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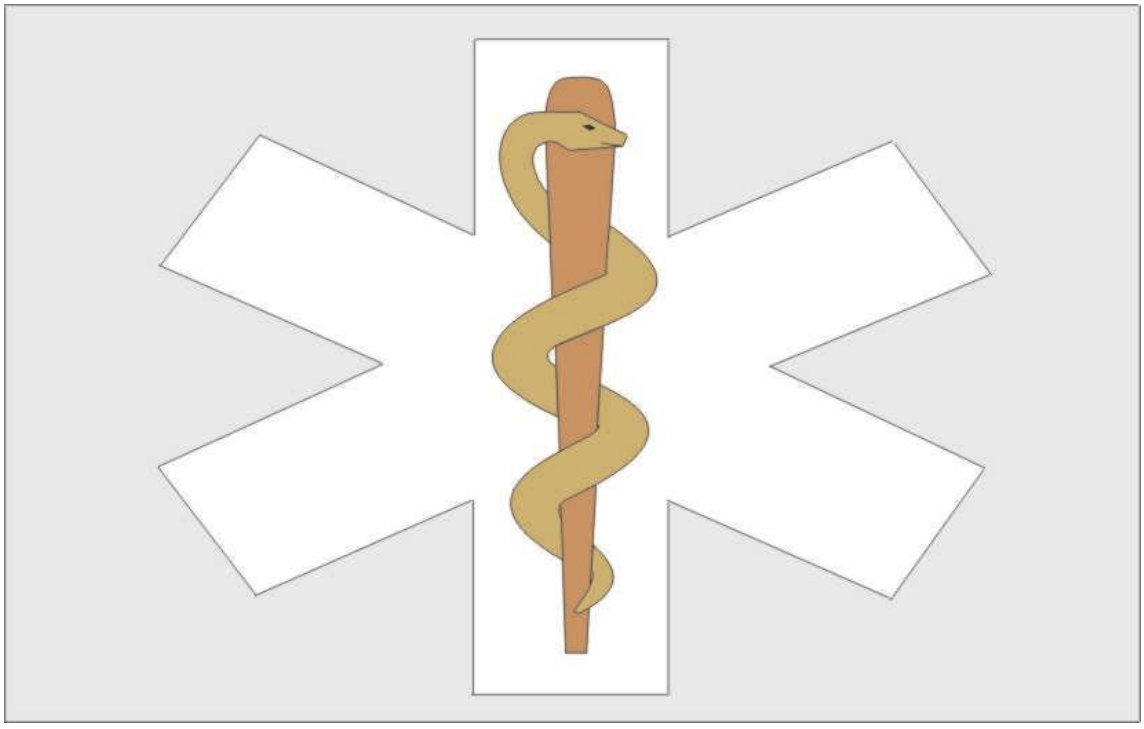
SCHOOL OF MEDICINE AND HEALTH SCIENCES
UNIVERSITY OF PAPUA NEW GUINEA



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Editorial Board

BULLETIN INFORMATION

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1. Scientists presenting at the Joint Divisional Seminars should produce proceedings of their presentation in 2 – 3 pages using font size 10.
2. Experimental and research findings papers should be produced under the following headings: Introduction; Materials and Methods; Results; Discussion/Conclusion; and references.
3. General/Review papers should be produced under the following headings: Introduction; Discussion/Conclusion and references.
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5. References in text should be numbered according to the Vancouver style of referencing.

Example – Cardiac pacemaker cells exhibit the property of automaticity because of a gradual depolarisation of the membrane potential *during electrical diastole (1).*

6. In the reference section, references should be entered as follows:
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MEDICAL SCIENCES BULLETIN
Divisions of Basic and Health Sciences,
School of Medicine and Health Sciences
University of Papua New Guinea

November 2003

Volume 1

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FOREWORD

I am delighted to see the publication of the first issue of the Medical Sciences Bulletin. I am equally impressed with the fact that this publication is the result of research and scientific collaboration between staff and research students of the Divisions of Basic Medical Sciences and the Division of Health Sciences.

The leadership of the School of Medicine and Health Sciences recognizes the importance of research and technology in the overall academic activities of the University. We live in a time of unprecedented change. Advances arising out of scientific research are altering almost every aspect of the way societies operate. Papua New Guinea is no exception to this general trend. It is therefore important that research findings should be disseminated. I see this bulletin as a means of achieving this goal.

I am informed that the bulletin will cover researches, seminar proceedings and findings from all aspects of medical sciences, from the cutting edge exploration of cell function by molecular tools to the integrative view of complex functions, as they become important when health workers are called upon to help patients in their plight. I therefore advise researchers and scientists in the School to take advantage of this medium to publish their findings.

This bulletin will not only facilitate the exchange of scientific information within the School and the University academic community, - it will also familiarize us withy the research areas of our colleagues and peers. This in itself will lead to scientific collaboration and friendship. The main mission of this publication therefore is to foster the scientific intercourse between the various scientists and disciplines of the School. I also know that with time, this healthy relationship will spread to other schools of the University with related research interests.

