyte count as surrogate for CD4 cell count in monitoring response to antiretroviral therapy. Niger Postgrad Med J 2001; 8: 105 – 111.

20. Schecter M, Zajdenverg R, Machado LL, Pinto ME, Lima LA and Perez MA. Predicting CD4 counts in HIV infected Brazilian individuals: a model based on the WHO staging system. J Acquir Immune Defic Syndr 1994; 7: 163 – 168.

21. Stevens S, Kaye S and Corrah T. Antiretroviral therapy in Africa. BMJ 2004; 328: 280 – 282.

22. Laniece I, Ciss M, Desclaux A, Diop K, Mbodj F, Ndiaye B, *et al*. Adherence to HAART and its principal determinants in a cohort of Senegalese adults. AIDS 2003; 17 suppl 3: S103 – 8.

23. Orrell C, Bangsberg DR, Badri M and Wood R. Adherence is not a barrier to successful antiretroviral therapy in South Africa. AIDS 2003; 17: 1369 – 1375.

24. Weiser S, Wolfe W, Bangsberg DR, *et al*. Barriers to antiretroviral adherence for patients living with HIV infection and AIDS in Botswana. Journal of Acquired Immune Deficiency Syndrome 2003; 34: 281 – 8.

25. World Health Organization (WHO). Global Tuberculosis Programme: report of ad hoc committee on the tuberculosis epidemic (WHO/TB/98.245). Geneva: WHO, 1998.

26. World Health Organization (WHO) report 2002. Global Tuberculosis report. Geneva: WHO, 2002.

27. Habib AG, Babashani M, Borodo MM, Dutse AI, Mahmoud M, Yakubu U. Role of HIV infection in morbidity and mortality in hospitalized adult patients in Kano, Nigeria (in preparation).

28. Lucas SB, Hounnou A, Peacock C, *et al*. The mortality and pathology of HIV infection in a West African city. AIDS 1993; 7: 1569 – 79.

29. Nelson AM, Perriens JH, Kapita B, *et al*. A clinical and pathological comparison of the WHO and CDC case definitions for AIDS in Kinshasa, Zaire: is passive surveillance valid? AIDS 1993; 7: 1241 – 1245.

30. Habib AG, Keshinro IB, Gebi UI, Olatunde BOM, Onyemelukwe GC and Kangave D. Clinical presentation of HIV infection in northern Nigeria and its relationship to CD4 T-cell counts. Nigerian Medical Practitioner 1998; 35: 3 – 8.

31. De cock KM, Katabira ET. Approach to the
management of HIV/AIDS in developing countries. In: Sexually transmitted diseases. Ed King K. Holmes *et al*. 3rd ed, 1391 – 1397. Mc Graw Hill, 1999.

32. AIDS / STD Unit: Clinical management of HIV infection in adults. Vol II. Botswana Guidelines for Health Posts, Clinics, and Primary Hospitals. Ministry of Health P. Bag 00451, Gaborone, Botswana, 1993.

33. Velasco-Hernandez JX, Gershengorn HB and Blower SM. Could widespread use of combination antiretroviral therapy eradicates HIV epidemics? Lancet Infect Dis 2002; 2: 487 – 493.

34. Stover J, Walker N, Garnett GP, Salomon JA, Staneki KA, Ghys PD, *et al*. Can we reverse the HIV/AIDS pandemic with an expanded response? Lancet 2002; 360: 73 – 77.

35. The Voluntary HIV-1 Counselling and Testing Efficacy Study Group. Efficacy of voluntary HIV-1 counselling and testing in individuals and couples in Kenya, Tanzania and Trinidad. Lancet 2000; 356: 103 – 12.

36. Grosskurth H, Mosha F, Todd J, *et al*. Impact of improved treatment of sexually transmitted diseases on HIV infection in rural Tanzania: randomized control trial. Lancet 1995; 346: 530 – 536.

37. Wawer MJ, Sewankambo NK, Serwadda D, *et al*. Control of sexually transmitted diseases for AIDS prevention in Uganda: a randomized community trial (Rakai Project Study Group). Lancet 1999; 353: 525 – 535.

38. Grosskurth H, Gray R, Hayes R, Mabey D and Wawer M. Control of sexually transmitted diseases for HIV-1 prevention: understanding the implications of the Mwanza and Rakai trials. Lancet 2000; 355: 1981 – 1987.

39. Mitka MP MTCT-Plus program has two goals: end maternal HIV transmission + treat mothers. JAMA 2002; 288: 153 – 154.

Current Concepts in Tuberculosis Diagnostics

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SUMMARY

The inability of the laboratory to adequately diagnose Tuberculosis (TB) using smear microscopy especially in those with latent infections, TB/HIV co-infections, paediatric and extra-pulmonary infections has led to an upsurge in TB epidemics in the community. While attention is being focused on HIV/AIDS pandemic, little is being heard of TB, especially in the areas of laboratory diagnosis (except of recent) despite the fact that the disease is the commonest cause of death in people living with HIV/AIDS. Efforts should be geared towards diagnostic TB research in developing countries to facilitate early diagnosis of cases and prompt initiation of therapy for TB control programme to have a meaningful impact in the community.

INTRODUCTION

Tuberculosis (TB) is of great public health concern worldwide, more so in the developing countries of Africa and Asia where 95% of cases are seen and 98% of deaths attributable to the disease occur [1]. As a result of the high burden of the disease, the United Nations has fashioned out Millennium Development Goals (MDGs) targets for TB control. These targets are:

(i) By the year 2005, to detect 70% of smear–positive TB cases annually, and to successfully treat 85% of these cases.

(ii) By 2015, to halve the prevalence and death rates associated with TB.

In order to achieve the MDGs for TB control, more efforts should be geared towards TB diagnostics.

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A diagnosis of tuberculosis is undisputed when the causative organism is isolated from the clinical specimen. The extent to which this is achieved depends largely on the diagnostic capacity of the mycobacteriology laboratory. Tuberculosis is a preventable and curable disease. Research studies and clinical trials have shown that the treatment of this disease is not only effective but is also among the most cost-effective ways of prolonging healthy living [2,3]. This means that the scourge should have been eradicated by now or reduced to a mere shadow of itself. In fact, there are more cases of TB in the world today than in previous epochs of human history [3]. The problems posed by this disease necessitated the World Health Organization (WHO) to label it a global emergency in 1993. The situation in sub-Saharan Africa is even more worrisome. This is as a result of poor environmental living conditions, ignorance, poverty, HIV/AIDS scourge and more importantly absence of rapid diagnostic tools to facilitate an early diagnosis of the infection leading to a wide spread of the disease.

Situation on Ground

Rapid and accurate diagnosis of symptomatic patients is the cornerstone of global TB control strategies. Remarkable progress has recently been made upgrading the speed and quality of TB diagnostic services in developed countries but for most of the world where TB is a large public health burden, these gains are still unrealized [4]. Thus, the primary laboratory tool supporting case detection in vast majority of cases in disease endemic countries remains microscopic examination of the stained sputum smear. The shortcomings of this method seriously limit the extent and quality of its application, and ultimately, its impact in TB control.

Smear microscopy performs poorly in latent infections and in patients with TB/HIV co-infections. It is not specific as both pathogenic and environmental mycobacteria are indistinguishable. Apart from this, it is grossly inadequate for the diagnosis of paediatric and extra-pulmonary infections. Culture on Lowenstein-Jensen medium requires six to eight weeks incubation to detect TB isolates thus contributing to diagnostic delay associated with TB. This often leads to widespread transmission of the disease.

Good TB control depends on a balanced equation of case detection and treatment delivery. The global expansion of "DOTS" (Directly Observed Treatment Short Course) - a WHO strategy to combat TB) and the advent of Global Drug Facility (GDF) have contributed significantly to good accessibility of TB drugs and improved cure rates. This is good news but the other side of the equation, that is, diagnostics - case detection was left unattended to for many years. For example, WHO recommended diagnostic tool, smear microscopy has been in use since 100 years ago. Reports from twenty-two high TB burden countries show that sixteen reported treatment success rate of over 70% but alarmingly, only four high burden countries have overall smear positive detection rates of over 60%.[5] Majority of cases remained undiagnosed thus perpetuating the epidemic.

How Did We Find Ourselves in this Predicament ?

Two factors are responsible for this. The first is smear microscopy as a case defining diagnostic tool. This tool is insensitive, as it requires a minimum of 10,000 Acid Fast Bacilli (AFB) per high power field to be reported positive, it requires multiple visits by the patients and is technically burdensome, apart from other drawbacks that have been enumerated previously. Clearly, simpler, more sensitive and more patient-friendly diagnostic tools are urgently needed. The Bills and Melinda-Gates funded TB Diagnostic Initiative (TDI) at the United Nations Development Programme/World Back/WHO Special Programme for Research and Training in Tropical Diseases (TDR), along with commercial and academic partners are currently working on new tools that will be affordable and adapted for use in developing countries with high TB burden.The international TB community and general medical community itself, which has always emphasized quality of treatment over quality of diagnosis. In part because of the urgent need to increase cure rate and in part because public health thinking has been dominated by clinicians without much input from microbiologists, hence, drug treatment has always remained higher on global TB agenda than diagnostics.

At present, TB diagnostic services receive little attention. Laboratories are marginalized by TB control programmes and too often are staffed with overworked and unmotivated laboratory scientists who are forced to make do with sub-standard reagents and inadequate or broken down equipment.

The poor state of the laboratories leads to poor performance, perpetuating a vicious cycle of laboratory mediocrity reinforcing clinical irrelevance. This is dramatically illustrated in the HIV- prevalent regions of sub-Saharan Africa. Here the percentage of symptomatic pulmonary TB suspects who are sputum smear positive is so low that there is an inevitable drift towards syndromic management.

Countdown to New Diagnostic Tools

If one may ask! What is new in TB diagnostics in Nigeria? The answer is "Not much" This scenario is disturbing because Nigeria rank 4th out of the 22 TB high burden countries globally and it has the highest number of new TB cases in sub-Saharan Africa [5].

New tools that have been developed to be adapted for use in developing countries are:

(i) Radiometric liquid culture systems eg Bactec 460^{TB} are commonly used in level III mycobacteriological laboratories in developed countries but the difficulty working with radioactive materials, necessity of expensive equipment for detection of radioactive gas and cost of materials seriously limit its use in poor resource countries.

(ii) Alternative new solid culture media was developed by TB Diagnostic Initiative (TDI) based at WHO headquarters in Geneva. The activities of TDI later gave birth to FIND (Foundation For Innovative Diagnostics for Infectious Diseases). FIND was formed with the intention of developing

tools for diagnosis of infectious diseases that will be affordable and adapted for use in poor countries with high burden of diseases. Tuberculosis was taken as a prototype of such infectious diseases. In July 2004, FIND in collaboration with an American Pharmaceutical Company (SALUBRICS INC.) [6] started piloting the use of TK medium as an alternative to the Lowestein-Jeesen medium. This new medium shortens TB detection time to half and its speed and sensitivity is comparable to automated systems.

•TK medium indicates growth of Mycobacterium by changing colour thereby avoiding the need to wait for colonies to become apparent on culture media. Speed is enhanced by the medium's ability to detect the metabolic activity of the bacteria, which changes the colour from red to yellow for a positive isolate while a contaminant will change from red to green. "The speed of the test results, simplicity and its' discriminating capacity improves the relevance of culture and make it ideal for use in developing countries" says Mark Perkins. Mark Perkins was formerly Medical Officer in charge of TB Diagnostic Initiative and now the Scientific Director of FIND.

Fig. : Salubrics TK Medium

Summary of Salubrics' Product

•*Rapid culture medium*

•*Original red color turns to yellow by mycobacterial growth before the colonies become visible.*

•*It differentiates contamination by turning to green when many other species of bacteria or fungi grow*

•*It is not radioactive. It does not create a radioactive waste problem*

•*Protective cap makes inoculations and subcultures easy and safe*

•*TK SLC is the selective type containing five different antimicrobials to inhibit the growth of other bacterial species and fungi*

•*TK PNB allows rapid differentiation of tuberculosis and non-tuberculosis mycobacteria*

•*TK Anti-Tb Kit allows susceptibility test easy and fast.*

In December 2004, FIND entered into a collaboration with Becton Dickson BD & Co. aimed at improving the diagnosis of pulmonary TB in HIV infected patients in developing countries using a more sensitive and rapid diagnostic kit. TB is particularly difficult to diagnose in HIV/AIDS patients because they produce few TB bacteria in their sputum. Thus while smear microscopy is insensitive in these patients, culture on Lowestein-Jensen medium is notoriously slow. FIND in conjunction with BD & Co.[7] has developed an improved culture method called BD MGIT^{TM} (Mycobacteria Growth Indicator Tube) system, which provides results within 10-14 days. FIND plans to conduct demonstration projects on this product in conjunction with WHO, StopTB Partnership and Consortium To Respond Effectively To AIDS /TB Epidemics (CREATE) based at John Hopkins Center For TB Research, United States of America with the aim of promoting the use of the product in poor resource countries with high burden of TB.

(iii) Serology: Existing commercialized serologic tests make use of well described immunodominant antigens to detect immunoglobulinG or other immunoglobulin classes in dipstick or Elisa format. Promising research developments in serology include:

(a) Availability of highly purified and recombinant antigens

(b) Improved understanding of the heterotypic nature of humoral response to TB and the development of multi-antigen tests that maintain high

(iv) Phage systems: Phage replication systems (Luciferase Reporter Mycobacteriophages and FastPlaque kits by Biotec Laboratories) detect live mycobacteria in clinical samples or in young liquid cultures using phages that infect and replicate in mycobacterial cells as indicators.

Nigerian Institute of Medical Research, Lagos in collaboration with Biotec laboratories carried out a demonstration project on FastPlaque kits in 2002. Main problem then was the cost of the kits which made it unaffordable for use for generality of people.

(v) Molecular Techniques: This determines the presence of *Mycobacterium tb* in clinical specimens by detecting specific nucleic acid sequences after being amplified. Nucleic acid amplification assays (NAA) have been found to be more sensitive than smear microscopy but less sensitive than culture.[2] Even though commercially available NAA Kits are simple and reliable to use, cost, degree of technical support and quality control requirements limit their use in poor countries.

(vi). New in-vitro assays are in the pipeline to replace Tuberculin skin test, which is the only test currently used to detect latent infection. This is particularly important in high HIV prevalent areas. Tuberculin (PPD) test is not specific for TB because it shares a large number of antigens with BCG and environmental mycobacteria. Also it is plagued by errors due to readers' interpretation and the need for return patient visits.

The Way Forward (Diagnostic Needs Of High Prevalence Countries Like Nigeria)

•*Impediments to TB diagnostics in Nigeria include:*

(i) Widespread use of BCG vaccinations which may affect the specificity of immunologic tests.

(ii) High prevalence of HIV/AIDS infection

.•*Ideal new tools should address the followings:*

(a) Replacement for Microscopy:

(i) New test(s) should yield conclusive results in less than 2hrs while the patient is

(ii) Be simple enough for use by unskilled workers with less than 3 hrs of training;

(iii) Be specific enough to allow initiation of therapy;

(iv) Function well in HIV patients;

(v) require little or no interpretation.

(b) Replacement for culture:

(i) To augment microscopy for evaluation of complex patients;

(ii) Should be sensitive enough to detect the majority of smear negative culture positive TB patients including those co-infected with HIV; (iii) It must be fast, simple to perform and inexpensive to be implemented at the peripheral level.

(c) Screening tests: to rapidly screen symptomatic cases thus reducing laboratory workload and also to detect drug resistance within 2-4 weeks of sputum microscopy in areas with high multi-drug resistant (MDR-TB) load.

•Screening tests for latent infection must be specific for *M.tb*, must not require a return visit and must function well in HIV patients.

•Efforts are in top gear at global level to find a suitable vaccine that could prevent *M.tb* from overwhelming its victims. Many scientists have potential vaccines under investigation, and lots of laboratory experiments have suggested that they could work. But there has been no pharmaceutical interest in pushing any of these vaccines to a level required for use in humans. The barriers of financial risks, market forces and the high cost of vaccine development blocked the path between hope and cure. Drug companies could not afford to take the chance that a drug proven to be safe in mice would work in people, and research laboratories could not afford human trials.

•Here, efforts of Sequella Foundation (SF) should be applauded. SF is an international NGO founded by an Immunologist, Dr Carol Nacy, and being funded by Bill and Melinda Gates Foundations. By funding the critical intermediary steps

needed to launch vaccine testing in humans, Sequella Foundation is turning imagination to reality. Thus, Sequella can be the matchmaker between academic laboratory scientists and the pharmaceutical industry [8].

How Can We Improve Case Detection to Maximize the Impacts of Dots in Nigeria ?

(i) First step is to give TB laboratories the support they need, allowing them to offer high quality services through provision of equipment and reagents, training and support of laboratory staff, insistence on quality control and proficiency testing and sponsorship of communication links between clinical and laboratory services.

(ii) To coordinate international assistance for capacity building in TB laboratories in Nigeria. This is needed to support not only the performance of standard methodologies but also to support operational research. Strong collaboration between academic researchers and national TB control staff should be encouraged.

(iii) The third step is the development of new

diagnostic tools that respond to our needs. Accurate case detection is the Achilles' heel of the DOTS strategy. The success of current concerted efforts to stop TB depends on our ability to detect cases early enough, to institute curative therapy and interrupt the cycle of transmission.