Professor Mathias Sapuri
Executive Dean, School of Medicine and Health Sciences
University of Papua New Guinea

Message from Chairman, School of Medicine and Health Sciences Research Grant Committee

The Medical Sciences Bulletin has one important purpose: to document research and other academic activities of the Divisions of Basic Medical and Health Sciences. This is in response to the need for research and capacity strengthening in the School of Medicine and Health Sciences (SMHS), which has recently attained unprecedented dimensions. In the last few years, there has been an increase in research output, both by members of academia (both full-time and honorary) and students of the SMHS. Increasing numbers of students are now taking up challenges to pursue academic excellence through research. The first edition contains seven research papers and ten review articles (seminar series). All the research papers are original and findings are relevant to the practice of medicine in PNG, very useful source of information for anyone who is interested.

If the health workers of the developing PNG are to rise to their challenge, lead and teach, students of this School must also become experts in the methods of research and publishing research information so that they can do themselves, and later teach others the skill. This Bulletin provides such opportunities for acquisition of such skills. It is true that a considerable investment in capacity building for research and teaching has occurred over the last twenty years. There is however, greater need for increased investments for developing more PNG research scientists and research-oriented clinicians for the future. National medical and health experts are badly needed to enable the country to understand its own health problems through a solid health research base. There is also a need to develop expertise in institutional leaderships

so that the findings from clinical and field research can influence policies, and can be used effectively in national health systems.

I hope that the major legacy for this Bulletin will be the engagement of more nationals as research and clinical scientists. The impetus would be that the Institution in which these scientists work would become true centres of excellence: focused on research, teaching, and service in order to increase human resource capacity.

Francis W. Hombhanje
Chairman Research Committee,
School of Medicine and Health Sciences, University of Papua New Guinea

Message from Chairman, Division of Basic Medical Science, SMHS, UPNG

In retrospect, the roots of the Medical Sciences Bulletin go back several years, to the time when the Basic Medical Sciences Seminar Series started. The seminar series proved to be a great success, providing a forum for a vigorous exchange of academic thought and catalysing the tremendous research efforts by all our colleagues. The combined Basic Medical Sciences and Health Sciences Divisional Seminar Series provided an even wider, richer, and more challenging outlet for the flow of academic ideas. This created the need to document the proceedings of research communications and other academic exchanges – and the idea of our own bulletin was born. This initiative was discussed and unanimously accepted by all academics in both Divisions during the 2002 academic year.

The Medical Sciences Bulletin (Med. Sci. Bul) is a natural development in the active and scientifically productive academic life of the School of Medicine and Health Sciences – it fulfils the need to record, publish, and thus share the ideas and the research findings of our talented academics and research students.

This Bulletin will hopefully, give more voice to academics and research students, not only in the Divisions of Basic Medical Sciences and Health Sciences, but also to colleagues and research students in other Divisions in the School of Medicine and Health Sciences that are willing to participate in our divisional seminar series. It is also our hope that in the not too distant future, the Med. Sci. Bul will metamorphose into an outlet for the creative research activities of the University of PNG scientific community. That it keeps us all informed about the work being done in various sections of the university, as well as, in other national universities and science institutes in PNG.

We also hope that this bulletin will blossom into an internationally recognized scientific publication that will serve to link our university scientific community with other scientists around the world.

I wish on behalf of all academics and research students in the Division of Basic Medical Sciences to congratulate the members of the Editorial Committee for successfully producing this first issue of the Medical Sciences Bulletin.

Victor J. Temple, M. Sc., Ph. D., M. I. Biol., C. Biol.
Chairman Division of Basic Medical Sciences
School of Medicine and Health Sciences
University of Papua New Guinea

Message from Chairman Division of Health Sciences, SMHS, UPNG

On the occasion of the production of the first issue of the Medical Sciences Bulletin

Congratulations!

Yes, it is appropriate and is in order to give congratulations to all the staff and leaders of Health Sciences and Basic Medical Sciences for three reasons. First is the persevering with seminar presentations against all odds, for deciding to compile the summaries of the seminars in this bulletin form thereby producing a permanent record of their work and lastly being able to produce the bulletin itself and on schedule as planned. Particular mention needs be done of Dr. V. Temple the first seminar coordinator and his successor Dr. K. Adeniyi. It is no exaggeration to say that without their commitment the product we see now would not have materialized. It is important to give a big pat on the back to the editorial Board that has had to put this impotent work in a very short time and severe pressure from other commitment.

Two challenges lie ahead of us now: to sustain the tempo of the seminar in the years ahead and to keep the bulletin coming, particularly under limited resources. Obviously cheaper ways to produce the bulletin must and will be explored, particularly the electronic format.

I hope the bulletin will act as an added impetus for all the staff to work even harder and continue the cooperation that has been established. In this, I wish all of you well! On behalf of and for all Health Sciences staff I thank the Executive Dean and his administration for his committed support and all of you for the effort to get this marvellous work done.

Thank you.