REFERENCES

1. World Health Organization. Global Tuberculosis Control. WHO Report 2000,Geneva, WHO/CDS/TB/2000, 275

2. Perkins MD. New diagnostic tools for Tuberculosis. Int J Tuberc Lung Dis, 2000; 4: 182-188

3. Grange JM, Zuma A. The global emergency of tuberculosis:What is the cause. J Roy Soc for the Promotion of Health 2002, 122: 78-81

4. Kehinde AO, Obaseki FA, Cadmus SIB, Bakare RA. Diagnosis of Tuberculosis: Urgent Need to Strengthen Laborator Services. American Journal of National Medical Association 2005, vol 97 (3): 394-396

5. World Health Organization. WHO Report, Global Tuberculosis Control: Surveillance, Planning, Financing. WHO Geneva 2005, 1-12

6. www.salubrics.com _FINDS to invest TB test that will cut culture to half, July 2004

7. www.bd.com_FIND & BD combine International efforts to improve rapid TB Diagnosis for HIV positive patients in developing countries, Dec 2004

8. www.globalhealth.columbia.edu Sequella: Global Tuberculosis Vaccine Initiative

Otolaryngological Manifestations of HIV/ AIDS : A Review

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INTRODUCTION, EPIDEMIOLOGY AND PATHOLOGY

Human immunodeficiency virus (HIV) infection may be referred to as the epidemic of the 20th century. It was estimated that by the end of the 1990s, 10 million people worldwide would have become HIV-positive[1,2]. In the United States HIV seroprevalence varied between 0.45% - 27.5% while it is 1.2% - 12% in Nigeria, and estimated to have caused 0.25million deaths in the year 1999 [2,3].

HIV preferentially infects cells of the nervous and lymphatic systems. The most important cell infected is the T-helper cell, through the CD4 receptor, resulting in both functional impairment and numeric depletion of T helper cells.

It was reported initially that 41% of patients with AIDS had head and neck manifestations however, as awareness increased, recognition of these lesions also increased and now nearly 100 percent of patients with AIDS develop head and neck manifestations[4,5]. The otolaryngologic manifestations of HIV disease can be classified as infections, neoplasms, and primary neurological damage caused by HIV. The common complications are tabulated in Table 1 [6].

NECK

An enlarging neck mass was reported in up to 91% of HIV-infected patients with head and neck manifestations[7]. The etiology of these neck masses can be HIV lymphadenopathy, infectious processes or neoplasms[8,9].

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HIV Lymphadenopathy

Persistent generalized lymphadenopathy, also known as HIV lymphadenopathy, is defined as unexplained generalized lymphadenopathy involving two or more extra-inguinal sites and lasting more than three months[1]. It is one of the major criteria and the axilla and neck are the most common sites. Patients often have no symptom other than neck swelling. Tissue sampling should be performed when malignancy is suspected [10]. Indications for biopsy include recent weight loss and rapid increase in size.

Infectious Process of the Neck Related to HIV

Tuberculosis

Extrapulmonary disease has beeen reported to be predominant accounting for 50 to 67% of tuberculous infections in these patients[10,11]. The common sites include the cervical nodes, larynx and the bone marrow[12, 13, 14, 15]. The majority of the patients have no symptom other than an enlarging neck mass which is usually firm and nontender but 10% may be inflamed[14, 15, 16].

In the HIV-infected population, however, *Mycobacterium avium* complex (MAC) infection is the most common mycobacterial infection. MAC infection appears to originate from the lungs, but it can be isolated from lymph nodes, and other sites in up to 50% of affected patients[17, 18]. Histopathology of the involved tissue usually reveals poorly formed granulomas or no granulomas at all. Unlike *M. tuberculosis*, the response of atypical mycobacterial infections to traditional antimycobacterial drugs

is often poor[17, 18]. Newer regimens including azithromycin or clarithromycin are effective [19].

Laryngeal tuberculosis remains the most common granulomatous disease of the larynx. Studies linking laryngeal TB to AIDS have estimated the incidence to be up to about 30%[6, 18, 19, 20], however, as the epidemic continues, more cases are expected. A high index of suspicion and differentiation from cancer or other granulomatous diseases are crucial to management.

Pneumocystis Carini

Extrapulmonary *Pneumocystis* was previously associated only with overwhelming, often fatal, disseminated infection but the incidence is rising now due to the use of prophylactic treatment for pulmonary *Pneumocystis* [20]. More recently, reports have described cervical infections without systemic or pulmonary involvement including an enlarging cervical mass from *Pneumocystis* infection of lymph nodes or the thyroid gland [21, 22]. Thyroid involvement produces a diffuse goiter-like swelling and the patient can be clinically hypothyroid. The diagnosis should prompt a search for both pulmonary and systemic disease. These cervical infections usually respond rapidly to medical therapy as used for pulmonary infections.

Mycosis

Fungal infections, including cryptococcosis, histoplasmosis, and coccidioidomycosis, can manifest as a cervical mass in the HIV-infected patient. *Cryptococcus neoformans* is the most prevalent cause of deep-seated fungal infections in the HIV-infected population, occurring in 5 to 10% of these patients and commonly involves the lungs and the meninges[23]. Pulmonary and disseminated forms of histoplasmosis and coccidioidomycosis are becoming more widespread in patients with advanced HIV disease as the incidence of HIV infections increases in areas in which *Histoplasma* or *Coccidioides immitis* is endemic [23, 24, 25, 26].

Serum and cerebrospinal fluid antigen titers correlate well with active cryptococcal disease although the typical granulomatous lesions of fungal infections may be absent[26]. Therapy with amphotericin B is moderately effective.

Malignancies

The most common malignancy associated with HIV disease is Kaposi Sarcoma (KS), an idiopathic multiple sarcoma of the skin. The incidence reported is 47%[27]. The oral cavity is the most common

site, nearly 95% are found on the palate. Other sites include gingival surfaces of the oropharynx, external ear, larynx and nose. The clinical course is unpredictable. They may be asymptomatic, but some may become exophytic and ulcerated. Secondary infection often occurs, producing severe, increasing pain, difficulty with mastication and swallowing, and increasing difficulty maintaining good oral hygiene[28, 29]. The involvement of the pinna or the external auditory canal may lead to conductive hearing loss especially with tumor extension to the tympanic membrane or into the middle ear.

Treatment includes low-dose radiation therapy which is usually very effective, although the risk of radiation intolerance and mucositis is high in HIV-infected patients. Alternative therapy that has been successful in some cases of oral and epiglottic KS is intralesional injection of vinblastine[28, 30, 31]. Carbon dioxide and argon laser have been used in excision of canalicular or tympanic membrane lesions[32].The goals of therapy are to relieve symptoms and improve cosmesis.

Non-Hodgkins Lymphoma is the second most common HIV-associated malignancy. It commonly presents as a nontender, rapidly enlarging neck mass. The histopathologic findings are variable, but the majority of these lymphomas are high grade[33].The precise relationship between these and HIVdisease has not been defined, however, in the HIV-infected patient, NHL, Hodgkin's disease and squamous cell carcinoma tend to be more aggressive and less responsive to treatment[33, 34]. The work-up is the same as for the general population. The treatment includes surgery and chemotherapy, because HIV-infected patients tolerate radiotherapy very poorly.

Parotid

Xerostomia is a common complaint in AIDS. It is present in 10% of a group of patients with HIV infection, ARC and AIDS [30, 31, 32, 33, 34]. The cause is unknown, although CMV has been implicated in several studies. Treatment includes frequent saline rinses, sialogogues and topical fluoride applications. Cystic parotid enlargement is a well documented finding in AIDS. This may occur early in the The parotid masses are typically unilateral or bilateral multicystic, nontender enlargements resembling lymphoepithelial cyst. Needle aspiration is indicated for symptomatic relief and to rule out malignancy. Surgery should be avoided due to the refractoriness of the lesion and its underlying benign nature, as well as the risk of facial nerve damage.

Oral Cavity

The oral cavity represents one of the most common sites for HIV-related pathology. The spectrum includes infectious, benign inflammatory, neoplastic, and degenerative processes.

Candidiasis (Oral Thrush)

Oral candidiasis is by far the most common oral condition in HIV /AIDS patients. It occurs even in patients with CD4 counts from 200 to 500 mm^3. Typically, it is a recurring problem which presents as tender, white, pseudomembranous or plaque-like lesions with underlying erosive erythematous mucosal surfaces; however, the less typical atrophic or chronic hypertrophic form is also often encountered. Angular cheilitis is a variant of oral candidiasis which typically presents as a nonhealing fissure at the oral commissure. Diagnosis is usually made by potassium hydroxide preparation of scrapings from these lesions[35, 36].

Topical therapy with nystatin or clotrimazole can be effective. Systemic therapy with ketoconazole, fluconazole, Amphotericin B and prophylactic antifungal may be indicated in severe cases of immunosuppression[37, 38].

Herpes Simplex

Herpes labialis most commonly presents as crops of fever blisters on the palate, gingiva, or other oral mucosal surfaces. The lesion tend to be larger and more numerous, recur more frequently, and often persist longer than in non-HIV subjects. They can also extend onto adjacent skin and coalesce to form giant herpetic lesions[39, 40].

Treatment may not be necessary if the lesions are small, relatively asymptomatic, and beginning to heal. Otherwise, treatment consists of oral acyclovir for large or symptomatic lesions.

Hairy Leukoplakia

This usually presents as a white, vertically corrugated lesion along the anterior lateral border of the tongue. It occurs almost exclusively in HIV-infected patients, and is associated with more rapid progression to the full-blown AIDS. Epstein-Barr virus is associated with these lesions and is the probable cause. It is primarily an asymptomatic condition requiring little more than recognition and observation. Treatment is generally unnecessary [41, 42, 43].

Recurrent Aphthous Ulceration

This is typically a painful condition of the oral cavity formed by the coalescing of the smaller lesions into large ulcers and can present anywhere in the oral cavity or pharynx [40]. They are often associated with severe odynophagia leading to anorexia and dehydration, and thus contribute to AIDS morbidity and wasting. It may be worsened by secondary infection [41]. Surgical or laser excision of these lesions is the treatment of choice [18].

Otologic Manifestation

Sensorineural Hearing Loss

Sensorineural hearing loss has also been reported between 21 to 49% of HIV-infected patients [42, 43, 44]. It may be unilateral or bilateral, usually worsens steadily with increasing frequencies, but speech discrimination is usually preserved. The possible etiologies are a primary infection by HIV of the central nervous system or peripheral auditory nerve, cryptococcal meningitis and idiopathic [45, 46, 47].

Smith and Canalis [47] reported cases of otosyphilis in patients with HTLV III, they proposed that the virus alters the course and hastens the development of otosyphilis leading to sensorineural hearing loss, therefore, diagnostic work-up should include serologic testing for syphilis.

Otitis Externa

The epidemiological parameter of otitis externa is not different in the AIDS population, although the course could be more dramatic[48]. Predisposing factors are excessive irritation or mechanical trauma[8]. Patients usually present with hearing loss, otalgia and inflamed external auditory canal with purulent debris within it. Treatment requires prolonged suctioning of the exudate in the ear and topical antibiotic treatment [49].

As in other immunocompromised patients, persons with HIV/AIDS are predisposed to malignant otitis externa or osteomyelitis of the skull base. Clinical evidence suggesting malignant otitis externa includes severe, progressive pain, fever and granulation tissue within the ear canal. The causative agent is usually *P. aeruginosa,* although *Pneumocystis carinii,* M. tuberculosis and other common pathogens have been reported [49]. Treatment requires combination of prolonged intravenous antibiotics and, possibly, surgical debridement.

Otitis Media

The most common otologic problems reported in HIV-infected patients are serous otitis media and recurrent acute otitis media. These conditions frequently affect paediatric patients with HIV disease because eustachian tube dysfunction typical of this age group combined with depressed cell-mediated immunity markedly increases their susceptibility to middle ear infection [45, 50].

In HIV-infected adults, eustachian tube dysfunction can result from nasopharyngeal lymphoid hyperplasia, sinusitis, nasopharyngeal neoplasms, or allergies and their associated mucosal changes. In most of these patients with nasopharyngeal lymphoid hyperplasia, an adenoidectomy will improve eustachian tube function [50].

Rhinosinusitis

The prevalence of rhinosinusitis ranges from 20 to 70% in patients with AIDS [4]. Causative organisms include atypical opportunistic and common organisms responsible for sinusitis in hosts without AIDS. Opportunistic fungal sinusitis is caused by organisms such as *Alternaria alternata, Aspergillus,Pseudallescheriaboydii,Cryptococcus and Candida albicans* [9, 15, 36,48, 49, 50, 51 , 52]. The features of sinusitis are similar to findings in non-HIV subjects. Medical therapy is effective while surgery is often indicated to facilitate sinus drainage and to obtain tissue specimens to diagnose other infections and malignancies [52].

Nasal Allergy

Contrary to what would be expected, there is B – cell activation leading to increased production of cir culating immune complexes and immunoglobulins A, G and E. The excessive IgE production is associated with increased IgE-mediated allergic symptoms, including allergic rhinitis. Sample et al and others[53, 54, 55] have reported raised Ig E level and a two-fold increase in the incidence of allergic symptoms in HIV-infected men. Profuse rhinorrhoea and congestion is similar to the general population although the intensity may suggest chronic persistent bacterial rhinosinusitis.

Topical nasal steroid sprays and systemic antihistamines are effective. The newer, second-generation antihistamines are preferred in HIV-infected patients because of lesser anticholinergic activity resulting in decreased viscosity and surface adhesiveness of nasal secretions[55]. However, specific environmental allergens should be identified and avoided if possible[56].

The multiplicity of these pathologies may suggest enormous challenges to the otolaryngologists in the management of these patients however patient care also requires special considerations. These include the risk of transmission of the infection, recommendations for surgical procedures and concepts of post - exposure prophylaxis[56, 57].

In conclusion, with increasing incidence of HIV, more cases will be encountered by otolaryngologists in Nigeria and research into otolaryngologic peculiarities of HIV/AIDS will expectedly be an issue for the future.

REFERENCES

1. HIV/AIDS surveillance report. U.S. HIV and AIDS cases reported through June 1997. U.S. Department of Health and Human Services, Public Health Service. Atlanta: Centers for Disease Control and Prevention, 1997.

2. Lalwani AK, Sooy CD. Otologic and neurotologic manifestations of acquired immunodeficiency syndrome. Otolaryngol Clin North Am 1992;25:1183-1197.

3. Federal Ministry of Health. National AIDS/ STD control programme. 1999 HIV/ Syphillis sentinel seroprevalence survey in Nigeria. Technical report.

4. Sorvino D and Lucente FE. Acquired immunodeficiency syndrome—the epidemic. Otolaryngol Clin North Am 1992; 25(6):1147-1158.

5. Riederer AP, Grein GO and Bogner JR. High prevalence of opportunistic infections in the head and neck related to human immunodeficiency of otorhinolaryngologic disorders in 250 patients. Infection.1996; 24(6): 440-446.

6. Karsten M and Goldberg A N. HIV and head and neck cancer. Current Opinion in Otolaryngology and Head and Neck Surgery. 2002; 10(2): 85-90 **7.** Hadderingh RJ, Tange RA, Danner SA, et al. Otorhinolaryngological findings in AIDS patients: A study of 63 cases. Arch Otorhinolaryngol 1987; 244:11-14.

8. Lee KC, Cheung CW. Evaluation of the neck mass in the human immunodeficiency virus-infected patients. Otolaryngol Clin North Am 1992; 25: 1287-1305.

9. Burton F, Patete ML and Goodwin Jr WJ. Indications for open cervical node biopsy in HIV-positive patients. Otolaryngol Head Neck Surg 1992; 107:367-369.

10. Centers for Disease Control. Screening for tuberculosis and tuberculosis infection in high-risk populations and the use of preventive therapy for tuberculosis. MMWR 1990; 39:1-12.

11. Lee KC, Tami TA, Lalwani AK and Schecter G. Contemporary management of cervical tuberculosis. Laryngoscope.1992; 102: 60-64

12. Department of Public Health. Tuberculosis alert. San Francisco Epidemiol Bull 1991;7: 47-48.

13. Johnson MP, Chaisson RE. Tuberculosis and HIV disease. AIDS Clin Rev 1991; 109-126

14. Castro DJ, Hoover L, Castro DJ, *et al*. Cervical mycobacterial lymphadenitis: medical vs surgical management. Arch Otolaryngol 1985; 111: 816-819.

15. Beck K. Mycobacterial disease associated with HIV infection. J Gen Intern Med 1991; 6: S19-S23.

16. Sathe SS, Reichman LB. Mycobacterial disease in patients infected with the human immunodeficiency virus. Clin Chest Med 1989;10: 445-463

17. Montgomery AB. Pneumocystis carinii

pneumonia in patients with the acquired immunodeficiency syndrome: Pathophysiology, therapy, and prevention. Semin Respir Infect 1989; 4:102- 110.

18. Singh A, Georgalas C, Patel N and Papesch M**.**ENT presentations in children with HIV infection. Clin Otolaryngol Allied Sci. 2003 .

19. Gallant JE, Enriquez RE, Cohen KL, *et al.* Pneumocystis carinii thyroiditis. Am J Med 1988; 84: 303-306.

20. Ragni MV, Dekker A, DeRubertis FR, *et al.* Pneumocystis carinii infection presenting as necrotizing thyroiditis and hypothyroidism. Am J Clin Pathol 1991; 95: 489-493.

21. Grant IH and Armstrong D. Fungal infections in AIDS: Cryptococcosis. Infect Dis Clin North Am 1988; 2: 457-464.

22. Minamoto G and Armstrong D. Fungal infections in AIDS: Histoplasmosis and coccidioidomycosis. Infect Dis Clin North Am 1988; 2: 447-456.

23. Wheat LJ, Slama TG and Zeckel ML. Histoplasmosis in the acquired immune deficiency syndrome. Am J Med 1985; 78: 203-210.

24. Sugar AM. Overview: Cryptococcosis in the patient with AIDS. Mycopathologia 1991; 114: 153-157.

25. Dichtel WJ and Patow CA. The acquired immunodeficiency syndrome and otolaryngologic practice. In: Johnson JT, Blitzer A, Ossoff RH, et al., eds. Academy of Otolaryngology. Instructional Courses. Vol. 1. St. Louis: Mosby, 1988; 3-12.

26. Ficarra G, Berson AM, Silverman Jr S, et al. Kaposi's sarcoma of the oral cavity: A study of 134 patients with a review of the pathogenesis, epidemiology, clinical aspects, and treatment. Oral Surg Oral Med Oral Pathol 1988; 66:543-550.

27. Goffman TE, Fountain KS. Toxicities in the radiotherapeutic treatment of epidemic Kaposi's sarcoma. Radiat Oncol Biol Physics 1987;13:186.

28. Tami TA, Sharma PK. Intralesional vinblastine therapy for Kaposi's sarcoma of the epiglottis. Otolaryngol Head Neck Surg 1995; 113(3): 283-285.

29. Friedman M, Venkatesan TK and Caldarelli DD. Intralesional vinblastine for treating AIDS-associated Kaposi's sarcoma of the oropharynx and larynx. Ann Otol Rhinol Laryngol 1996;105: 272-274.

30. Singh B, Har-el G and Lucente FE. Kaposi's Sarcoma of the head and neck in patients with acquired immunodeficiency syndrome.Otolaryngol Head Neck Surg1994;111: 618-624.

31. Kaplan LD. AIDS-associated lymphomas. Infect Dis Clin North Am 1988; 2: 525-532

32. Lozada F, Silverman Jr S, Conant M. New outbreak of oral tumors, malignancies and infectious disease strikes young male homosexuals. CDA J 1982; 10: 39-42.

33. Dull JS, Sen P, Raffanti S, *et al*. Oral candidiasis as a marker of acute retroviral illness. South Med J 1991; 84: 733-735, 739.

34. Syrjanen S, Valle SL, Antonen J, *et al.* Oral candidal infection as a sign of HIV infection in homosexual men. Oral Surg Oral Med Oral Pathol 1988; 65:36-40.

35. Koletar SL, Russell JA, Fass RJ, *et al.* Comparison of oral fluconazole and clotrimazole troches as treatment for oral candidiasis in patients infected with human immunodeficiency virus. Antimicrob Agents Chemother 1990;34: 2267 - 2268.

36. Cohen SG and Greenberg MS. Chronic oral herpes simplex infection in immunocompromised patients. Oral Surg Oral Med Oral Pathol 1985; 59: 465-471.

37. Perna JJ and Eskinazi DP. Treatment of oro-facial herpes simplex infections with acyclovir: A review. Oral Surg Oral Med Oral Pathol 1988; 65: 689-692.

38. Greenspan D, Greenspan JS, Hearst NG, *et al.* Relation of oral hairy leukoplakia to infection with human immunodeficiency virus and the risk developing AIDS. J Infect Dis 1987; 155: 475-481.

39. Greenspan JS and Greenspan D. Hairy leukoplakia and other oral features of HIV infection. Immunol Ser 1989;44: 449-465.

40. Phelan JA, Eisig S, Freedman PD, *et al.* Major aphthous-like ulcers in patients with AIDS.

the Otolaryngologist. Alexandria, VA: American Academy of Otolaryngology-Head and Neck Surgery Foundation, 1993.

41. Greenspan JS, Greenspan D, Winkler JR. Diagnosis and management of the oral manifesta tions of HIV infection and AIDS. Infect Dis Clin North Am 1988; 2: 373-385.

42. Kohan D, Rothstein SG and Cohen NL: Otologic disease in patients with acquired immunodeficiency syndrome. Ann. Otol Rhinol Laryngol 1988; 97:636 – 640.

43. Bell AF, Atkins JS, Zajac R, *et al*. HIV and sensorineural hearing loss (SNHL). In: Program and Abstracts of the IV International Conference on AIDS. Stockholm, 1991; 7009.

44. Sooy CD. Impact of AIDS on otolaryngology head and neck surgery. In: Meyers EN, ed. Advances in Otolaryngology. Head and Neck Surgery. Vol 1. Chicago: Year Book 1987; 1-27.

45. Pagano MA, Cahn PE, Garau ML, *et al*. Brain-stem auditory evoked potential in human immunodeficiency virus-seropositive patients with and without acquired immunodeficiency syndrome. Arch Neurol 1992; 49:166-169.

46. Timon CI, Walsh MA. Sudden sensorineural hearing loss as a presentation of HIV infection. J Laryngol Otol 1989;103:1 071-1072.

47. Smith ME and Canalis RF.Otologic manifestations of AIDS: the otosyphilis connection. Laryngoscope1989; 99: 365 – 372.

48. Lasisi.O.A, Bakare.R.A, Usman.M.A. Human Immunodeficiency Virus and Invasive External Otitis - A Case Report. WAJM Jan-Mar 2003, 22 (1): 103-105.

49. Tami TA and Lee KC. SiPAC: AIDS and

50. Church J. Human immunodeficiency virus (HIV) infection at Children's Hospital of Los Angeles: Recurrent otitis media or chronic sinusitis as the presenting process in pediatric AIDS. Immunol Allergy 1987; 9: 25-32.

51. Rubin JS and Honigberg R. Sinusitis in patients with the acquired immunodeficiency syndrome. Ear Nose Throat J 1990; 69: 460-463.

52. Rubin JS and Honigberg R. Sinusitis in patients with the acquired immunodeficiency syndrome. Ear Nose Throat J 1990; 69: 460-463.

53. Sample S, Chernoff DN, Lenahan GA, *et al*. Elevated serum concentrations of IgE antibodies to environmental antigens in HIV-seropositive male homosexuals. J Allergy Clin Immunol 1990;
86: 876-880.

54. Grieco MH. Immunoglobulins and hypersensitivity in human immunodeficiency virus (HIV) infection. J Allergy Clin Immunol 1989; 84:1-4.

55. Wright DN, Nelson Jr RP, Ledford DK, *et al.*Serum IgE and human immunodeficiency virus (HIV). J Allergy Clin Immunol 1990; 85: 445 - 452.

56. Kantu S, Lee D, Nash M and Lucente FE. Safety awareness for the otolaryngologist caring for the HIV-positive patient. Laryngoscope 1996. 106(8): 982-986.

57. Murr, AH and Lee, KC. Universal precautions for the otolaryngologist: techniques and equipment for minimizing exposure risk. Ear, Nose, and Throat Journal. 1995; 74 (5): 338, 341-346.

Infectious Agents and Cancer

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Keywords: *Infectious, agents, cancer.*

SUMMARY

The epidemiology of several types of cancers indicate the involvement of several transmissible agents in their development, and in most cases, these seem to be viruses. The classic examples are Burkitt's lymphoma, nasopharyngeal carcinoma (EBV), hepatocellular carcinoma (HBV), and cervical carcinoma (HPV). Most of these cancers show substantial variations in their incidence in different parts of the world and in particular countries, they present significant health problems. Worldwide, infections account for up to 20% of all cancers. Also, there is now ample evidence implicating infection with the Helicobacter pylori in the occurrence of gastric carcinoma and gastric lymphoma, and infection with Schistosoma haematobium in the occurrence of the squamous cell carcinoma of the urinary bladder.The impact of these infections on the burden of cancer worldwide is becoming increasingly evident because they are largely responsible for the cascade of opportunistic malignancies associated with AIDS. The burden is heaviest among populations in developing countries, reflecting the impact of very early infection with these agents on subsequent risk of cancer. There are currently no vaccines available to prevent these chronic infections, other than for HBV. As a result, changes in behaviour hold the most promise for prevention.

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INTRODUCTION

The epidemiology of several types of cancers indicate the involvement of several transmissible agents in their development, and in most cases, these seem to be viruses. The classic examples are Burkitt's lymphoma, nasopharyngeal carcinoma (EBV), hepatocellular carcinoma (HBV), and cervical carcinoma (HPV). Most of these cancers show substantial variations in their incidence in different parts of the world and in particular countries, they present significant health problems. Worldwide, infections account for up to 20% of all cancers. Although it has been known for decades that naturally acquired viral infections in animals could cause malignancy, the evidence in humans has accumulated more slowly[1]. With the advent of new molecular research tools; there is now strong evidence for the role of several viruses in human malignancy. Also, there is now ample evidence implicating infection with the *Helicobacter pylori* in the occurrence of gastric carcinoma and gastric lymphoma, and infection with *Schistosoma haematobium* in the occurrence of the squamous cell carcinoma of the urinary bladder. Infectious agents constitute an important category of environmental agents causing cancer, as the cancers they cause are potentially preventable and in particular cases there are good prospects for cure using antimicrobial agents.

General Pathogenesis

Carcinogenesis is a multistage process that originates in a single cell, and results from the development and accumulation of multiple genetic alterations. Cancer is a term used to describe a group of malignant tumours with a common characteristic of uncontrolled growth of abnormal cells that have acquired the capability to spread and metastasize to distant site through the circulation. Cancer is of

multifactorial aetiology involving an interplay between genetic and environmental factors (that include infectious agents) leading to a cascade of genotypic and phenotypic changes that culminates in the formation of a malignant tumour[3] (Figure 1).

Figure 1: Flow chart showing a simplified scheme of the molecular basis of cancer. (*Modified from Robbin's Pathologic Basis Of Disease[3]*).

Chronic and Latent Infections

Infectious agents implicated in tumorigenesis share in common the ability to either establish latency- that is, for the viral genes to persist in a subset of cells following infection or to become chronic infections under certain conditions. An example of a latent infection is the Epstein-Barr virus (EBV), a member of herpes family, which is transmitted primarily via saliva. The EBV viral genes persist in conjunction with the host DNA in a subset of infected white cells and in the upper part of the throat for the remainder of the person's life. Periodically, the virus will replicate producing new viral particles that are neutralized by the immune response of the individual. Almost all adults have had an EBV infection and are thus carriers of these viral genes [2].

Although these infectious agents are transmissible from person to person, any subsequent malignancy that may develop is not transmissible to

another person. Table1 gives a list of infectious agents that have been associated with tumour formation.

Table1: Oncogenic infections associated with tumour formation.

Agent		*Malignancy*
Epstein-Barr Virus (EBV)	-	Non-Hodgkin's lymphoma, Hodgkin's lymphoma, Nasopharyngeal carcinoma.
Human T-cell leukaemia/ Lymphoma virus –1 (HTLV-1)	-	Adult T-cell leukaemia/ lymphoma.
Hepatitis B virus (HBC)	-	Hepatocellular carcinoma.
Hepatitis C virus (HCV)	-	Hepatocellular carcinoma.
Human papilloma virus (HPV)	-	Cervical cancer, other anogenital cancers, laryngeal cancer, oral cavity cancers
Oncorna virus	-	Lymphomas, leukaemia.
Human herpes virus type 8	-	Kaposi's sarcoma, primary effusion lymphoma
SV 40	-	Mesothelioma
Helicobacter pylori	-	Gastric carcinoma, gastric lymphoma.
Campylobacter jejuni	-	Intestinal lymphoma
Schistosoma haematobium	-	Urinary bladder squamous cell carcinoma
Schistosoma japonicum	-	Liver cell carcinoma
Opistorchis viverini	-	Cholangiocarcinoma.
Clornorchis sinensis	-	Cholangiocarcinoma.
Chlamydia trachomatis	-	? cervical cancer

HPV and Cervical Cancer

Dr. Zur Hausen and co-workers were the first to demonstrate that specific types of HPV DNA could be identified by southern blot hybridization in the majority of invasive squamous cell carcinomas of the cervix and a substantial number of cervical cancer precursors[4]. Shortly there after, HPV DNA was isolated in tissues from metastatic cervical carcinoma, [5] and in tumour cell lines established from cervical carcinoma, indicating that the HPV was an integral component of the tumours[6]. Case control studies [7] and long term prospective follow-up studies have provided evidence of a central role for persistence of infection with high – risk types of HPV in the pathogenesis of invasive cervical cancer and precursor lesions.

Mechanism of malignant transformation.

Molecular studies using tissues culture cells have shown that certain types of HPV such as HPV-16 and 18 produce three proteins with growth –stimulating and transforming capabilities, E5, E6 and E7. E5 is not essential for transformation as the E5 region in frequently deleted in cervical carcinoma cells[8]. The expression of the E6 and E7 open reading frames (ORFs) from high oncogenic risk HPVs such as types 16 and 18, in established tissues culture cell lines cause the cells to become completely transformed [9].

HPV E7 oncoprotein accounts for the major transforming and immortalizing activity in high risk types of HPVs[10]. It co-operates with activated ras oncogenes for transformation of cervical epithelial cells[11]. The binding of the HPV E7 protein to retinoblastoma (Rb) and the Rb-related pocket proteins block the cell proliferation – inhibitory function of these endogenous tumor suppressors. E7 also sensitizes p53 reactive cells to undergo apoptosis and enhance mutagenicity of chemical carcinogens[12].

The presence of E6 significantly enhance the immortalizing and transforming activities of E7

oncoprotein.. In HPV infected cells, p53 levels are low because E6 –associated, protein-mediated binding of p53 to the E6 protein results in the rapid proteolytic degradation of the bound p53 through an ubiquitin-dependent pathway [13]. This reduces the amount of p53 present within the cell and causes a loss of the p53 repair mechanism. Another possible important role of E6 is telomerase activation, which may occur through the myc oncogene.

Compelling epidemiologic evidence has supported the role of HPV in the development of invasive cervical carcinoma. However, it should be noted that other co-factors have been found to be important in the pathogenesis of HPV- associated invasive cervical carcinoma. These include high parity, low socioeconomic status, smoking, increasing number of sexual partners and a history of sexually transmitted diseases [14]. Based on data obtained from epidemiologic studies, the International Agency for Research on Cancer (IARC) of the World Health Organization (WHO) has classified HPV 16 and 18 as carcinogens in humans [15].

Some other cancer-associated viruses:
EBV is involved in the aetiopathogenesis of Burkitt's lymphoma; including almost all cases occurring among children in central Africa and about 20 percent of the cases elsewhere[2]. Malaria endemicity has also been identified as an important aetiologic factor in the development of this tumour. EBV is also clearly involved in about 35 percent to 50 percent of cases of Hodgkin's disease [16]. In addition; EBV is implicated in the occurrence of nasopharyngeal carcinoma. In this tumor, ethnically related genetic factors are thought to be important because the disease is most common in persons of southern Chinese origin [17].

Cancer of the liver can be caused by chronic infection with either HBV or HCV. Both viruses appear to act via chronic hepatitis, causing repeated cycles of cell death and regeneration. In these carriers, liver cancer usually occurs in the presence of cirrhosis. Chronic HBV infection is more common among Asian populations and among sub-Saharan Africans, including Mozambique and Nigeria.

H. pylori and Gastric Cancer

H. pylori infect approximately half the world's population and the infection has been linked to the development of gastric adenocarcinoma and gastric lymphoma. However, majority of infected persons remain asymptomatic throughout their lives,[18] suggesting that other factors such as genetic or environmental (particularly dietary factors) are involved in the pathogenesis. As far back as October 1994, The International Agency for Research on Cancer (IARC), has declared *Helicobacter pylori* infection in humans as carcinogenic and a definite cause of human gastric cancer based on epidemiological data [19].

An analysis of data from 13 countries showed a strong correlation between the incidence of gastric cancer and the prevalence of H. pylori infection[20]. Prospective serologic studies have reported that persons with H. pylori infection have a three to six fold higher risk of gastric cancer than those without infection[21,22]. This association seems largely restricted to intestinal – type cancers and cancers of the distal stomach[23]. A recent study, however, has shown that both intestinal type and diffuse- type cancers develop in the setting of H. pylori infection[24]. These studies have failed to demonstrate an association between gastric cancer and peptic ulcer disease, suggesting that the association of H. pylori with gastric cancer is independent of the link between the infection and ulcer disease [22].

Circumstantial evidence suggests that infection with H. pylori may also increase the risk of gastric non – Hodgkin's lymphomas. Sixty percent of gastric non – Hodgkin's lymphomas evolve from chronic gastritis a lesion usually caused by *H. pylori* [25]. A region in Europe with a high incidence of gastric non- Hodgkin's lymphoma had a higher rate of H. pylori infection than a region with low incidence. The validity of these associations has been given credence to by a report of the resolution of low-grade gastric lymphomas following eradication of *H. pylori* infection with antibiotic therapy [26].

Pathogenesis Of H. Pylori Induced Tumours

The concept of a pre-cancer sequence in the stomach derive from longitudinal studies in Finnish workers[27] and Correa *et al* [28]. These workers studied the natural history of chronic gastritis in circumscribed populations over many years and demonstrated that the common form of intestinal type gastric carcinoma arises on a background of chronic atrophic gastritis and intestinal metaplasia, through a multi-step progression, occurring over a period of 15-20 years from onset of infection. The observation made in some African countries (including Nigeria) [29] and India [30], where high prevalence of *H. pylori* infection is noted alongside a low gastric cancer rate has suggested that *Helicobacter pylori*
is unlikely to be the sole factor driving the precancer-cancer sequence. The view being presently advanced is that *Helicobacter pylori* is a form of promoting agent that provides a continuing source of inflammatory damage[31]. Epidemiological and histopathological studies,[32,33] have shown that the development of diffuse – type cancer is also closely related to *H. pylori* infection.

Most *H. pylori* strains express 95 kD vacuolating cytotoxin, *VacA*,[34] and possess the ca*g pathogenicity island (*cag-PAI*)* a 37 kb genomic fragment which encodes for a 120-kD protein CagA [35]. They also elaborate urease, alcohol dehydrogenase and mucolytic factors. All these agents contribute to the development of cancer following *H. pylori* infection. Accumulating evidence suggests that bacterial surface components, particularly BabA, a 78-kD outer membrane protein that binds to the fucosylated Lewis B blood group antigen and pro-inflammatory polymorphisms of the interleukin-1ß gene favour the development of gastritis that precede the development of gastric carcinoma [36].