Dr. Phillip G. K. Kigodi

Chairman Division of Health Sciences

School of Medicine and Health Sciences,

University of Papua New Guinea

RESEARCH PAPERS

ASSESSING THE STATUS OF IODINE NUTRITURE IN CHILDREN 6 – 12 YEARS OLD IN HELLA REGION (TARI AND KOROBA DISTRICTS) SOUTHERN HIGHLAND PROVINCE, Papua New Guinea

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Introduction:
Iodine is a micronutrient that is essential for biosynthesis of thyroid hormones {*Tetraiodothyronine* or *thyroxin* (T_4) and *Triiodothyronine* (T_3)}. An adequate dietary intake of iodine is required for the maintenance of euthyroid state. World Health Organization (WHO), United Nations Children's Fund (UNICEF), International Council for the control of iodine deficiency Disorders (ICCIDD) recommend that the daily requirement of iodine is 150μg to 200μg for adults, (pregnant and lactating mothers) and 90μg - 120 μg for infants and children (1,3,5). Inadequate dietary intake of iodine or diet containing anti-metabolites

(goitrogens) impairs uptake of iodine and the biosynthesis of thyroid hormones causing adverse effects on body metabolism, particularly the brain at its crucial formative stages of development (1,2,3,5,6).
Inadequate production of thyroid hormones because of inadequate intake and improper utilization of iodine causes Iodine deficiency disorders (IDD). Mild to moderate iodine deficiency can cause sub clinical disorders in children (1,2,3,4,6,7). Iodine deficiency is the world's major cause of preventable mental retardation (1,3,5,6). Universal Salt Ionization (USI) is the agreed strategy for achieving iodine sufficiency (1,4,5,6).

Concentration of urinary iodine (UI) is the prime biochemical index of choice for evaluating the degree of iodine deficiency and for developing strategies aimed at eliminating IDD (1,6,8). UI is an important indicator of the status of a person's nutritional iodine status and a key biochemical indicator of the very recent iodine intake, because 85% of the ingested iodine is excreted in the urine (1,3,6,8). WHO/UNICEF/ICCIDD expert committee reported that the iodine status of a given population could be accurately determined by assessing the median UI concentration (3,5,6). According to WHO/UNICEF/ICCIDD criteria, the goal for IDD elimination as a public health problem is that less than 50% of the population should have UI concentration < 100ug/L and less than 20% of the population should have UI < 50 ug/L (3,5,6).

In PNG, IDD was identified as far back as 1957 (9). Data from different provinces of PNG suggests that IDD is a public health problem (9,10). Salt iodisation to combat IDD has been a policy of the government since 1973 (9). However, its effectiveness has not been assessed in many areas of the country (9). A limited survey on the iodine status of pregnant women in Lae was carried out by Betty Amoa et. al. (11). There are no scientific publications on the urinary iodine (UI) concentration among children in PNG.

In view of the lack of scientific data and in line with one of the nutritional objective in the National Health Plan (Health Vision 2010) - to eliminate Iodine Deficiency Disorder by 2010(12); this research was carried out.

The aim of this study was to carry out a cross- sectional survey on the status of IDD as measured by median urinary iodine in children (6 to 12 years) in the Hella region Southern Highlands Province of Papua New Guinea.

Materials and Method:
Out of about 60 schools in the Hella region in SHP, PNG, ten schools (elementary and primary) were randomly selected for the study. On spot, casual urine samples were collected in screw -capped 50mL plastic bottles from 360 randomly selected children, 6 – 12 years (Koroba –280; Tari – 80) over a period of four weeks. Before sample collection in each school, the surrounding communities/villages and the students were made aware of the aim of the project (short awareness seminars). Analysis of urine samples was carried out in the Biochemistry laboratory (Basic Medical Science- UPNG) and urinary iodine concentration was estimated using the sensitive colorimetric method of Sandell-Kolthoff reaction after digesting the urine with Ammonium persulfate in water – bath at 100°c. Results were analyzed using the excel data analysis package. Ethical clearance was obtained from the Ethical committee, School of Medicine and Health Sciences, University of PNG and the Health Authorities in Hella Region.

Results and Discussion:
Preliminary results are presented because further analysis is still on going. Analysis of the urine samples showed that the median UI concentration for children in Hella region was 48ug/L. This result indicated moderate iodine deficiency according to the criteria of the WHO/ UNICEF/ICCIDD (5,6). According to the criteria the urinary iodine concentration for most of the children were in the severe (< 20ug/L) to optimal (100 - 199 ug/L) range of iodine.

UI concentrations for 25.35% of the children were in the severe range of iodine deficiency, 27.46% were in the moderate range, 21.83% were in the mild range and 21.83% were in the optimal range. A total of 2.82 % of children had UI concentration in the range for risk of IIH. None of the children had UI concentration > 300ug/L (risk of adverse health consequences).

According to the WHO/UNICEF/ICCIDD criteria, the goal for IDD elimination as a public health problem is that the less than 50% of the population should have UI concentration < 100ug/L and less than 20% if the population should have UI < 50ug/L (3,5,6). In total, 52.46% of the children had UI concentrations < 50ug/L. This is higher than the 20% cutoff indicated by WHO/UNICEF/ICCIDD as criteria for eliminating IDD as a public health problem. This indicates that IDD is a public health problem among children (6 – 12 years old) in the Hella region Southern Highland Province, PNG.

There is a statistically significant ($p = 0.05$) difference between the median UI concentration of girls (median UI of 44.0 ug/L) and boys (median UI of 67. 0ug/L). This signifies that female children are at greater risk of UI deficiency than male children are.