Schistosoma Haematobium and Urinary Bladder Cancer

Chronic infection with parasitic trematode worms (Schistosomes) is associated with the development of urinary bladder carcinoma in Egypt and elsewhere [37]. Urinary tract disease is a specific trait of infection with *S. haematobium*. Squamous cell carcinoma of the bladder associated with *S. haematobium* tend to be well differentiated and to metastasize locally. In Egypt, squamous cell carcinoma of the bladder accounts for 18 to 28% of all cancers, with an incidence of 10.8 per 100,000 population [38]. The association appears to be consistent in many sub-Saharan nations as well [39]. However, large autopsy series have failed to demonstrate a consistent association with a particular type of tumour [40] and squamous cell carcinoma of the bladder is prevalent in some countries that have a very low prevalence of *S. haematobium* or none at all. *S. haematobium*-associated bladder cancers are often associated with mutations of the p53 and cyclin – dependent kinase inhibitors-2 tumour – suppressor genes [39]. HLA-B16 and Cw2 have been associated with S. haematobium-related bladder cancer patients in Egypt [41]. At present, the evidence is sufficient to conclude that *S. haematobium* has a role in causing some type of bladder cancer. However, other risk factors including male sex, tobacco smoking and chemical substances play a role.

Fungal Carcinogenesis

There are conflicting views on the association between fungi and tumour formation [42, 43].Fungi are thought to act indirectly, by producing chemical substances (mycotoxins), which induce tumour formation. Chief among the fungal products examined was aflatoxin, a mold-produced contaminant of several important food commodities such as grains, cereals and groundnuts. A report in favour of a possible role for aflatoxin in the pathogenesis of hepatocellular carcinoma, based its conclusion on epidemiological studies and animal models, which suggested that aflatoxin and HBV act synergistically to increase the risk of HCC [42]. On the contrary, another study found aflatoxin to be a potent carcinogen for laboratory rats and suggested that humans are probably refractory to carcinogenic effect of aflatoxin[43]. This study flawed previous epidemiological evidence on the basis of not controlling for confounding cofactors such as HBV infections endemic in the study populations. However, further studies are needed in the area to further ascertain this relationship.

HIV/AIDS and Cancer

Infection with HIV–1 is characterized by a progressive loss of T-cell function and is reflected clinically by opportunistic infections and neoplastic disease, especially virus associated cancers. This association of cancers with HIV infection has been recognized since the beginning of the AIDS pandemic and has served as an important AIDS defining condition.

Tumours arising in HIV infected persons are similar in many respects to those observed in other immunodeficiency disorders and include Kaposi's sarcoma, non-Hodgkin's lymphoma and anogenital carcinoma[44]. HIV weakens the hosts immune defense, consequently, the increased incidence of neoplasia in HIV infection reflects, at least partially, immune dysregulation and inefficient immune surveillance of cancer cells.

Table 2 : HIV-associated cancers.

Kaposi's sarcoma	Leukaemia
Non-Hodgkin's lymphoma	Lung cancer
Primary CNS lymphoma	Skin cancers (Squamous cell carcinoma)
Squamous cell carcinoma of cervix	Multiple myeloma
Hodgkin's disease	Germ cell tumours in testis
Lip cancer	Leiomyosarcoma in children.

Pathogenesis

HIV is currently, not thought to cause cancer directly. By crippling the immune system, infection with the virus increases a person's risk of getting several types of cancers, especially those linked to other viruses, e.g. HHV-8 and HPV. Loss of B-cell maturation control has been demonstrated by studies of immunoglobulins associated with AIDS related lymphoma. Many other tumours have been described in greater frequency in HIV –infected individuals, some of these cancers are listed in table 3, but they are not considered AIDS-defining illnesses.

Cancer Prevention

The identification of infectious agents of cancer has become more and more important as vaccines are available to prevent the onset of carcinogenesis or at least limit the possibility of cell transformation.Two examples of cancer promoting factors that, with vaccination, could potentially reduce the risk of carcinogenesis have been identified [45]. "The first one is the hepatitis B vaccine, which, since 1985, has been in use in Taiwan. In that country every newborn baby is vaccinated against hepatitis B. There is already first data available, which seems to point to the preventive effect of the vaccination against liver cancer.

Furthermore intervention by immunization of infants at high risk – now underway in many populations in which the infection is prevalent – is likely to prevent the disease in future generations.

The other example cited was the human papillomaviruses 16 and 18 and their role in lesions of the cervix. Results of clinical trials currently being conducted in Germany demonstrate that the vaccines protect against the high-risk papillomavirus infections, which are responsible for cervical cancer and most squamous lesions of the cervix. This provides a basis for hope that a vaccine will be also very effective. In view of the high number of cervical cancers globally, one could theoretically speculate that if every woman would be vaccinated at an age of 10 to 12 years that we would have a tremendous preventative potential, preventing in part close to 12 percent of all cancer cases, which occur presently in females on a global scale.

CONCLUSION

The impact of these infections on the burden of cancer worldwide is becoming increasingly evident because they are largely responsible for the cascade

The burden is heaviest among populations in developing countries, reflecting the impact of very early infection with these agents on subsequent risk of cancer. There are currently no vaccines available to prevent these chronic infections, other than for HBV. As a result, changes in behaviour hold the most promise for prevention.

REFERENCES

1. Evans AS, and Mueller N. Virus and cancer :causal associations**.**Ann Epidemiol 1990; 1: 71 –72.

2. Evans AS and Mueller NE. Malignant lymphomas. In Evans AS, Kaslow R (Eds) Viral infection in humans: Epidemiology and control, Fourth Edition.1997 Plenum publishers. New York.

3. Cotran RS, Kumar V and Collins T, (Eds). Neoplasia. In Robbin's Pathologic Basis of Disease, Sixth Edition. WB Saunders Company. 1999. Philadelphia.

4. Durst M, Kleinheinz A, Hotz M, *et al.*The physical state of human papillomavirus type 16 DNA in benign and malignant genital tumours. J. Gen Virol 1985; 66: 1515-1522.

5. Lancaster WD, Castellano C, Santos C, *et al.* Human papillomavirus Deoxyribonucleic acid in cervical carcinoma from primary and metastatic site Am J Obstet Gynecol 1986; 154:115-119.

6. Boshast M, Gissman L, Ikenberg H, *et al*. A new type of papillomavirus DNA, its presence in genital cancer biopsies and in cell lines derived from cervical cancer. EMBO J 1984; 3: 1151-1157.

7. Josefsson AM, Magnusson PK, Yitalo N, *et al*. Viral load of human papillomavirus 16 as a determinant for development of cervical carcinoma in-situ: a nested case-control study Lancet 2000; 355: 2189-2193.

8. Schmarz E, Freese UK, Gissman L, *et al.* Structure and transcription of human papillomavirus sequences in cervical carcinoma cells.Nature 1985; 314: 111-114.

9. Crook T, Morgenstern JP, Crawford L, *et al.* Continued expression of HPV 16 E7 protein is required for maintenance of thethe transformed phenotype of cells co-transformed by HPV – 16 plus EJ ras. EMBO J 1989; 8: 513-519.

10. Kjaer SK, Chackerian B, van den Brule AJ, *et al.* High-risk human papillomavirus is sexually transmitted: evidence from a follow-up study of virgins starting sexual activity(intercourse). Cancer Epidemiol Biomark prev 2001; 10: 102-106.

11. Bedell MA, Jones KH and Laimins LA. The E6-E7 region of human papillomavirus type 18 is sufficient for transformation of NIH 3T3 and rat-1 cells. J Virol 1987; 61: 3635-3640.

12. Iglesias M, Yen K, Gaiotti D *et al.* Human papillomavirus type 16 E7 protein sensitizes cervical keratinocytes to apoptosis and release of interleukin-1-alpha. Oncogene 1998; 17: 1195-1205.

13. Scheffner M, Huigregtse JM, Vierstra RD, *et al.* The HPV 16 E6 and E6-AP complex functions as a ubiquitin-protein ligase in the ubiquitination of p53. Cell 1993; 75: 495-505

14. Ngelangel C, Munoz N, Bosch FX *et al.* Course of cervical cancer in the Philippines: a case control study. J Natl cancer Inst (1998) 90:43-49

15. IARC Human papillomaviruses1995; 64:407.

16. Mueller N. Hodgkin's disease. *In* Schottenfeld D, Fraumeni JF Jr, Eds. Cancer Epidemiology and Prevention 2nd Edition. New York.1996. Oxford University Press.

17. de-The G, Ho JHC, Muir CS. Nasopharyngeal carcinoma. In Evans AS ed. Viral infections in Human: Epidemiology and control, Third Edition 1991. Plenum Press, New York.

18. Parsonnet J, Friedman G.D. Rodriguez L *et al*. *Helicobacter pylori* infection and gastric lymphoma. N Engl J Med. 1994; 330:1267-1271

19. IARC Monographs on the evaluation of carcinogenic risks to humans. Volume 61 Schistosomes, liver flukes and *Helicobacter pylori.* Lyon, IARC 1994;. 220.

20. The Eurogast study group. An international association between *Helicobacter pylori* infection and gastric cancer. Lancet 1993; 341: 1359-62 (Erratum, Lancet 1993; 341, 1668)

21. Nomura A, Stemmermann GN, Chyou P – H, Kato I, Perez – Perez GI and Blaser MJ.

Helicobacter pylori infection and gastric carcinoma among Japanese Americans in Hawaii.N.Engl J Med 1991; 325:1132-11dn6.

22. Parsonnet J, Friedman GD, Vandersteen DP *et al*. *Helicobacter pylori* infection and the risk of gastric carcinoma. N Engl J Med 1991; 325: 1127 -1131.

23. Forman D, Newell DG, Fullerton F, *et al*. Association between infections with *Helicobacter pylori* and risk of gastric cancer: evidence from a prospective investigation BMJ 1991; 3 02: 1302 -1305.

24. Naomi U Okamoto S. Yamamoto S. *et al*. *H pylori* infection and the development of gastric cancer. N Engl J Med 2001; 345: 784-785.

25. Brooks JJ, Enterline HT. Primary gastric lymphomas: a clinicopathologic study of 58 cases with long term follow up and literature review. Cancer 1983; 51: 701-711.

26. Wotherspoon AC, Doglioni C, Diss TC *et al*. Regression of primary low grade B cell gastric lymphoma and mucosa-associated lymphoid tissue type after eradication of *Helicobacter pylori*. Lancet 1993; 342: 575-577.

27. Ihamaki T, Kekki M, Sipponen P, *et al.* The sequelae and course of chronic gastritis during 30-40 years biopsy follow-up study. Scand. J Gatroenterol. 1985; 20: 485 - 491.

28. Correa P. Haenszel W, Cuello C, *et al*. Gastric precancerous process in a high-risk population: Cross-sectional studies. Cancer Res. 1990; 50: 4731- 4736.

29. Holcombe C. *Helicobacter pylori*; The African Enigma. Gut. 1992; 33: 429- 431.

30. Mohandas KM. *Helicobacter pylori,* Gastric cancer and the Indian enigma. Challenge; Newsletter of the European School of Oncology. 1997; 1(11): 2 .

31. Levine T, Price A. The precancer-cancer sequence in: Northfield TC, Mendall M, Goggin PM (eds).*Helicobacterpylori* infection . Pathophysiology, Epidemiology and Management.London: Kluwer, 1993; 88-98.

32. Kikuchi S, Wada O, Nakajima T, *et al*. Serum anti-*Helicobacter pylori* antibody and gastric carcinoma among young adults.Cancer1995;75:

33. Kokola A, Ville J Haapiainen R, Sipponen P. Kivilaakso E, Puolakkainen P. *Helicobacter pylori* infection in young patients with gastric carcinoma. Scand J Gastroenterol 1996; 31: 643 - 647.

34. Montecucco C, Papini E, de Bernard M, *et al*. *Helicobacter pylori* VacA vacuolating cytotoxin and HP-Nap neutrophil activating protein. In Achtman M, Suerbaum S, Eds. *Helicobacter pylori* molecular and cellular biology. Wymondham, United Kingdom: Horizon Scientific Press, 2001: 245 - 263.

35. Censini S, Lange C, Xiang Z *et al*. cagA pathogenicity island of *Helicobacter pylori,* encodes type I-specific and disease-associated virulence factors. Proc Natl Acad Sci U S A 1996; 93: 14648- 14653.

36. Gerard M, Hirmo S, Wadstrom T, *et al*. *Helicobacter pylori*, an adherent pain in the stomach. In: Achtman M, Suerbaum S, (Eds). *Helicobacter pylori*: molecular and cellular biology. Wymondham, United Kingdom: Horizon Press, 2001; 185-206.

37. McManus DP, Ross AGP, Bartley PB *et al*. Schistosomiasis. N Engl J Med 346:1212-1220.

38. Elsebai I. Parasites in the etiology of cancer – Bilharziasis and bladder cancer. Cancer J Clin 1977; 27: 100 -106.

39. King CH. Disease in *Schistosoma haematobium*.In: Mahmoud AAF, ed. Schistosomiasis. London: Imperial College press, 2001:265 - 295.

40. Cheever AW. Schistosomiasis and neoplasia.
J Natl cancer Inst 1978; 61:13-18.

41. Wishahi M, el Baz HG and Shaker ZA. Association between HLA-A, B, C and DR antigens
and clinical manifestations of *Schistosoma haematobium* in the bladder. Eur Urol 1989;16: 138-143.

42. Sylla A, Diallo M.S, Castegnaro J and Wild CP. Interactions between hepatitis B virus infection and exposure to aflatoxin in the development of hepatocellular carcinoma: a molecular epidemiological approach. Mutation research 428:187-196.

43. Stoloff L. Aflatoxin is not a probable human carcinogen: the published evidence is sufficient. Regul Toxicol Pharmacol. 1989; 10(3): 272-283.

44. Williams CKO, Kashala LO and Giraldo G, de The GB, Beth Giraldo E. AIDS-Associated cancers. In: AIDS in Africa. Essex M, Mboup S, Kanki PJ, Kalengayi M. Eds. 1994. Raven press.

Current Concepts in the Management of Pelvic Inflammatory Disease

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INTRODUCTION

Pelvic inflammatory disease (PID) occurs when exogenous or endogenous micro organisms, mostly bacteria, infect the cervix, uterus, fallopian tubes, ovaries, parametrial structures[1] and the pelvic peritoneum.

It is a major public health problem in the developing countries where its control is hampered by suboptimal diagnosis, substandard treatment and virtually no contact tracing. The management and control of PID continue to be the subjects of extensive research.

Epidemiology

The disease occurs mostly in the reproductive age group when sexual activities are highest. Adolescents often experiment with sex [2], whereas they are usually inexperienced in bargaining with their partners regarding the use of condoms. Furthermore, adolescents in most developing countries are not entitled to free health services compared with those from other parts of the world. Although this group forms only 10% of the US and UK populations, they account for about 26% in the UK and up to 50% in the USA, of all cases of gonorrhoea [3,4,5]. Orji and Esimai [6] studied the sexual behaviour and contraceptive use among 300 secondary school students aged 13 to 19 years in Ilesa, Southwest Nigeria. Half of the girls were sexually active; with 68.7% of them having multiple sexual partners and 86.7% not using contraception. Thirty two of the 40 students who were contracepting used condom, and most only commenced its use about one year after the onset of sexual activity. These facts are confirmed by studies from other countries [6,7,8]. Similar findings are noted among medical students [9] and undergraduates in the same Southwest Nigeria [10].

Apart from the immediate symptoms of pain, vaginal discharge, dysuria and dyspareunia, long-term complications of chronic pelvic pain, infertility [11], marital disharmony, low productivity and ectopic pregnancy contribute to the complexity of this condition. Sometimes complications such as septicaemia can be fatal; and when HIV infection progresses to acquired immunodeficiency syndrome (AIDS), death usually results eventually. Among the sexually transmitted organisms, chlamydial infection is now more common than gonorrhoeal disease in virtually all countries [3,12,13,14].

Although mostly acquired sexually in the primary cases, PID may also follow septic abortion [15], douching [16,17] or complicate the puerperium. It sometimes complicates pelvic instrumentations such as dilatation and curettage or insertion of intrauterine contraceptive devices. Secondary infections can occur from intraperitoneal spread of organisms causing appendicitis [18].

Clinical Diagnosis

The triad of fever, lower abdominal pains and vaginal discharge strongly suggests the presence of PID. Other symptoms include vomiting, diarrhoea, dysuria, coital difficulties and abnormal uterine bleeding. Unfortunately many cases are symptomless [16] or mimic conditions like urinary tract infection, appendicitis and ovarian cyst. Examination may show a distressed patient, more likely, in acute infections than in chronic cases. The temperature may

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be elevated and abdominal tenderness, brownish or yellowish and offensive vaginal discharge may be present. All these form the syndromic approach to diagnosis advocated for use in resource poor nations. Its usefulness still needs to be ascertained by larger randomised controlled trials[19], even though its diagnostic accuracy has been quoted by some authors to be around 35 – 65% [18].

The use of the laparoscope has revolutionised the diagnosis of pelvic inflammatory disease, since its first use in the early sixties [20]. Findings in acute cases include erythema, oedema and swelling of the fallopian tubes with seropurulent exudation from the fimbrial ends[18]. Pyogenic membranes may also be evident. The severity of these changes has been grouped into mild, moderate and severe [18]. In chronic cases filmy and / or thick adhesions with abscess cavities are obvious. Following chlamydial infection, filmy adhesions over the liver is suggestive of perihepatitis (Fitz-Hugh-Curtis syndrome).

Laboratory Diagnosis

Laboratory diagnosis helps to establish the causative organisms and the effects of the disease on the body's systems, to determine the best antibiotic therapy and to monitor the effectiveness of treatment. It is however expensive compared to clinical diagnosis [21]. Swabs taken from the vaginal fornices, endocervix, urethra or the rectum confirm diagnosis. These swabs and midstream urine specimen are sent for microscopy, culture and sensitivity. Chlamydial infection is diagnosed by Nucleic Acid Amplification Tests (NAAT) using either polymerase chain reaction (PCR) or ligase chain reaction (LCR) on urine and cervical swabs. However, NAAT may not be readily available in developing countries.