Conclusion:
Our result indicates mild to moderate iodine deficiency in children 6 – 12 years old in Hella region Southern Highland Province, PNG. The prevalence of iodine deficiency is greater in female children than in male children. There is an express need for intensive monitoring of the situation in this region and intensification of awareness campaign on the utilization of adequately iodized salt in households.

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BIRTH DEFECTS IN PAPUA NEW GUINEA

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Birth Defects (BD) are not well defined and many synonyms are used. Some synonyms may include; congenital anomalies, congenital defects and congenital malformations, which describe the structural, behavioral, functional and metabolic disorders present before or at birth and are serious enough to interfere with the individual's everyday life. Congenital anomalies may be inherited or sporadic, isolated or multiple, apparent or hidden, gross or microscopic. Major structural anomalies occur in 2-4 % live born infants, an additional 2-3 % is recognized in children, and by age, five a total of 4-7.5 % are recognized.
Incidence varies with the type of defect and the geographic area due to genetic and/or environmental factors and cultural practices (consanguineous marriages increase the risk of genetic abnormalities). Increasing

age, grand multiparity and previous abortion had also been described to be associated with higher frequency of some birth defects. Other studies elsewhere have also stated that the rate of birth defects increased greatly with decreased birth weight.

Etiology of birth defects may involve genetic (15%) and/or teratogenic factors (20-25 %). In 40-60 % of all birth defects, the cause is unknown. Different factors operating at the same period of organogenesis may produce identical defects. Genetic factors may cause many single anomalies and syndromes. Some syndromes, such as Down syndrome, result from chromosomal abnormalities. Teratogenic factors include environmental toxins, radiation, diet, drugs, infection, and metabolic disorders. Birth defects are causes infant mortality and morbidity. They are the 5th leading cause of potential life lost prior to age 65 in developed countries and are major contributors to disabilities. They influence lives of family members and provision of education and health care services hence are public health issues. In order to understand the nature of birth defects, possible risk factors should be identified. Therefore, studies providing epidemiological data relevant to birth defects are needed. These data may have important implications for prevention, clinical care and etiologic research.

This study aims to observe gender, distribution of BD, Identify common systemic BD and common BD within each system, see the trends of Birth Defects in ten years (1987 1996), and calculate the incidence rate of Birth Defects in PNG and compare the rate with that of other parts of the world. The results may be useful in providing epidemiological data needed for prevention, clinical care and etiological research in this country.
Since PMGH is the largest referral hospital in the country and situated in the Nation's Capital where multi-ethnic Papua New Guineans live, it is assumed that the finding may represent the entire country.

Though this is a retrospective study, which is susceptible to inaccuracy, it is hoped that this would give some clue on the statistics of Birth Defects in PNG, which may prompt active action from relevant authorities to look into ensuring prevention, etiological research and clinical care.

This was a retrospective study where records of PMGH labor ward and special care nursery (SCN) registries for a ten-year period (1987-1996) thoroughly examined. Hospital Numbers for the mothers who delivered babies with birth defects and for the babies themselves were carefully checked to make sure, the same defect not repeated. Diagnoses were taken as that made by medical officer at that time. Those birth defects that were not specifically diagnosed were excluded in this study. Major abnormalities occurring together were taken as single entities. Computer and calculator were used in performing a descriptive statistical analysis of the results. A 5-digit British Pediatric Association ICD-9 System was used in classifying Birth Defects.

From this study it is seen that incidence of birth defects in PNG (73 /10,000 live births) is one of the lowest in the world and shows a male predominance. There has also been an increase in the trend of birth defects in PNG over the ten-year period. Concerning the systemic defects, musculoskeletal system (33.5%) was commonly affected followed by gastro-intestinal system (28.7%) and central nervous system (11.8%). Of these systemic defects, only gastro-intestinal system was found to have a decreasing trend over the ten-year period while the other two defects had an increasing trend. Only CNS defect showed female preponderance while the other systemic defects showed male predominance.

Some of the common specific defects in decreasing order of incidence were, talipes, inperforated anus, cleft lip and palate and neural tube defects. All these defects were found to be increasing except imperforated anus, which is taking the opposite direction. They all have a male predominance except neural tube defects, which shows female preponderance. Other less common defects are diaphragmatic hernia and Down's syndrome, which have male preponderance.

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CROSS SECTIONAL STUDY OF THE ULTRASONOGRAPHIC RENAL MEASUREMENTS OF THE NORMAL INDIGENOUS PAPUA NEW GUINEANS

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Introduction

Background knowledge of the normal renal dimensions (RD) may help in the diagnosis of renal diseases as renal dimensional variations occur in nephropathies due to hypertrophic or atrophic process (1). Currently there is no information regarding the normal sizes of the kidneys in the indigenous Papua New Guineans.

In Papua New Guinea renal pathology is often investigated via ultrasonography using the baseline RD produced by studies of other races via standard Anatomical Textbooks. This goes on to show that it is generally accepted that the normal sizes of the kidneys in Papua New Guineans are similar with other races without its own indigenous studies to confirm it.

Thus, the aim of the study was to investigate the variations of the renal parameters in the indigenous Papua new Guineans with the objectives to establish some preliminary data on the ultrasonographic RD of the normal kidneys and the effects of age, gender, height, weight, and BMI on the RD. This study is important clinically as it will provide the radiologists/doctors with the baseline dimensional indices to relate to when performing renal ultrasonographic examinations in renal pathologies.

Materials and Methods

A cross sectional study was conducted from April to May 2003 at the Port Moresby General Hospital with the Department of Radiology in collaboration with the Discipline of Anatomy, University of Papua New Guinea.

The study subjects were recruited from normal volunteers and out patients undergoing ultrasonography as part of their clinical investigations with their verbal consent Male and female subjects were randomly selected.

The subjects were scanned using the Toshiba and Medico scanners, utilizing the 3.5 MHz frequency transducer. Examinations of the kidneys were done with subjects in supine to oblique and lateral decubitus positions.

The renal length was obtained as the greatest longitudinal dimension of the kidney measured from the capsular margin of the superior pole to the capsular margin of the inferior pole. The renal width was taken as the longitudinal diameter taken on the same plane as the renal length; measurement was taken at the mid point of the lateral capsular margin to the medial capsular margin of the kidney. The renal thickness was obtained as the cross sectional diameter of the kidney; measurement taken from the anterior capsular margin to the posterior capsular margin of the kidney and taking the renal sinus as the reference point

Results

A total of 129 normal volunteers without known renal pathologies were scanned. Eighty-four subjects were male (69.1%) and 45 were female (34.9%).

Results are expressed as mean ± standard deviation (X ± SD). Comparison of renal dimensions by age, height, weight and BMI of subjects was done by using Pearson's correlation coefficient and comparisons with the Student's T- test. Comparison of renal dimensions of the sides and genders were done with the paired t test. The differences were considered to be statistically significant when $p<0.05$.Comparision of the renal dimension by place of origin was done using the chi – square test.

Age ranged from 15 to 80 years old (35 ± 13 for females and 30 ± 11 for men), body weight ranged from 39 to 103 kg (67. ±11 for men and 62 ± 12 for women), and height ranged from 1.42 to 1.88 m (1.67± 0.07 for men and 1.59 ± 0.07 for women). BMI ranged from 15 to 35.7 (24.1±15.1 for men and 24.7±4.5 for women).

The mean kidney length was 10.1±0.8 cm, mean thickness 5.0±0.7 cm and mean width 4.1± 0.6 cm. The RD did not differ significantly between ethnic regions ($p >0.05$). The renal width and thickness differed significantly with respect to gender ($p < 0.05$). The left kidney was bigger than the right kidney regardless of gender. Age had a negative effect on the entire Renal Dimension while height and weight showed a positive correlation to the renal dimensions. BMI, however, showed significant positive correlation to the right renal width and thickness.

Discussion

Having the knowledge of the normal RD becomes an additional tool to study renal morphology. Ultrasound can be employed to evaluate the dimensions however its measurements obtained are usually less than those obtained by IVP (8). This is probably due to geometric magnification and the osmotic diuresis distension effect caused by the contrast medium that occurs in IVP. (1)

The present data showed that the absolute renal dimensions obtained are below those found in European population - Moell (6), Pakistani population - Buchholz ,(10) Danish population - Emamian (3) & Brazilian population (1).

Between gender, there was no significant variation found in the mean length ($P>0.05$) but the mean renal width and thickness differed significantly ($p < 0.05$) with respect to the right kidney, males having wider and slightly thicker right kidneys than the females. This result was quiet different from other studies conducted with different populations (races) which showed that the right renal length, width and area were all significantly higher in males than in females (6).

Comparison of mean renal parameters by side revealed that they all differed significantly ($p < 0.05$) the left kidney having longer, wider, thicker and greater surface area and volume than the right kidney. This result differs from the study done by Buchholz (10), who found that renal length was not significantly different between the left and the right but width and thickness were in a Pakistan population. However, this result was shown by several other studies (1,3,9,10).

Correlation of the renal parameters with age showed that aging has a negative effect on the renal dimensions ($p<0.05$) both genders. This trend was also seen by several other studies (6,3,10,1,4,9,10). This finding may be due to the sclerosis of the artery, arterioles and the renal tubules associated with aging which causes a decreased perfusion by 1% per year after the 3rd decade. Hence, there is a progressive loss of renal tissue (2,5,6).

Fernandes et al (2002) stated that renal length decreased from the 7th decade compared with others. However, the renal parameters in indigenous Papua New Guineans decreased significantly from the 5th decade and onwards. This was also seen by other studies (7,10). Correlation of the renal parameters with height and weight all showed significant positive correlation. This finding was seen by several other studies too (1). BMI showed no significant correlation in length but showed significant positive correlation of the right kidney width, thickness, volume and area. Buchholz (10) reported in univariate analysis that the mean renal size correlated with age, sex, side & BMI. This was not consistent with the indigenous Papua New Guineans relative to BMI. The reason for this phenomenon in the study is not known.

Renal area is not usually employed as a method for assessing neither renal size nor its morphology but was shown by Fernendes (1) as a sensitive parameter in his study and was shown to be a sensitive measurement in this study. Renal area correlated well with age, height, and weight but not with BMI.

Renal volume in general is seldom used for assessing renal size nor is its morphology used likewise. However, Emamian (3) used it and stated that the most exact measurement of renal size is the renal volume, which showed the strongest correlation with height and weight. This was also seen in this study. However, in the present study renal volume also correlated strongly with age.