In complicated cases with haemolysis following septicaemia, or after menorrhagia, the packed cell volume may be low. Although leucocytosis frequently occurs with PID, in sinister situations, leucopenia may accompany gram-negative infection.

In suspected pelvic tuberculosis with endometritis or pelvic abscess, pelvic ultrasound scanning and endometrial biopsy may be helpful [22, 23, 24, 25].

Treatment Options

The syndromic approach to treatment, incorporated into the primary health care system of developing countries is effective when properly used and continuously evaluated [18, 21]. Cure rates of up to 70% have been documented by Mwijarabi and Mayaud in Mwanza, Tanzania with the advantage of single clinic visits [26], and at rates as low as one fifth that of the laboratory based approach in one study from Cote d'Ivoire [27]. Unfortunately, problems of poor policy formulation, implementation and evaluation usually lead to malfunctioning of the healthcare system. This threatens the success of this otherwise cheap and effective method of management.

Undermining the advantages of syndromic treatment however are the possibilities of overtreatment [21]; poor detection rates for chlamydial and gonorrhoeal infections [28, 29]; and low presentation rates in cases where there are no symptoms [29, 30].

Results of laboratory tests are usually not available before the commencement of antibiotic therapy especially in acute cases. Therefore, empirical, broad spectrum drugs are employed against *Chlamydial trachomatis*, *Neisseria gonorrhoea*, gram negative facultative bacteria, anaerobes and *streptococci* [22, 31]. Such patients are usually hospitalized and given parenteral antibiotics like the third generation cephalosporins, quinolones, in combination with doxycycline, and metronidazole for 24-72 hours followed by oral therapy to complete a 14–day course.

Ideally such antibiotic use should be determined by regularly reviewed local protocols to prevent bacterial resistance[32]. Analgesics including nonsteroidal anti-inflammatory drugs [33] and other supportive therapy are also given.

Infection by *Mycobacterium tuberculosis* is endemic in some countries like India, and parts of Africa [16] and requires anti tuberculosis therapy. All patients with STD ideally should be screened after counselling for HIV infection. In order to reduce the spread of infection, contact tracing is essential.

MANAGEMENT OF COMPLICATIONS

Infertility

Advances in laparoscopic and microsurgical techniques have improved the success rates associated with tubal surgery. Adhesiolysis, salpingostomies and tubal re-anastomosis can now be expected to result in pregnancy rates of 20-50% at the end of the first year following surgery.

Artificial Reproductive Techniques (ART) including in vitro fertilization and embryo transfer (IVF), Intra Cytoplasmic Sperm Insemination (ICSI) can be employed to achieve pregnancy in cases of fallopian tube occlusion with or without male factor contributions. If obstructive azoospermia results from STD, surgical sperm retrieval techniques are now available, including in many developing countries. Additionally, when PID has destroyed the ovaries or when oophorectomies have been performed for intractable tuboovarian abscess, egg donation with IVF is an alternative method of achieving conception. Adoption is increasingly being accepted even in developing countries.

HIV / AIDS

In PID due to sexually transmitted organisms there is an associated risk of acquiring HIV / AIDS [34], an epidemic that is ravaging many people in low resource countries. As at December 2002, over 42 million people have been infected worldwide [35]. The highly active antiretroviral therapy (HAART) being made widely available promises to prolong life in these patients. There is increased susceptibility of HIV-infected patients, to cervical squamous intraepithelial neoplasia compared to those non-infected [36, 37, 38, 39]. Some workers have thus advocated that HIV-infected patients be screened more frequently.

Pelvic abscess

Following diagnosis and failure of medical therapy, early and conservative surgical management through colpotomy is advocated. Percutaneous drainage with guidance from ultrasound or computed tomography scan can also be used[22], with less operative morbidity. Unfortunately in the developing world where late and suboptimal use of antibiotics results in much abdominopelvic adhesion, drainage by means of laparotomy is preferred, resulting in increased cost and hospital stay.

PID in Pregnancy

This is very rare due to the protection offered by the cervical mucus. However the occurrence of pelvic abscess associated with pregnancy has been reported [40], and this may pose management difficulties.

Ectopic Pregnancy

The use of high resolution transvaginal scan together with colour Doppler and serial estimation of quantitative β – human chorionic gonadotrophin (β – HCG) has reduced the need for laparoscopic intervention in the diagnosis and treatment of unruptured ectopic pregnancy [41]. In such cases, systemic methotrexate given as medical therapy is a promising treatment that is associated with better preservation of fertility and little morbidity when compared to surgery [2, 41].

PREVENTION

Pelvic inflammatory disease is associated with reproductive and sexual ill health in individuals with dire consequences on the society as a whole. Most countries especially the resource limited ones have poor control of STDs, the major causative organisms of PID [42].

Primary prevention involving health education of the susceptible individuals is the most effective method of controlling the disease [43, 44]. The best time to start health education has been a matter of debate, although most authors will now favour an earlier age [38, 45].

Unfortunately most of the adolescents (especially in the developing countries) who are sexually active and desire barrier contraception are barred from its use due to their young age and unmarried status [46] or because of high cost. Prompt and accurate diagnosis coupled with early and effective treatment constitutes the secondary form of prevention.

CONCLUSION

PID is a major reproductive health issue in all the countries of the world on account of its complica-

including HIV / AIDS. The current concepts concerning its management and control especially in the developing world have been highlighted.

REFERENCES

1. Jonathan Ross. Sexual health: Pelvic inflammatory disease.Clinical Evidence Concise. 2005; 463 – 464. BMJ Publishing Group Ltd.

2. John Tripp and Russell Viner. ABC of adolescence: Sexual health, contraception and teenage pregnancy. BMJ 2005; 330: 590 – 593.

3. Berry PL, Schubiner H and Giblin PT. Issues in adolescent gynaecological care. Obstet Gynecol Clin N Am 1990; 17 (4): 837 – 849.

4. Sheil O and Turner M. Adolescent gynaecology.In: Progress in Obstetrics and Gynaecology. Ed. John Studd. 1996; 12: 215 – 234. Churchill Livingstone.

5. Monteiro EF, Lacey CJN and Merrick D. The interrelation of demographic and geospatial risk factors between four common sexually transmitted diseases. *Sex Transm Infect* 2005; 81: 41-46.

6. Orji E. O and Esimai O. A. Sexual behaviour and contraceptive use among secondary school students in Ilesha, Southwest Nigeria. JOG 2005; 25 (3): 269 – 272.

7. Alan Guttmacher Institute (AGI). Sex and Americas teenagers. 1994; 88.

8. Contraception Report (CR). Contraception and Adolescents: highlights from the NASPAG conference. Contraception Report 1995; 6: 4 – 11.

9. Oladapo OT, Sule – Odu AO, Daniel OJ and Fakoya TA. Sexual behaviour and contraceptive practice of future doctors in Southwest Nigeria. JOG 2005; 25 (1): 44 – 48.

10. Arowojolu OA, Ilesanmi AO, Roberts AO and Okunlola MA. Sexuality, contraceptive choice and AIDS awareness among Nigerian undergraduates. African Journal of Reproductive Health. 2002; 6: 60 – 70.

11. Hillis SD, Joesoef R, Marchbanks PA, Wasserheit JN, Gates Jr W, Westrom L. Delayed care of pelvic inflammatory disease as a risk factor for impaired fertility. Am. J. Obstet. And Gynecol. 1993; 168: 1503 – 9.

12. Navarro C, Jolly A, Nair R and Chen Y. Risk factors for genital chlamydial infection. Can. J.

13. Gaydos CA, Howell MR, Pare B, Clark KL, Ellis DA, Hendrix RM *et al*. Chlamydia trachomatis Infections in female millitary recruits. N. Engl. J. Med. 1998; 339: 734 – 44.

14. Buve A, Weiss HA, Laga M, Van Dyck E, Musonda R, Zekeng L *et al.* The epidemiology of gonorrhoea, chlamydial infection and syphilis in four African cities. AIDS 2001; 15 (4 Suppl): S79 – 88.

15. Brabin L, Kemp J, Obunge OK, Ikimalo J, Dollimore N, Odu NN, Hart CA and Briggs ND. Reproductive tract infection and abortion among adolescent girls in rural Nigeria. Lancet 1995; 345: 300 – 304.

16. O'Connor V and Kovacs G – *Editors*. Common problems.In: Obstetrics, Gynaecology and Women's health. First edition. 2003; 453 – 498. Cambridge University Press.

17. Zhang J, Thomas AG and Leybovich E. Vaginal douching and adverse health effects: a metaanalysis. Am J Public Health. 1997; 87 (7): 1201 – 11.

18. Gordon Stirrat – Editor. Pelvic infections.In: Aids to Obstetrics and Gynaecology for MRCOG. Fourth edition. 1997; 230 – 233. Churchill Livingstone.

19. Sangani P, Rutherford G and Wilkinson D. Population-based interventions for reducing sexually transmitted infections, including HIV infection. In: The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.The Cochrane Database of Systematic Reviews 2005; Issue 3.

20. Jacobson L and Westrom L. Objectivised diagnosis of acute pelvic inflammatory disease. Diagnostic and prognostic value of routine laparoscopy. Am. J Obstet. Gynecol. 1969; 1; 105 (7): 1088 – 98.

21. William K. Bosu. Syndromic management of sexually transmitted diseases: is it rational or scientific? Tropical Medicine & International Health 1999; 4, 2, 114.

22. Soper DE. Genitourinary infections and sexually transmitted diseases. In: Novak's Gynaecology. Ed. Jonathan S. Berek. Thirteenth edition: 2002; 453 – 470. Lippincott Williams and Wilkins.

23. Westrom L. Diagnosis and treatment of

salpingitis. J. Reprod. Med. 1983; 28: 703 – 708.

24. Soper DE. Diagnosis and laparoscopic grading of acute salpingitis. Am. J. Obstet. Gynecol. 1991;164: 1370 – 1376.

25. Okaro E, Condous G and Bourni T. The use of ultrasound in the management of gynaecological conditions. In: Progress in Obstetrics and Gynaecology. John Studd – *Editor*. 2003; 15: 273 - 298. Churchill Livingstone.

26. Mwijarabi E and Mayaud P. Tanzania: integrating STD management. Lancet 1997; 349.

27. La Ruche G, Lorougnon F and Digbeu N. Therapeutic algorithms for the management of sexually transmitted diseases at the peripheral level in Cote d'Ivoire: assessment of efficacy and cost. Bulletin of the World Health Organization 1995; 73: 305 – 313.

28. Ronsmans C, Bulut A, Yolsal N, Agacfidan A, and Filippi V. Clinical algorithms for the screening of Chlamydia trachomatis in Turkish women. Genitourinary Medicine 1996; 72: 182 – 186.

29. Mayaud P, Grosskurth H, Changalucha *et al.* Risk assessment and other screening options for gonorrhoeal and chlamydial infections in women attending rural Tanzanian antenatal clinics. Bulletin of the World Health Organization 1995; 73: 621 – 630.

30. Grosskurth H, Mosha F, Todd *et al*. Impact of improved treatment of sexually transmitted diseases on HIV infection in rural Tanzania: randomised controlled trial. Lancet 1995; 346: 530 – 536.

31. Walker CK, Workowski KA, Washington AE, Soper D and Sweet RL. Anaerobes in pelvic inflammatory disease: implications for the Centres for Disease Control and Prevention's guidelines for treatment of sexually transmitted diseases. Clin Infect
Dis. 1999; 28: Suppl 1: S29 – 36.

32. Ross JD. European guideline for the management of pelvic inflammatory disease and perihepatitis. Int J STD AIDS 2001; 12 (Suppl 3): 84 – 7.

33. Downing SJ, Tay JI, Maguiness SD *et al.* Effect of inflammatory mediators on the physiology of the human Fallopian tube. Hum Fertil 2002; 5 (2): 54 – 60.

34. Recchia O, Massi M, Graciani C *et al.* Seroepidemiological study of the association between HIV and Chlamydia trachomatis infection. 1991. 7th International Conference on AIDS, Florence, Italy. Abstract WC 3099.

35. WHO / UNAIDS. HIV / AIDS Epidemic Update 2003.

36. Cardillo M, Hagan R, Abadi J and Abadi MA. CD4 – T cell count, viral load and squamous intraepithelial neoplasia in women infected with HIV. Cancer 2001; 93: 111 – 114.

37. Davies AT, Chakraborty N, Flowers L and Mosunjac MB. Cervical dysplasia in women infected with HIV: a correlation with HIV viral load and CD4 count. Gynecology and Oncology 2001; 68: 233 – 239.

38. Asuzu MC, Odor OE, Asuzu CO and Oyejide CO. Health education needs assessment and curriculum development for formal adolescent education in human sexuality and family life. J Comm Med and PHC. 1990; 189; 2: 72–80.

39. Chama CM, Nggada H and Gashau W. Cervical dysplasia in HIV infected women in Maiduguri, Nigeria. 2005; JOG 25 (3): 286 – 288.

40. Khawaja N, Walsh T, Gleeson R and Geary MPP. Tubal abscess in pregnancy: a case report. JOG 2005; 25 (2) : 210.

41. Ashis Sau and Diana Hamilton – Fairley. Nonsurgical diagnosis and management of ectopic pregnancy. The Obstetrician & Gynaecologist 2000; 5: 29 – 33.

42. Adler MW. Sexually transmitted diseases control in developing countries. Genitourinary Medicine. 1996; 72, 83 – 88.

43. Genius SJ and Genius SK. Managing the sexually transmitted disease pandemic: A time for reevaluation. Am J Obstet Gynecol.2004; 191: 1103 – 12.

44. Hogle J, Green EC, Nantulya V, Stoneburner R and Stover J. What happened in Uganda? Declining HIV prevalence, behaviour change, and the national response. Washington (DC): US Agency for International Development, Office of HIV / AIDS, Bureau of Global Health 2002.

45. Owolabi AT, Onayade AA, Ogunlola IO, Ogunnuyi SO and Kuti O. Sexual behaviour of

secondary school adolescents in Mesa, Nigeria.

implications for the spread of STIs including HIV / AIDS.JOG 2005; 25 (2): 174 – 178.

46. Zlidar VM, Gardner R, Rustein SO, Morris

I, Goldberg H and Johnson K.New Survey Findings:

The Reproductive revolution continues. Population reports. 2003; Vol. XXXI (1): 8 – 31.

Links to Web Resources on Infectious Diseases

www.cdc.gov/ncidod/eid/ www.hopkins-id.edu/ www.who.int/topics/en/ www.nfid.org/ HYPERLINK "http://www.niaid.nih.gov/" www.niaid.nih.gov/ HYPERLINK "http://www.iom.edu" www.iom.edu HYPERLINK "http:// www.cartercenter.org" www.cartercenter.org HYPERLINK "http://www.journals.uchicago.edu/JID/home.html" www.journals.uchicago.edu/JID/home.html HYPERLINK "http://www.biotech-register.com" www.biotech-register.com HYPERLINK "http://www.who.int/topics/infectious_diseases/en" www.who.int/topics/infectious_diseases/en www.lib.uiowa.edu/hardin/md/micro.html HYPERLINK "http://www.biomedcentral.com/bmcinfectdis/" www.biomedcentral.com/bmcinfectdis/ HYPERLINK "http://www.pidj.com/" www.pidj.com/ HYPERLINK "http://www.idsociety.org/" www.idsociety.org/ HYPERLINK "http://www.usamriid.army.mil/" www.usamriid.army.mil/ HYPERLINK "http://www.infectiousdiseasenews.com/" www.infectiousdiseasenews.com/ HYPERLINK "http://www.isid.org/" www.isid.org/ HYPERLINK "http://www.cidrap.umn.edu/" www.cidrap.umn.edu/ HYPERLINK "http://www.mic.ki.se/Diseases/C01.html" www.mic.ki.se/Diseases/C01.html HYPERLINK "http://www.vaccineplace.com" www.vaccineplace.com HYPERLINK "http://www.mayoclinic.com/findinformation/conditioncenters/center" www.mayoclinic.com/findinformation conditioncenters/center ... HYPERLINK "http://www.webpages.charter.net/deziel"

Conference News

Following is a list of some of the up-coming conferences holding in the 2nd half of 2005. Included are the dates of commencement and the host cities.

GENERAL

AUG. 03: 3RD INTERNATIONAL HEALTH CONFERENCE 2005: CLINICAL PRACTICE ON THE EDGE Johannesburg, South Africa.

AUG. 16: HEALTHCOM 2005 INTERNATIONAL CONFERENCE ON HEALTH COMMUNICATION Kuala Lumpur, Malaysia

AUG. 21: HEALTH CHALLENGES OF THE THIRD MILLENNIUM Istanbul, Turkey.

AUG. 22: FLORIDA CONFERENCE ON AGING. Orlando, Florida.