Obviously, one cannot estimate the normal renal dimensions of a person by taking the average renal dimension of the population concerned because the renal dimensions are strongly influenced by height, weight and age. However, age and height seem to have less association with other variables (e.g. obesity). Therefore, to reduce the rate of error using the least squares regression equations performed regression analysis. This enabled a more correct estimation of the normal renal dimension by only knowing a person's age and height.

Thus, in linear regression, if only age is known the renal length, width and thickness can be calculated by using the following univariate equations. These equations were all found to be statistically significant.

Length = 10.73 – 0.024*Age (b) Width = 11.00 – 0.021* Age (c) Thickness = 4.186 – 0.008*Age.

However, for a better estimation of the normal renal dimension the multiple linear regressions was carried out stratified by gender in which the regression equations for the right and left kidney length involving age and height were found to significant as follows:

RK Length = 6.55 - 0.00183x age + 2.447 x height; ($p< 0.05$)
LK Length = 6.526 - 0.00150 x age + 2.612 x height; ($p< 0.005$)

Thus, the RK and LK length can be best estimated by knowing a person's age and height. These formulae can be used to best estimate the normal renal dimensions. This could help in comparing the best estimated normal renal dimensions with the nephropathic kidney dimensions obtained with USG and enable classification of an enlarged kidney (as in amyloidosis / hydronephrosis) or an atrophic kidney (as in chronic renal diseases), even if the previous normal USG measurements were not recorded.

Conclusion

In summation, the preliminary results of this study show that the renal parameters/dimensions in the indigenous Papua New Guineans do not follow the normal patterns defined by other studies and therefore needs research that is more extensive.

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COMPARISON OF THE EFFECTS OF CHRONIC SMOKING AND BETEL NUT CHEWING ON THE RESPIRATORY AND CARDIOVASCULAR PARAMETERS IN MELANESIAN MALE POPULATION

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Introduction:

It is interesting to study and understand the effects of two common addictions of cigarette smoking and betel nut chewing on the young Melanesian male persons in Papua New Guinea in their lung function tests, blood pressure and pulse rate. Nicotine present in cigarette is absorbed systemically through the lungs. Its effects on the respiratory and cardiovascular systems have been extensively studied in both humans and animals (8). Nicotine acts in the body by activating the nicotinic cholinergic receptors at the autonomic ganglia and on the skeletal neuromuscular receptors (2, 3). Nicotine in smaller doses stimulates the autonomic ganglia and in large doses blocks them in both sympathetic and parasympathetic nervous systems. On the other hand, Betel nut, the seed of the areca palm contains three major alkaloids: arecoline, pilocarpine and muscarine. Arecoline, the principal alkaloid, is a muscarinic cholinergic agent that has actions on the autonomic nervous system through muscarinic cholinergic receptors (3). Therefore, it is expected that betel nut chewing should also have effects on cardiovascular and respiratory systems. Though considerable researches have been done on these parameters, yet the data available are not conclusive. However, the present research is taken up, to compare the chronic effects of smoking and betel nut chewing on respiratory and cardiovascular parameters in young Melanesian male persons of Papua New Guinea.

Material and Methods:

Melanesian males aged 18 to 40 years were recruited randomly after distribution of a questionnaire. Total ninety-nine (99) subjects free of any cardiovascular, respiratory and other systemic diseases were selected and divided into three groups. Normal control (n= 33, mean age = 25.5), who neither smoked nor chewed

betel nut ever; Chronic smokers (n = 33, mean age = 24.7), who smoked cigarettes 3-5 per day for 2-5 years and Chronic betel nut chewers (n = 33, mean age = 25.3), who chewed betel nut 3-5 per day for 2-5 years. The study excluded those who are both smokers as well as betel nut chewers.

Spirometric measurements of lung functions were done for tidal volume (TV) and maximum ventilation volume (MVV). The forced vital capacity (FVC) and forced expiratory volume in first second (FEV_1) were done using the vitalograph.

The surface area of each subject was measured and compared. Cardiovascular parameters, such as radial pulse was counted by palpatory method and systolic and diastolic blood pressure, were measured by sphygmomanometer.

The best of the three results were used for analysis in all the parameters used above and statistical analysis was done for interpretation of the results.

Results:
All the results were tabulated and compared with the normal control group (n=33). In the normal control group, (mean ± SE) values were TV 477.27L± 21.55, FVC 3.90L ± 0.08, FEV1 3.53L ± 0.091, and MVV 134.11L ± 2.46 and ratio of FEV1/ FVC 90.62%.

n smokers group (n=33), the TV 436.36L ± 23.96, had no significant changes, though FVC 3.51L ± 0.06, FEV1 3.19L ± 0.062, MVV 104.37L ± 1.92, had significant deleterious effects on the lung functions.

The ratio of FEV1/ FVC was 91.06%. In chronic betel nut chewers group (n= 33), the TV 450L ± 23.13 did not changed significantly statistically.

However, the FVC, FEV1 and MVV showed a significantly consistent decrease in their values (FVC 3.48L ± 0.07, FEV1 3.12L ± 0.42, and MVV 106.46L ± 1.62).

The ratio of FEV1/ FVC was 89.65%. This study indicated that the subjects of smokers and betel nut chewers group had significantly reduced FVC, FEV1 and maximum ventilation volume (MVV) compared to the control group (Fig. 1, 2 & 3).

Interestingly betel nut chewers had a much lower mean volume for each FEV1 and FVC as compared to the smokers group (Fig. 1, 2).

The p- values between these two groups did not show any significant differences statistically. All the subjects of betel nut chewer group showed lowered values of FEV1/ FVC compared to the smokers group, though the values were well within physiological limits.

However, in the case of MVV, the betel nut chewer group had consistently higher values in all the subjects compared to the smoker group (Fig. 3).

The TV did not show any significant differences statistically in all the three groups (Fig.4) though there was a slight decrease in the volume.

Figure 1: Graph illustrating FVC results for control, smokers and betel nut chewers.

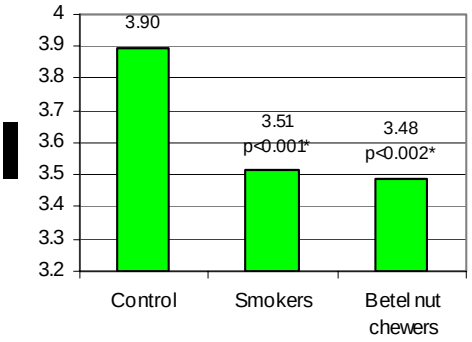


Figure 2: Graph illustrating the FEV1 results for control, smokers and betel nut chewers.

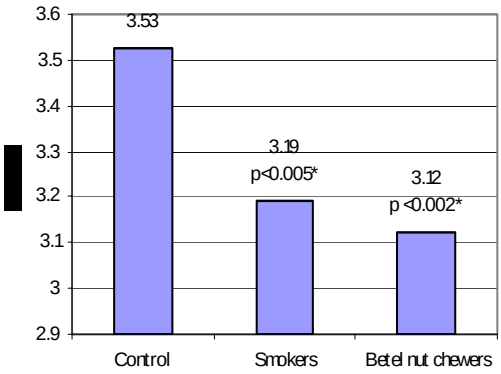


Figure 3: Graph showing the MVV results in control, smokers and betel nut chewers.

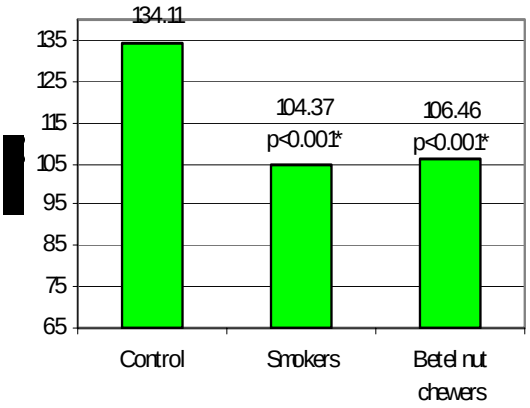


Figure 4: Graph showing the variations in TV in control, smokers and betel nut chewers.

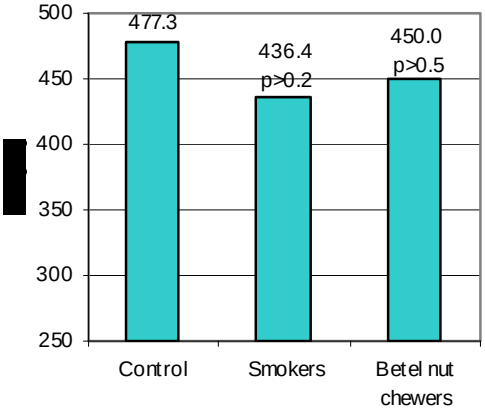


Figure 5: Graph showing the pulse for control, smokers and betel nut chewers.

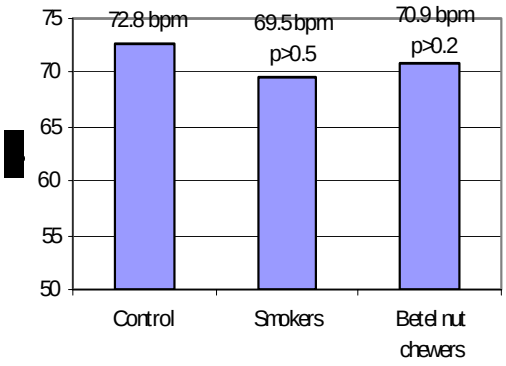
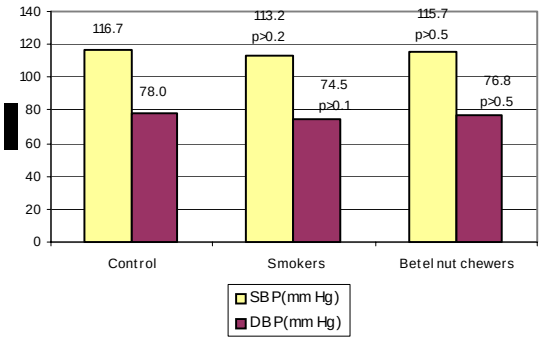