SEPT.19: INTERNATIONAL OCCUPATIONAL HYGIENE ASSOCIATION 6TH SCIENTIFIC CONFERENCE. North West Province, South Africa

SEPT. 29: WORLD AGEING & GENERATIONS CONGRESS 2005. St Gallen, Switzerland

OCT. 03: HIV/AIDS, TUBERCULOSIS AND MALARIA IN AFRICA: FROM KNOWLEDGE SHARING TO IMPLEMENTATION. Durban, South Africa

NOV. 04: INTERNATIONAL CONFERENCE ON MALARIA. New Delhi, India

NOV. 08: 3RD QATAR INTERNATIONAL MEDICAL CONGRESS.Doha, Qatar

NOV. 13: 4TH MIM PAN AFRICAN MALARIA CONFERENCE Yaounde, Cameroon,

NOV. 15: 9TH INTERNATIONAL UNION AGAINST SEXUALLY TRANSMITTED INFECTIONS: WORLD CONGRESS Bangkok, Thailand

NOV. 25: ELNIPS SUMMIT 2005 HIV/AIDS PREVENTION and ITS GLOBAL CHANGLEGES Calgary Canada

DEC. 01: 2005 NATIONAL WORLD AIDS DAY CONFERENCE Miami Florida

ANAESTHESIA

AUG. 12: PAIN MANAGEMENT AND PALLIATIVE CARE San Francisco, USA

AUG. 18: PARTNERS IN PAIN: PATIENTS, CLINICIANS AND PAIN MANAGEMENT, Sydney, Australia

AUG. 21: 11TH WORLD CONGRESS ON PAIN Sydney, Australia

OCT. 08: PAIN MANAGEMENT 2005 - CRUISE CONFERENCE Sails From Ft Lauderdale, Florida, USA

OCT. 22: AMERICAN SOCIETY OF ANESTHESIOLOGISTS ANNUAL MEETING New Orleans, United States

NOV. 00: NIGERIAN SOCIETY OF ANAESTHESIOLOGY ANNUAL CONFERENCE Port Harcourt, Nigeria

DEC. 09: 59TH POSTGRADUATE ASSEMBLY IN ANESTHESIOL - OGY New York, United States.

CARDIOLOGY

JUL. 15: CORONARY HEART DISEASE UPDATE Mackinac Island, United States

JUL. 16: 12TH WORLD CONGRESS ON HEART DISEASE. Vancouver, Canada

SEPT. 19: CURRENT PRACTICE OF CARDIOVASCULAR IMAGING; DISEASE BASED APPROACHES TO CT, MR, ECHO AND NUCLEAR IMAGING Las, Vegas, United States

SEPT/ OCT: NIGERIAN CARDIAC SOCIETY CONFERENCE Kaduna, Nigeria

OCT. 6: CONTROVERSIES IN THE TREATMENT OF CARDIOVASCULAR DISEASE: THE FIFTH IN THE SERIES Santa Monica, United States

OCT. 10: ADULT ECHOCARDIOGRAPHY Winston-Salem, United States.

OCT. 15: INTERNAL MEDICINE CARDIO-CARDIOLOGY CRUISE CONFERENCE SailsFrom Civitavecchia (Rome) Italy

OCT 29: 6TH INTERNATIONAL CONGRESS ON CORONARY ARTERY DISEASE (ICCAD6) Istanbul Turkey

NOV. 3: THE 16TH GREAT WALL INTERNATIONAL CONGRESS OF CARDIOLOGY Beijing, China

CARDIOTHORACIC SURGERY

SEPT. 18: 4TH WORLD CONGRESS OF PEDIATRIC CARDIOLOGY & CARDIAC SURGERY Buenos Aires, Argentina

SEPT. 30: VASCULAR EMERGENCIES AND COMPLICATIONS Los Angeles, USA

OCT. 24: AUSTRALASIAN SOCIETY OF CARDIAC AND THORACIC SURGEONS CONFERENCE 2005 Noosa, Australia

DENTAL SURGERY

AUG. 26: THE 4TH INTERNATIONAL CONFERENCE ON OROFACIAL PAIN AND TEMPOROMANDIBULAR DISORDERS Sydney, Australia

OCT. 05: ANNUAL MEETING OF THE AMERICAN COLLEGE OF DENTISTS Philadelphia, USA

OCT. 06: 146TH ANNUAL SESSION OF THE AMERICAN DENTAL ASSOCIATION Philadelphia, Pennsylvania

OCT. 19: ANNUAL MEETING OF THE AMERICAN ACADEMY OF IMPLANT DENTISTRY. Phoenix, USA

OCT. 31: 20TH INTERNATIONAL CONGRESS OF PAEDIATRIC DENTISTRY Sydney, Australia

NOV. 00: NIGERIAN ASSOCIATION OF ORAL & MAXILLOFACIAL SURGEONS ANNUAL CONFERENCE Venue to be announced

DERMATOLOGY

AUG. 21: 20TH ANNUAL HOT SPOTS IN DERMATOLOGY Lanai Hawaii

AUG. 21: AESTHETIC MEDICINE AND DERMATOLOGY Alaska Cruise, Canada.

SEPT. 06: 6TH WORLD CONFERENCE ON MELANOMA. Vancouver, Canada

OCT. 12: THE 14TH CONGRESS OF THE EUROPEAN ACADEMY OF DERMATOLOGY & VENEREOL-OGY. London, United Kingdom

DEC. 12: DERMATOLOGY FOR THE PRACTICING PHYSICIAN Sarasota, United States

ENDOCRINOLOGY

JUL. 16: NEUROHYPOPHYSEAL HORMONES: FROM GENOMICS AND PHYSIOLOGY TO DISEASE STEAMBOAT SPRINGS COLORADO

SEPT. 03: 7TH EUROPEAN CONGRESS OF ENDOCRINOLOGY Goteborg, Sweden

OCT 18 THE 11TH WORLD CONGRESS ON THE MENOPAUSE Buenos Aires, Argentina

OCT. 30: 13TH INTERNATIONAL THYROID CONGRESS Buenos Aires, Argentina.

NOV. 6: ENDOCRINOLOGY IN PRIMARY CARE Caribbean Cruise, United States

NOV. 19: ENDOCRINOLOGY CONFERENCE Sonoma, USA

FAMILY MEDICINE

JUL. 31: HOT TOPICS IN PEDIATRIC PRIMARY CARE Jackson Hole, United States

AUG. 14: MEDICAL MANAGEMENT 2005 - CRUISE CONFERENCE Sails From Seward, Alaska

SEPT. 01: EMERGENCY MEDICINE FOR PRIMARY CARE AND EMERGENCY PHYSICIANS Florida, United States

SEPT. 28: AMERICAN ACADEMY OF FAMILY PHYSICIANS San Francisco, USA

NOV. 6: ENDOCRINOLOGY IN PRIMARY CARE Caribbean Cruise, United States

DEC. 26: UPDATE IN ADULT INFECTIOUS DISEASES FOR THE PRIMARY CARE PHYSICIAN Sarasota, United States

NOV. 02: CANADIAN ASSOCIATION FOR ADOLESCENT HEALTH 2005 CONFERENCE Toronto Canada

NOV. 29: GASTROENTEROLOGY AND HEPATOLOGY FOR GI SPECIALISTS, HEPATOLOGIST AND PRIMARY CARE CLINI CIANS Maui Hawaii

GASTROENTEROLOGY

SEPT. 07: 15TH WORLD CONGRESS OF THE INTERNATIONAL ASSOCIATION OF SURGEONS AND GASTROENTEROLOGISTS Prague, Czech Republic

SEPT. 09: 1ST ANNUAL GI CANCER SYMPOSIUM San Antonio Texas

SEPT. 12: WORLD CONGRESS OF GASTROENTEROLOGY 2005 Montreal Canada

OCT 02: 12TH INTERNATIONAL SYMPOSIUM ON HEPATITIS C VIRUS AND RELATED VIRUSES. Montreal Canada

NOV. 29: GASTROENTEROLOGY AND HEPATOLOGY FOR GI SPECIALISTS, HEPATOLOGIST AND PRIMARY CARE CLINICIANS Maui Hawaii

DEC. 01: CROHN'S &COLITIS FOUNDATION OF AMERICA (CCFA) NATIONAL RESEARCH & CLINICAL CONFERENCE: 4TH ANNUAL ADVANCES IN ` THE INFLAMMATORY BOWEL DISEASES Miami Beach Florida

GENERAL SURGERY

SEPT. 07: 15TH WORLD CONGRESS OF THE INTERNATIONAL ASSOCIATION OF SURGEONS AND GASTROENTEROLOGISTS Prague, Czech Republic

SEPT. 23: 6TH ANNUAL PERSPECTIVES IN COLORECTAL CANCER Chicago, USA

OCT. 16: AMERICAN COLLEGE OF SURGEONS ANNUAL CLINICAL CONGRESS San Francisco, United States

OCT. 30: 13TH INTERNATIONAL THYROID CONGRESS Buenos Aires, Argentina

HAEMATOLGY

AUG. 06: XXTH CONGRESS OF THE INTERNATIONAL SOCIETY OF THROMBOSIS AND HAEMOSTASIS. Sydney, Australia

SEPT. 16: XI INTERNATIONAL WORKSHOP ON CLL Brooklyn, United States

SEPT. 26: ADVANCED HAEMATOPATHOLOGY London, United Kingdom

OCT. 27: 3RD INTERNATIONAL CONGRESS ON MYELOPROLIFERATIVE DISEASES AND MYELODYSPLASTIC SYNDROMES Washington, DC USA

MICROBIOLOGY

AUG. 6: INFECTIOUS DISEASE REVIEW Vancouver, Canada

SEPT. 05: 11TH INTERNATIONAL WORKSHOP ON VIRUS EVOLUTION AND MOLECULAR EPIDEMIOLOGY. Petropolis, Brazil

OCT. 02: 12TH INTERNATIONAL SYMPOSIUM ON HEPATITIS C VIRUS AND RELATED VIRUSES. Montreal, Canada

NOV. 11: FOCUS ON HOSPITAL ACQUIRED INFECTIONS: ADVANCES IN MANAGEMENT AND CONTROL. Miami, Florida

NEPHROLOGY

JUL. 01: SATELLITE MEETING ON HYPERTENSION & THE KIDNEY Perth, Western Australia Australia

SEPT. 18: MANAGEMENT OF CHRONIC RENAL FAILURE Coventry, United Kingdom

NOV. 08: 38TH ANNUAL MTG & SCIENTIFIC EXPOSITION OF AMERICAN ACADEMY OF NEPHROLOGY Philadelphia, USA

NEUROSCIENCES

SEPT. 11: THE INTERNATIONAL SOCIETY FOR PEDIATRIC NEURO SURGERY 33RD ANNUAL MEETING Vancouver, Canada

SEPT. 17: NEUROLOGY 2005 - CRUISE CONFERENCE Sails From Ft. Lauderdale Florida

SEPT. 21: DEVELOPING AND OPERATING NEUROSCIENCE CENTERS OF EXCELLENCE Chicago, United States

SEPT 26: 130TH ANNUAL MEETING OF THE AMERICAN NEUROLOGICAL ASSOCIATION. San Diego, USA

OCT. 07: CONGRESS OF NEUROLOGICAL SURGEONS ANNUAL MEETING Boston, United States.

NOV. 05 XVIII WORLD CONGRESS OF NEUROLOGY Sydney, Australia

NOV. 12: 35TH ANNUAL MEETING OF SOCIETY FOR NEUROSCIENCE Washington DC, USA

NOV. 12: 3RD EMIRATES NEUROSCIENCE CONFERENCE Dubai, U.A.E.

OBS & GYN.

SEPT. 10: DUBAI INTERNATIONAL OBS/GYNE AND FERTILITY CONFERENCE & EXHIBITION Dubai, United Arab, Emirates

SEPT. 14: THE AMERICAN GYNECOLOGICAL AND OBSTETRICAL SOCIETY Venue to be announced, United States

SEPT. 23: 6TH ATHENS CONGRESS ON WOMAN'S HEALTH AND DISEASE Athens, Greece

OCT. 15: 61ST ANNUAL MEETING OF THE AMERICAN SOCIETY FOR REPRODUCTIVE MEDICINE (ASRM 2005) Montreal, Canada

OCT. 16: 12TH PRIORITIES IN REPRODUCTIVE HEALTH AND HIV CONFERENCE Stellenbosch South Africa

OCT. 18: THE 11TH WORLD CONGRESS ON THE MENOPAUSE Buenos Aires, Argentina

NOV 00 SOCIETY OF OBSTETRICS & GYNEACOLOGY OF NIGERIA CONFERENCE, Ibadan, Nigeria

DEC. 5: INTERNATIONAL CONGRESS OF THE FETUS AS A PATIENT Istanbul, Turkey

DEC. 06: CHALLENGES IN GYNECOLOGY New York, USA

ONCOLOGY

JUL. 03: 11TH WORLD CONFERENCE ON LUNG CANCER – THE INTERNATIONAL ASSOCIATION FOR THE STUDY OF LUNG CANCER (IASLC) Barcelona, Spain

SEPT. 09: 1ST ANNUAL GI CANCER SYMPOSIUM San Antonio Texas USA

SEPT. 10: CURRENT CANCER ISSUES - CRUISE CONFERENCE CRUISE Sails from Vancouver, Canada

SEPT. 21: 37TH CONGRESS OF THE INTERNATIONAL SOCIETY OF PAEDIATRIC ONCOLOGY Vancouver, Canada

SEPT 22: 5TH PRINCESS MARGARET HOSPITAL CONFERENCE ON NEW DEVELOPMENTS IN CANCER MANAGEMENT Toronto Canada

SEPT. 23: 6TH ANNUAL PERSPECTIVES IN COLORECTAL CANCER Chicago, USA

OCT. 9: ONCOLOGY: CLINICAL ISSUES AND TRENDS Seattle, United States

OCT. 14: 11TH ANNUAL PERSPECTIVES IN BREAST CANCER Boston USA

OCT. 14: GERIATRIC ONCOLOGY CONFERENCE Mumbai, India

OCT. 28 UPDATE IN SURGICAL ONCOLOGY 2005. Toronto, Canada

NOV. 04: 10TH ANNUAL PERSPECTIVES IN THORACIC ONCOLOGY New York, USA

NOV. 11: 2ND INTERNATIONAL BREAST CANCER CONFERENCE, Muscat Oman

NOV. 11 5TH ANNUAL PERSPECTIVES IN BLADDER CANCER. Nice France

NOV. 11: ADVANCES IN BREAST CANCER: MOLECULARLY TARGETED THERAPIES FOR METASTATIC DISEASE. Toronto, Canada

OPHTHALMOLOGY

SEPT. 4: OPTHALMOLOGIICAL SOCIETY OF NIGERIA 2005 CONGRESS Abeokuta, Nigeria

OCT. 15: AMERICAN SOCIETY OF CONTEMPORARY OPHTHALMOLOGY 2005 Orlando, United States.

OCT. 16: AMERICAN ACADEMY OF OPTHALMOLOGY (AAO) 2005 Chicago, USA

ORTHOPEADIC SURGERY AND TRAUMA

JUL. 21: 2ND ANNUAL INNOVATIVE TECHNIQUES IN SPINE SURGERY, Los Cabos, Mexico

AUG. 18: AUSTRALIAN ORTHOPAEDIC FOOT & ANKLE 2005 Darwin, Australia

OCT. 9: 65TH ANNUAL SCIENTIFIC MEETING: AUSTRALIAN ORTHOPAEDIC ASSOCIATION Perth, Australia

OCT. 10: COMBINED ORTHOPAEDICS MEETING OF THE ENGLISH SPEAKING WORLD Perth, WA, Australia

OCT. 31: IMPROVING PRACTICE IN ORTHOPAEDICS: IMPROVING QUALITY AND MANAGING RISK London , United Kingdom

NOV. 2: ADVANCED CRITICAL CARE AND TRAUMA Nashville, United States

DEC. 14: CURRENT CONCEPTS IN JOINT REPLACEMENT Orlando, United States

OTORHINOLARYNGOLOGY

SEPT. 25: AMERICAN ACADEMY OF OTOLARYNGOLOGY Los Angeles, USA

NOV 00 OTORHINOLARYNGOLOGICAL SOCEITY OF NIGERIA . Port Harcourt, Nigeria

PATHOLOGY

AUG. 20: 7TH WORLD CONGRESS ON INFLAMMATION 2005, Melbourne, Australia

OCT. 5: THE ROYAL COLLEGE OF PATHOLOGISTS' ANNUAL CONFERENCE , London, United Kingdom

PAEDIATRICS

JUL. 30: PEDIATRICS 6TH ANNUAL CONFERENCE Copenhagen, Denmark

SEPT. 14: 29TH UNION OF MIDDLE EASTERN & MEDITERRANEAN PEDIATRIC SOCIETIES Istanbul, Turkey

SEPT. 16: SECOND ANNUAL PAEDIATRIC EMERGENCY MEDICINE CONFERENCE Toronto, Canada

SEPT. 18: 4TH WORLD CONGRESS OF PEDIATRIC CARDIOLOGY AND CARDIAC SURGERY Buenos Aires, Argentina

SEPT. 21: 37TH CONGRESS OF INTERNATIONAL SOCIETY OF PAEDITRIC ONCOLOGY Vancouver, Canada

OCT. 19: CLINICAL RISK MANAGEMENT IN PAEDIATRICS AND CHILD HEALTH London, United Kingdom

OCT. 19: CLINICAL ISSUES IN PEDIATRICS New Orleans, United States

OCT 19 3RD ANNUAL SYMPOSIUM ON ADVANCES IN PERINATAL CARDIOLOGY St. Petersburg, USA

PLASTIC SURGERY

SEPT. 21: THE 11TH EUROPEAN BURNS ASSOCIATION CONGRESS Estoril, Portugal

NOV. 10: PAEDIATRIC PLASTIC SURGERY 2005, Melbourne, Australia

PSYCHIATRY

AUG. 03: ANNUAL PSYCHIATRY CONFERENCE Aspen, United States

SEPT. 02: 6TH INTERNATIONAL MENTAL HEALTH CONFERENCE Gold Coast, Australia

SEPT. 04: THE 28TH CONGRESS OF THE WORLD FEDERATION FOR MENTAL HEALTH: EQUITY AND MENTAL HEALTH Cairo, Egypt

SEPT. 10: XIII WORLD CONGRESS OF PSYCHIATRY Cairo, Egypt

SEPT/OCT: ASSOCIATION OF PSYCHIATRISTS OF NIGERIA ANNUAL CONFERENCE Venue to be announced, Nigeria

OCT. 18: 52ND ANNUAL MEETING OF THE AMERICAN ACADEMY OF CHILD & ADOLESCENT PSYCHIATRY Toronto, Ontario, Canada

NOV. 02: INTERNATIONAL SOCIETY FOR TRAUMATIC STRESS STUDIES ISTSS 21ST ANNUAL MEETING Toronto, Canada

NOV. 07: 18TH ANNUAL US PSYCHIATRIC & MENTAL HEALTH CONGRESS Las Vegas, USA

NOV. 09: 5TH INTERNATIONAL FORUM ON MOOD AND ANXIETY DISORDERS Vienna, Austria

PUBLIC HEALTH

AUG. 11: ASSOCIATION OF COMMUNITY PHYSICIANS OF NIGERIA ANNUAL CONFERENCE. Ibadan, Nigeria

SEPT. 18: CANADIAN PUBLIC HEALTH ASSOCIATION'S 96TH ANNUAL CONFERENCE Ottawa Canada

NOV. 05: AMERICAN PUBLIC HEALTH ASSOCIATION (APHA) 133RD ANNUAL MEETING / EXPOSITION. New Orleans USA

PULMONOLOGY

AUG. 9: INTERNAL MEDICINE: PULMONARY AND CRITICAL CARE Copenhagen, Denmark

DEC 11: MANAGING RESPIRATORY DISEASE Orlando, United States

RADIOLOGY

SEPT. 19: CURRENT PRACTICE OF CARDIOVASCULAR

IMAGING; DISEASE BASED APPROACHES TO CT, MR, ECHO AND NUCLEAR IMAGING Las Vegas, United States

SEPT. 25: XVII EUROPEAN CONGRESS OF ULTRASOUND IN MEDICINE AND BIOLOGY Geneva, Switzerland

DEC. 13: INTERVENTIONAL RADIOLOGY WORKSHOP Riyadh, Saudi Arabia

DEC. 31: 15TH WORLD CONGRESS ON ULTRASOUND IN OBSTETRICS AND GYNAECOLOGY South Africa.

UROLOGY

SEPT. 29: INTERNATIONAL SOCIETY OF UROLOGY (SIU) MEETING ON PROSTATIC DISEASE. Bariloche, Argentina

OCT. 07: UROLOGIC ONCOLOGY CONFERENCE, ADVANCES IN CLINICAL PRACTICE Houston, USA

OCT. 21: UROLOGY UPDATE 2005 Toronto, Canada

NOV/DEC: NATIONAL ASSOCIATION OF UROLOGICAL SURGEONS CONFERENCE 2005 Lagos, Nigeria.

Research Digest

Compiled by Drs M.A. Salami and S.O. Michael

Hypertension is Almost Unavoidable if You Live Long Enough

The latest study of 5296 people from the Framingham cohort has found that compared with younger age groups, adults aged more than 80 are more likely to be hypertensive, and less likely to be adequately treated. Treatment of elderly women is particularly ineffective, achieving adequate control of blood pressure in only 23% of hypertensive women aged over 80. The link between blood pressure and risk of serious cardiovascular events remains as strong as ever in older people, starting at 9.5% for those with normal blood pressure and rising to 24.7% for anyone taking antihypertensive drugs or with an untreated systolic blood pressure of 160 mm Hg (hazard ratio compared with normal blood pressure 2.4; 95% confidence interval 1.2 to 4.6). Hypertension is unavoidable for most people living beyond 80. Fewer than one in 10 (6.9%) of the oldest Framingham participants had normal blood pressure. Three quarters of those aged over 80 were already hypertensive (74%), and the rest (19.1%) were getting there, with systolic blood pressure of 120-129 mm Hg or diastolic blood pressure 80-89 mm Hg. Since people over 80 are the fastest growing age group in the US, the authors of this analysis call for urgent research into the best and safest way to treat them, because doing so would prevent a substantial number of heart attacks, strokes, and other cardiovascular events.

JAMA 2005; 294: 466-472

β Blockers Reduce Mortality in High Risk Patients Having Major Surgery

β Blockers are often prescribed to help prevent perioperative myocardial infarction in patients having major surgery, despite mixed results from randomised trials. Researchers have recently analysed data from a retrospective cohort of 782, 969 patients who had had major non-cardiac surgery in 329 US hospitals during 2000-1. Of the 663, 635 patients without contraindications to the drugs, 122, 338 (18%) had prophylactic β blockers. When patients were stratified according to their preoperative cardiac risk, high risk patients who were given β blockers had a significantly lower mortality in hospital than those who were not. The researchers scored patients' cardiac risk, giving one point each for ischaemic heart disease, cerebrovascular disease, poor renal function, diabetes, and high risk surgery. Patients scoring 3-5 had significantly reduced mortality risk with prophylactic β blockers, and those scoring of 4 showed the greatest benefit (odds ratio 0.57, 0.42 to 0.76). The authors think their result is enough to justify doctors prescribing β blockers to high risk patients before they have major non-cardiac surgery.

New England Journal of Medicine 2005; 353:349-61

Inpatients with Stroke are More Likely to Have Left Sided than Right Sided Cerebral Pathology

Fifty six per cent (11 328) of German adults admitted to hospital with a stroke or transient ischaemic attack, according to an analysis of data (1997-2002) from a national stroke register had damage to the left cerebral hemisphere, and only 44% (8769) had damage to the right hemisphere, an important difference that the researchers think is caused by an imbalance in admissions, not an imbalance in the pathology of stroke. The symptoms of left sided ischaemia include aphasia and paralysis of the right arm, both of which are hard to miss. The symptoms of right sided ischaemia, such as neglect of the affected side, are more subtle and potentially harder to recognise. This could mean fewer admissions to hospital for patients with right sided ischaemia. Further analyses of the same data support this theory; the gap between left and right increased with

patients' age and was most marked among patients with mild or moderate symptoms, especially those with transient ischaemic attack. The difference was not evident at all among patients with intracerebral haemorrhage, who tend to have severe symptoms. Most importantly, patients with left sided ischaemia were more likely to be admitted in time for thrombolysis (within three hours). Fifty eight per cent of patients who had thrombolysis had left sided pathology.

Lancet 2005; 366:392-393

Antiretroviral HIV Programs Effective in the Developing World

In resource-poor settings, comprehensive antiretroviral treatment programs result in HIV viral load suppression in roughly 57% of patients at 12 months. This rate is similar to that achieved elsewhere, investigators report in the July 15th issue of Clinical Infectious Diseases.

Some authors have hitherto expressed concern that, in developing countries, programs for treating HIV infected patients may not be feasible or may be less successful than in the developed world, because of logistics and lack of infrastructure in many poor countries. The investigators conducted a meta-analytic review of 10 observational studies that documented virologic outcomes for 2,464 HIV-infected patients who were treated mostly in Africa. The vast majority were ART-nave. The most important observation is that the proportion of patients with undetectable viral load at 12 months in ART programs in resource-poor settings is no different from that in the developed world.

The data also show that patients who received ART at no charge had an almost 30% higher probability of having an undetectable HIV viral load at 6 and 12 months than did patients who had to pay for all or part of their drug therapy.

These findings should be considered in the planning and developing of HIV treatment programs worldwide, the team concluded.

Clin Infect Dis 2005; 41: 217-226.

Handwashing Can Reduce Childhood Disease Fatalities

Diarrhea and lower respiratory tract infection are the most important causes of childhood deaths globally. However, handwashing with soap can prevent these diseases, researchers report in the July 16th issue of The Lancet. The results also show that handwashing with daily bathing can help prevent impetigo.

The challenge for the public-health community now is to identify cost-effective techniques for handwashing promotion that can reach the hundreds of millions of households at risk The findings are based on a study of squatter settlements in Karachi, Pakistan. Approximately 600 households in 36 neighborhoods were randomized to a handwashing or control group. The handwashing group was further randomized to receive either plain soap or antibacterial soap. Fieldworkers visited each household every week for a year to encourage handwashing and to record disease symptoms.

Handwashing with soap was associated with a 50% drop in the incidence of pneumonia among young children relative to no handwashing. Similarly, diarrhea and impetigo among children and adolescents fell by 53% and 34%, in households given plain soap.

Further analysis showed no benefit for antibacterial soap over plain soap in reducing the disease burden, the investigators point out.

Lancet 2005; 366:185-187, 225-233.

Long Term Anticoagulation Reduces Recurrence of Venous Thromboembolism

Patients who survive an episode of venous thromboembolism are at risk of a recurrence, which is why they are usually treated with warfarin. But how long should this treatment continue? Randomised controlled trials investigating the impact of different durations of anticoagulation have reported conflicting results. A meta-analysis helps to resolve the discrepancies, but there is probably no straightforward answer. Fifteen randomized

controlled trials evaluating different durations of anticoagulation in terms of risk of recurrence were included in the meta-analysis. The investigators found that the discordance between trials that reported large benefits and others that reported only small or no benefit was largely explained by differences in the periods used for defining recurrence rates. Differences in the baseline prevalence of risk factors accounted for much of the variation in event rates between studies. The investigators conclude that long term anticoagulation in patients with venous thromboembolism does reduce the risk of recurrence. The magnitude of this risk reduction is greatest while the patient is receiving treatment, but even after treatment is stopped there is benefit. The incremental benefit of prolonging anticoagulation decreases as the duration of anticoagulation increases but lasts for at least six months.

JAMA 2005; 294:706-15

Combination Antibiotic Susceptibility Testing Doesn't Improve Outcomes in Cystic Fibrosis

Antibiotic resistance is a problem all over the world. People with cystic fibrosis are particularly badly affected, with 25-45% of adults with the disease chronically infected with multiresistant bacteria in their airways. Combination therapy with two antipseudomonal antibiotics is better than monotherapy for treating pulmonary exacerbations. It extends the time to next exacerbation, but it's difficult to know which combination of antibiotics to select when the bacterial organisms are multiresistant to antibiotics on routine sensitivity testing. In recent years, methods for in vitro testing of combinations of double and triple antibiotics for bactericidal activity against multiresistant bacterial isolates have been devised. Disappointingly, the results of a randomised controlled trial show that, even when these methods are used, outcomes are not improved. A total of 251 patients with cystic fibrosis who were chronically infected with multiresistant Gram negative bacteria gave sputum at intervals of three months for conventional culture and sensitivity tests and for combination antibiotic susceptibility tests. During the study, 132 of them developed an exacerbation during the study period and were randomised to receive a 14 day course of any two intravenous antibiotics, which were chosen on the basis of the results of either the conventional test or the combination test. The treatment failure rate was the same in the two groups. After 14 days of intravenous antibiotic therapy, changes in lung function, dyspnoea, and sputum bacterial density were similar in both groups. The time to the next pulmonary exacerbation was also the same in the two groups. The authors speculate that non-bactericidal effects of antibiotic therapy are important in cystic fibrosis. Azithromycin, for example, an antibiotic that has no bactericidal effects against *Pseudomonas aeruginosa*, improves clinical outcomes, perhaps because of its anti-inflammatory effects. Another possibility is that in vitro antibiotic susceptibility is a poor indicator of clinical response.

Lancet 2005; 366: 463-471

Non-Melanoma Skin Cancer is Increasing in Young Adults

Non-melanoma skin cancer is predominantly a disease of older people and its incidence is known to be rising, probably because of increased cumulative exposure to ultraviolet light. A population based study from the US finds that the incidence of non-melanoma skin cancer is increasing in younger people too. Using data from the Rochester epidemiology project, the investigators identified incident basal cell carcinomas and squamous cell carcinomas in people under 40, and estimated change in incidence over the period 1976-2003. In total, they found 451 basal cell carcinomas and 70 squamous cell carcinomas. Most had been confirmed histologically. The incidence of basal cell carcinoma had increased significantly during the study period among women, but not men, whereas the incidence of squamous cell carcinoma increased in both sexes. The age adjusted annual incidence of basal cell carcinoma was 25.9/100 000 for women and 20.9/100 000 for men. The incidence of squamous cell carcinoma was similar for men and women, with an average age adjusted incidence of 3.9/100 000. The authors think it unlikely that the rising incidence can be accounted for by greater public awareness or better surveillance because there was no trend of

decreasing size in tumours at diagnosis. They suspect that it's the result of sunbathing and the use of tanning parlours.

JAMA 2005; 294: 681- 690

Delayed Insertion of Tympanostomy Tubes Does Not Affect Developmental Outcomes at Age 6

Otitis media with effusion is extremely common in young children, and myringotomy with the insertion of tympanostomy tubes is often undertaken to relieve it, mainly out of concern that the conductive hearing loss associated with otitis media might have lasting adverse effects on cognitive, language, or psychosocial development. It now looks as if this concern may have been exaggerated. A study in the US enrolled 6350 healthy infants younger than 2 months and evaluated them regularly for middle ear effusion. Those who developed persistent middle ear effusion before the age of 3 years were randomly assigned to have tympanostomy tubes inserted either promptly or, if the effusion persisted, up to nine months later. These children had a full assessment of intelligence, language skills, central auditory processing, behaviours and emotion at the age of 6 years. No significant differences between the groups were seen on any of the 30 measures that were used. Measures of intellectual and language ability at the age of 6 are strongly predictive of later academic performance so that, even though the children continue to be followed up, it seems unlikely that developmental difficulties will become apparent later.

New England Journal of Medicine 2005; 353: 576-586

Adolescents with HIV Show Inadequate Medication Compliance

Poor adherence to antiretroviral therapy is common among HIV-infected adolescents, according to a report in the August issue of Archives of Pediatrics and Adolescent Medicine.

Failure to maintain long-term adherence in HIV-positive adolescents is significantly associated with younger age and depression. Those who are depressed may therefore need both treatments for depression as well as assistance in adhering to new antiretroviral treatment regimens.

Murphy and associates investigated the longitudinal adherence among 231 adolescents with HIV. At baseline, just under 70% of the participants reported being adherent in the preceding month. Those who were adherent had significantly lower viral load measures than those who were not adherent. Adherence at baseline was significantly associated with lower intensity of alcohol use and not dropping out of high school.

About half of the 65 initially adherent subjects became nonadherent a median 12 months after enrollment into the study, the authors report. Younger adolescents were 89% less likely to become nonadherent, whereas depressed adolescents were more than twice as likely to become nonadherent to their antiretroviral regimen.

During the year of follow-up, self-reported adherence to highly active antiretroviral therapy was significantly associated with a lack of viral rebound, the investigators report.

Overall, the findings from this study indicate an urgent need for better interventions to assist adolescents infected with HIV with their medication regimens the authors concluded. Based on the findings from this study, intervention should include assisting adolescents in problem-solving issues concerning substance use and lowered adherence.

Arch Pediatr Adolesc Med 2005; 159: 764 - 770.

Adult Somatic Cells Reprogrammed to Become Stem Cells

Through fusion to an embryonic stem cell, adult somatic cells can be reprogrammed to enter an embryonic state, according to research conducted at Harvard University in Cambridge, Massachusetts.

This represents a new system for studying what happens when one does nuclear transplantation into oocytes. It is known that if we take an adult human cell nucleus and put it into an egg, restraints normally placed upon that cell as an adult cell - its limited ability to become other cell types of the body

can be released, so we can make a stem cell. The

advantage of their new system is that it can generate far more material than can be obtained from nuclear transfer into oocytes, and the cells can be genetically manipulated for conducting biochemical and genetic analyses of disease states.

The ultimate goal is to be able to directly turn adult cells into embryonic cells without using an egg or an embryo thus avoiding the ethical concerns currently inhibiting this type of research.

As reported in the August 26th issue of ***Science***, the researchers incubated embryonic stem cells with human fibroblasts in the presence of polyethylene glycol to promote cell fusion. Because they had transduced each cell with resistance markers they were able to confirm that resulting cells contained DNA from both cell types.

The hybrid cells exhibited the immortal growth characteristics and morphology of embryonic stem cells rather than the spindle-shaped fibroblasts. Pluripotency was demonstrated when teratomas and embryoid bodies derived from hybrid cell lines grew cells from all three germ layers. The transcriptional profiles of the hybrid cells lines varied minimally from that of the embryonic stem cells.

However, the genes regulating developmental pluripotency were transcribed from the adult fibroblast cell. Their research showed that greater than 99% of the transcripts from the somatic cells were reprogrammed to the embryonic program. The research team reproduced these findings using bone cells, demonstrating that the ability to reprogram the somatic genome is not restricted to a particular somatic cell line.

The way it stands now, the hybrid cells are not suitable for therapeutic use because they contain chromosomes from both the somatic and the embryonic cells.

In the future, the researchers hope to address this problem by seeing if it is possible to use a portion of an embryonic stem cell's cytoplasm without DNA to reprogram adult cells without making tetraploid cells.

Science 2005; 309:1369 -1373.

Decompressive Surgery Preserves Ambulation in Cancer Metastatic to the Spine

In patients with spinal cord compression due to metastatic cancer, direct decompressive surgery followed by radiotherapy is more effective than radiotherapy alone in maintaining or restoring the ability to walk, according to results of a trial that was closed early because of favorable results.

In the past when surgical options for spinal cord compression were restricted to laminectomy, outcomes were no better than with radiation therapy, Dr. Roy A. Patchell and his associates point out in their report in the August 20th issue of The Lancet. This is likely due to the fact that laminectomy removes posterior elements of the spinal cord, whereas most spinal metastases are located in the vertebral body, anterior to the spinal cord. Several uncontrolled studies of circumferential decompression suggested favorable results, Dr. Patchell, from the University of Kentucky Medical Center in Lexington, and his associates add. They therefore conducted a prospective randomized trial comparing direct decompressive surgery plus radiotherapy with radiotherapy alone.

The trial was restricted to patients whose epidural spinal cord compression was confined to a single area, and whose tumors were not considered to be particularly radiosensitive, such as lymphomas, leukemia, and multiple myeloma or germ-cell tumors. If paraplegia was present it had to be of no more than 48 hours' duration.

The 51 patients randomized to radiotherapy alone received a total dose of 30 Gy given in 10 fractions. The 50 patients assigned to surgery underwent direct circumferential decompression followed by stabilization if spinal instability was present; with radiation therapy initiated 14 days later.

Post-treatment ambulatory rates were 84% in the surgery group and 57% in the radiation only group ($p = 0.001$). The ability to walk was also retained for significantly longer in the surgery group

(median 122 days versus 13 days, p = 0.003).

Of the 16 patients in each group who were paraplegic at trial entry, 10 in the surgery group and 3 in the radiotherapy group regained the ability to walk (p = 0.012).

The physicians also observed that surgery resulted in significantly better maintenance of continence, muscle strength and functional ability, as well as survival time. Median daily doses of corticosteroids and opioid analgesics were also lower in the surgery group.Moreover, there was no excess morbidity or mortality due to surgery.

The authors theorize that surgery, as opposed to first-line radiation, provided immediate decompression before irreversible vascular injury could occur, and that its prolongation of the ability to walk was due to removal of tumor. Despite these positive findings, Dr. Martin J. van den Bent, from Daniel den Hoed Oncology Center in Rotterdam, Netherlands, points out practical difficulties in a related editorial: "It will ... be a great clinical challenge to select patients for this type of intervention and to identify those patients in whom the improved outcome outweighs the efforts and costs of surgical intervention."

It will also be challenging to organize the surgical care of patients with metastatic epidural spinal cord compression, he adds, since it requires an emergency procedure involving several medical disciplines.

Lancet 2005; 366:609-610, 643-648.

Indoor Air Pollution Heightens Lung Cancer Risk

While uncommon in developed nations, heating and cooking indoors with solid fuels contributes to an increased risk of developing lung cancer, according to the results of a multicenter study.

In the August 15th American Journal of Epidemiology, the investigators reported the results of a large case-control study to evaluate the contribution of combustion fumes from cooking and heating at home to the development of lung cancer.

Ever having used solid fuel for cooking or heating increased the odds of lung cancer by 22%, the authors report, compared with never using solid fuel for cooking or heating. The risk for lung cancer increased with increasing time that solid fuel was used for cooking or heating, the report indicates. After adjustments were made for the time solid fuel was used for cooking or heating, the effect of heating with solid fuel on lung cancer risk disappeared, the researchers note, while the effect of cooking with solid fuel increased slightly.

Those who used solid fuels for cooking throughout their lives faced an 80% higher risk of getting lung cancer, the investigators report, compared with a 16% increase among those who had switched to modern fuels.

The data suggest a modestly increased risk of lung cancer related to solid-fuel burning in the home, possibly due to cooking rather than heating the authors concluded. Shifts to higher quality, low-emission fuels, such as kerosene, gas, or electricity, reduced the health impact of household use of solid fuel.

Am J Epidemiol 2005; 162:326-333.

Massage Aids Gastric Motility and Weight Gainin Preterm Infants

Moderate-pressure massage therapy increases weight gain in preterm neonates by increasing vagal activity and gastric motility, investigators at the University of Miami School of Medicine report.

Clinical trials have documented greater weight gain in premature infants after 5 to 10 days of massage, even though caloric consumption and total sleeping time are not increased, Dr. Miguel A. Diego and his associates point out in their report in the July issue of Journal of Pediatrics.

To determine the mechanism behind massage's beneficial effects, the group randomized medically stable preterm neonates to moderate-pressure massage therapy, light massage sham therapy

or a control group (16 in each group).

Electrocardiograms and electrogastrograms were collected before, during, and after the treatment sessions on the first day of the trial.

Moderate massage therapy was applied with the infant in the prone position, with pressure sufficient to produce a slight skin color change from pink to white in a white infant or slight indentation in the skin. Sham treatment was identical to true treatment except that massage produced no skin color change or skin indentation. Stimulation sessions included two 5-minute phases with massage and a 5-minute phase of kinesthetic stimulation in which arms and legs were flexed and extended. Treatment was provided for three 15-minute periods per day for 5 days.

The investigators found that infants in the true massage group gained 27% more weight than those in the control groups, but caloric intake was not affected. Results showed significant increases in cardiac vagal index, vagal tone, and gastric motility and decreased tachygastria in the moderate-pressure massage group only.

Correlation analyses showed that relative weight gain was significantly related to changes in vagal tone during massage and changes in gastric motility after the massage. These moderate- versus light-pressure massage therapy findings suggest the involvement of pressure receptors and/or baroreceptors, the investigators observed.

They concluded that further validation of this model will require assessing the effects of vagal activity and gastric motility on food absorption and digestive hormones during massage therapy while controlling for other potential mediating factors in a larger sample.

J Pediatr 2005; 147: 50 -55.

Microarrays Help Identify Distinct Breast Cancer Classes

Immunocytochemical techniques involving high-throughput tissue microarray technology have defined six distinct classes of breast cancer, UK researchers report in the September 1st issue of the International Journal of Cancer.

The study identified that essentially similar biological classes of breast cancer can be identified using simple laboratory techniques which could be used in routine clinical practice. The group immunohistochemistry techniques to evaluate 1076 tissue microarray preparations from invasive breast cancer tumors. They employed a number of criteria, including well-characterized commercially available biomarkers and gene products known to be altered in some cancers, to classify the tumors.

The team identified five groups with distinct patterns of protein expression. A sixth group, was also identified but involved only four cases. The researchers also found significant differences among the classes in established prognostic factors, such as tumor grade and differences in patient outcome.

The authors concluded that the method of immunocytochemistry is cheap, established in most routine pathology labs and are standardized, inferring that this approach could be used routinely, at low cost and reliably.

Int J Cancer 2005;116:340-350.

Modification of Meningococcal Vaccine Widens Protection

A modified version of the meningococcal outer membrane vesicle (OMV) vaccine, featuring over expression of a neisserial antigen, provides broader protection against disease than a conventional OMV vaccine, according to findings from an animal study reported in the August 14th issue of the Journal of Infectious Diseases.

OMV vaccines have proven useful in preventing meningococcal disease in humans, say the investigators. However, these vaccines are limited in that they induce an antibody response to PorA, a major porin protein that can differ greatly between meningococcal strains.

In an effort to broaden the antibody response, the investigators created an OMV vaccine with a strain that was engineered to over express genome-derived neisserial antigen (GNA) 1870.

Previous reports have shown that GNA1870 can elicit antibody responses against many different strains.

Mice immunized with GNA1870-OMV vaccine showed a broader antibody response than those given GNA1870 or the OMV vaccine alone. In addition, use of GNA1870-OMV vaccine seemed to enhance complement deposition on the surface of live microbes and provide greater passive protection against meningococcal organisms in infant rats. The modified vaccine also showed stronger activity than the others against a bacterial mutant with decreased PorA expression.

The authors concluded that defining the mechanisms by which the modified GNA1870-OMV vaccine elicits serum antibodies that have broader functional activity that those elicited by the rGNA1870 protein will require further study.

J Infect Dis 2005; 192: 580-590.

Noninvasive Fetal ECG Provides Detail at Lower Risk

A noninvasive fetal ECG displays intrapartum fetal ECG waveforms and uterine contractions simultaneously and avoids the risks of invasive monitoring with a fetal scalp electrode, according to a report in the August issue of BJOG: an International Journal of Obstetrics and Gynecology.

Dr. Gardiner and colleagues evaluated the noninvasive acquisition of fetal ECG and uterine contractions during early and late labor using 12 abdominally sited electrodes in 15 women. They successfully obtained continuous fetal ECG recordings within 15 minutes in 12 of the women (80%), allowing measurement of PR, QRS, QT and other parameters. The recordings displayed true beat-to-beat heart rate and measures of heart rate variability, as well as uterine electrical activity, the report indicates.

Thirteen term fetuses were delivered in good condition with normal birth weights, the researchers note, and the two cases with threatened preterm la bor did not deliver within 24 hours of the fetal ECG recordings. "The chief advantage of our technique is that signal separation does not rely critically upon the number or the location or configuration of the electrodes and a reduction to eight or less is expected with further refinement and experience of the technique," the investigators explain.

BJOG 2005; 112:1016-1021.

Pediatric Skull X-ray May Be Omitted in Head Injury Assessment

Physicians can safely omit the skull x-ray in children 1 to 14 years old who present with a head injury, according to a team of Scottish investigators whose findings were published in the August issue of the *Archives of Diseases in Childhood.*

Abandoning the x-rays does not result in significant increase in admission rate, radiation dose per head injury, or missed intracranial injuries, the authors reported. "We suggest that routine skull x rays have no place in the [pediatric] emergency department for those children aged 1 year and over," Matthew J. Reed, MD, and colleagues write. "Mechanism of head injury ... a history of drowsiness or loss of consciousness, and a reduced score on the Glasgow coma scale [GCS] are probably the most important indicators of serious head injury in children."

The investigative team conducted a retrospective cohort study to assess the effect of a policy change at their institution, which has taken the focus off of performing skull x-rays in children in this age group. Dr. Reed and his co investigators are affiliated with the Royal Hospital for Sick Children in Edinburgh, U.K.; Dr. Reed practices in the Accident and Emergency Department.

The new policy views the following as the most important indicators of serious head injury in children: the mechanism of the injury, with higher risk assigned to falls of more than 1 m and motor vehicle crashes; a history of drowsiness and loss of consciousness; and a reduced score on the GCS. A

reduced GCS score is defined as less than 14. These findings are cause for an immediate computed tomography (CT) of the head.

The 1,535 patients who came to the emergency department with head injuries between Aug. 1, 1998, and July 31, 1999, served as controls. The 1,867 who presented between Aug. 1, 2002, and July 31, 2003, the first year of the new policy, served as the investigative group. The team analyzed the hospital notes, computer records, and other data for all patients presenting with a head injury.

Among the controls, 340 (22.1%) had skull x-rays, while none were ordered in the intervention group. Among those who were x-rayed, 328 (96.5%) had normal x-rays.

Among the controls, 44 patients (2.9%) were considered to have "very serious" or "urgent" status; the remaining 1,491 patients (97.1%) were considered to have less severe and less urgent injuries. In the investigative group, 50 patients (2.7%) were considered to have "very serious" or "urgent" status, and the remaining 1,817 patients (97.3%) were considered to have less severe and less urgent injuries. During the control period, 16 patients had CT head scans, of which four (25%) were abnormal; in the investigative period, 39 patients underwent CT scans, of which 10 (25.6%) were abnormal. Among those with abnormal scans in the investigative group, the most common causes of injury were falls of more than 1 m and motor vehicle crashes.

There were 154 patients admitted during the control period and 203 admitted during the investigative period. Patients seen in the control period had a total radiation dose of 69.65 mSv vs a total of 78.0 mSv in the investigative period. The radiation dose per head injury was 0.045 mSv in controls and 0.042 mSv in the investigative period.

The investigators concluded that children seen after the institution of the new policy were spared more than 300 fewer normal skull x rays. Although the percentage of children undergoing CT scans increased, the authors noted that the rate of abnormal CT scans did not change. They also noted no significant change in the admission rate and a slight decrease in the radiation dose per head injury (0.042 vs 0.045 mSv).

As a result of comparing these two groups, the investigators concluded that physicians can safely discontinue skull x-rays in head injuries for children 1 to 14 years old.

Arch Dis Child. 2005;90:859-864

Scientists Identify New Respiratory Virus

Using a general strategy for molecular virus screening, scientists have identified a new human parvovirus, provisionally named human bocavirus, in the respiratory secretions of children, according to a report in the August 22nd PNAS Early Edition.

The researchers used molecular virus screening to search for viruses in nasopharyngeal aspirates submitted for diagnosis of respiratory tract infections. Among seven viruses discovered in the first experiments, two had been uncharacterized at that time, including a group 2 coronavirus subsequently identified in Hong Kong and new sequences similar to known parvoviruses. The new virus is similar to bovine parvovirus and canine minute virus, two related members of the genus Bocavirus, the authors report. Consequently they propose the name "human bocavirus (HBoV)" for the new virus. The two isolates of the new virus differed at only 26 nucleotide positions, the report indicates, including 18 differences in the capsid gene.

In a later series of screenings, 17 of 540 nasopharyngeal aspirates (3.1%) proved to be positive for HBoV, the researchers note, and in 14 cases it was the only virus detected. All 14 children with HBoV for whom records were available had respiratory distress of 1-to-4-day duration prior to hospital admission. None of the HBoV-infected children had gastrointestinal symptoms, conjunctivitis or rash, the results indicate.

PNAS Early Edition 2005.

Universal Newborn Screening May Increase Diagnosis of Childhood Hearing Loss

Universal newborn screening (UNS) can substantially increase the rate at which children with permanent childhood hearing impairment (PCHI) are assessed and diagnosed, according to a team of British investigators whose findings were published in the Aug. 20 issue of *The Lancet.*

The authors had followed up children who had previously been involved in a trial to test the validity of UNS for hearing loss for eight years. The method of screening used in the trial consisted of an initial screen of all children and a follow-up test for those whose screening results were positive for a PCHI of at least 40 decibels. "Our results suggest that this two-stage method of UNS was effective in increasing the percentage of all cases of bilateral PCHI >/= 40 dB hearing level in children aged 7 - 9 years who were referred for hearing assessment before the age of 6 months from 31% to 74%," Colin Kennedy, MD, and colleagues write. "This finding lends support to our earlier report and strengthens the conclusions through follow-up of the children to an age when almost all true cases, including progressive losses, are likely to have been identified in the UK health system."

Dr. Kennedy is a consultant in the Department of Pediatric Neurology at Southampton General Hospital in Southampton, U.K.

The follow-up study consisted of a follow-up of the birth cohort of babies enrolled in a trial of UNS that was designed to see whether the practice would give more diagnoses of true cases of PCHI among children seven to nine years old who had been referred early for hearing assessments. The original trial called for eight years of follow-up to test this hypothesis.

Of the 53,781 live births in this cohort, born between Oct. 1, 1993, and Oct. 31, 1996, 26,609 were born after UNS was instituted. Of these, 21,279 (83%) received screening, 74% were referred for hearing tests before they were six months old, and 392 (2%) had positive screening results. In September 2003, the investigators documented 66 children with bilateral PCHI of 40 dB or more who had initially been identified through UNS. Among these, seven had progressed in severity. "Of 31 cases of PCHI in September 2003, among children born during periods with UNS, a positive screening with UNS was confirmed in 22 (71%)," the authors write.

In contrast, among the 28,372 children born in the years without UNS, 31 were referred for hearing tests, 12 were referred for further hearing assessments; in addition, six had false-negative results for the distraction test.

Although the study showed the value of UNS, it also showed a disconcerting follow-up regarding hearing correction, write Patricia Mutton, MD, and Kenneth Peacock, MD, in an accompanying editorial. "[I]t is quite disconcerting that despite the big increase achieved by the researchers in early identification of deaf infants ... the management (usually involving the fitting of hearing aids and starting early intervention) did not occur in roughly half of cases until the child was over 18 months of age," the editorialists write. These delays mean that children get less benefit from the management of their hearing loss, the authors added. Drs. Mutton and Peacock are affiliated with the Deafness Center at Children's Hospital in Westmead, Australia.

Lancet. 2005; 366:612-613, 660 - 662

V*isual Function after Cataract Extraction May Decrease Over Time in Some Patients*

Drs. Mats Lunstrom and E. Wendel, from Blekinge Hospital, Sweden, examined how long patients' improved visual function lasts following a cataract extraction. They used a questionnaire before and 6 months after a cataract extraction to evaluate self-assessed visual function in 615 subjects who had

undergone a cataract extraction between 1995 and 2002. The subjects were followed up with a final questionnaire between 1 and 8 years after surgery. In 77.3% of all respondents, the total disability score sum (DS) was lower at follow up than it was before surgery, showing that the benefits of the operation had lasted, the researchers observe. In 9.4% the score was unchanged and in 13.3% the DS was higher than before surgery, showing that their condition had worsened.

After 7 years, approximately 50% of patients were still alive and overall, 80% still had improved visual function compared with before surgery. Ocular comorbidity in the operated eye or self-assessed poor visual function before surgery were significantly associated with deteriorated visual function at follow-up.

In an accompanying editorial, Dr. N. Congdon of Johns Hopkins Medical Institute, Baltimore, Maryland, notes that although the proportion of subjects reporting improved vision after surgery declines, the fact that "80% still have improved function 7 years after surgery is, none the less, extremely encouraging."

Br J Ophthalmol 2005; 89: 1017-1020

Clinical Quiz

(1) A 1-day-old neonate is noted to be cyanotic. Physical examination reveals a grade 2–3/6 systolic murmur and a single loud second heart sound. The chest radiograph reveals a normal-sized heart and decreased pulmonary vascular markings. The electrocardiogram (ECG) reveals left ventricular dominance. The next step in the management of this neonate is to administer.

(A) Sodium bicarbonate
(B) Morphine
(C) Postaglandin E_1
(D) Digoxin
(E) Positive Pressure Ventilation

(2) The most likely diagnosis in the patient described in Question 1 is ?

(A) Persistent pulmonary hypertension
(B) Transposition of great arteries
(C) Truncus arteriosus
(D) Pulmonary atresia
(E) Total anomalous venous return

(3) A 12-year-old female experienced diarrhea, which lasted for 3 days, 2 weeks before manifesting progressive weakness and inability to walk. She has intermittent tingling of her fingers and toes. Physical examination reveals marked peripheral muscle weakness without atrophy or fasciculations. The deep tendon reflexes are absent in her ankles and 1+at her knees. Findings on the sensory

examination are normal. Motor involvement is symmetric. The most likely diagnosis is ?

(A) Transverse myelitis
(B) Guillain-Barré syndrome
(C) Polio
(D) Myasthenia gravis
(E) Mononeuritis multiplex

[4] The patient described in Question 3 is admitted to the hospital and now experiences progressive weakness and areflexia of the knee and ankle reflexes. An important test to perform is

[A] urine specific gravity
[B] electrocardiogram (ECG)
[C] serum CPK determination
[D] muscle biopsy
[E] pulmonary function test

ANSWER
1. C
2. D
3. B
4. E