Figure 6: Graph showing the variation in Blood pressure for each groups



There were no significant changes statistically in the blood pressure (Fig. 6) and radial pulse rates (Fig. 5) in both smokers and betel nut chewer in all these young subjects. In all the three groups the systolic/diastolic blood pressure (SBP/DBP) was not significantly different. The average blood pressure in control group were SBP/DBP 116.70 $\pm$ 0.98 / 78 $\pm$ 0.77 mm of Hg, in smokers group SBP/DBP 113.21$\pm$ 1.30 / 74.48 $\pm$ 1.65

mm of Hg and in betel nut chewers group SBP/DBP were 115.73 ± 1.51 / 76.79 ± 1.24 mm of Hg. The pulse rate in control group was 72.79 ± 1.03, in smokers 69.48 ± 8.1.396 and in betel nut chewers 70.9 ± 1.17 (no significant change in all the three groups).

Discussion

This study was done to compare the effects of the chronic habits of smoking and betel nut chewing, on the respiratory and cardiovascular parameters in young Melanesian male population. Chronic smoking (3-5 cigarettes per day) or betel nut chewing (more than 3 per day) for 2-5 years, decreased lung functions by reducing FVC, FEV1 and MVV significantly, though the values were within normal limits.

Chronic betel nut chewing increased airway resistance decreasing FEV1/ FVC in normal healthy persons. This result was comparable to the acute effects of betel nut chewing in asthmatic patients shown by Kiyingi and Saweri in 1991 and 1994 respectively (5, 6).

Chronic cigarette smoking on lung function tests have shown reduced lung volumes and capacities, as in many earlier studies taken up globally in many ethnic groups (1, 4, 7). However, the present study did not show any lowering of FEV1/ FVC in smokers. Betel nut chewers showed a consistent decrease in the FEV1/ FVC in all the subjects, signifying a trend of increased airway resistance. These results indicate that stimulation of muscarinic receptors by betel nut chewing leads to more airway resistance than the nicotinic receptor stimulation in cigarette smokers.

Interestingly betel nut chewers had higher MVV values than the smokers, signifying higher breathing capacity. So in the long-run, smoker's overall maximum breathing capacities are expected to be more handicapped than the betel nut chewers.

The cardiovascular parameters like the heart rate and pulse rate did not show any significant changes in both the smokers and betel nut chewer group, reported earlier (9,10)

Summary and conclusions:

In this study, it seems that chronic smoking and betel nut chewing, both have significant deleterious effects on the respiratory functions and smoking is more comparatively harmful than betel nut chewing. However, smoking cigarettes and chewing betel nut for more than two years and less than five years did not show significant changes in cardiovascular parameters.

Like Framingham's study or Lung Health Study (1), this study of lung function tests and cardiovascular parameters should be followed up in the same subjects, to determine, if there is any progressive deterioration of these parameters, related to these two common addictions of cigarette smoking and betel nut chewing.

Acknowledgements:

I am grateful to Mr. Sam Grant for his technical assistance and Dr. I. Kitur for statistical advice. Also not forgetting the volunteers, without their selfless cooperation this study could not have been performed.

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PHYTOCHEMICAL DIVERSITY AND HUMAN HEALTH: DIETARY CHANGE AND TYPE 2 DIABETES MELLITUS IN TRANSITIONAL COMMUNITIES OF PAPUA NEW GUINEA

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Dietary phytochemicals are increasingly recognized as significant mediators of health and physiology. Epidemiological and experimental studies have demonstrated the benefits of functional foods in reducing the risk of type-2 diabetes (DM2). Adequate exposure to health-promoting phytochemicals is therefore contingent on adequate exposure via dietary diversity. This has particular relevance to Indigenous populations susceptible to DM2 who undergo changes in food systems due to acculturation. The prevalence of DM2 in Papua New Guinea (PNG) is rising dramatically in urban regions. A comparative analysis of food and plant medicines consumed in urban, semi-rural and rural PNG communities would allow insight in the functionality of dietary components in relation to health and disease.

We postulate that urban diets are less varied, and have reduced functionality relative to rural diets, which may affect DM2 development. Our goal is to identify and examine plants that may possess antidiabetic activity, and related pharmacological findings to patterns of use.

A modified 7-day quantitative food frequency questionnaire will be administered to 300 individuals in three communities at different stages of modernization in Central Province, PNG. Individuals older than 18, excluding pregnant and lactating women, will be selected by stratified random sampling according to gender and socioeconomic status.

Dietary diversity and nutrient adequacy ratio will be calculated from the FFQ. A *Phytochemical Exposure Ratio*, defined as the ratio of functional foods to total foods in the diet, will be used to emphasize the role of functional foods. These parameters will be regressed against proxy-indicators of DM2 (e.g. adiposity, blood pressure), adjusted for age, gender, socioeconomic status and level of physical activity. Traditional medical lore and potential anti-diabetic plants will be determined using an ethnomedial questionnaire administered to a sub-sample of the population.

A select number of these plants will be screened for their ability to mediate glucose transport and metabolism in cell culture using isolated mouse abdominal muscle tissue and ^{14}C and ^{3}H isotopes. Those with significant activity will be tested for their ability to attenuate insulin resistance and hyperglycemia in genetically obese ZDF/Gmi-*fa* diabetic Zucker rats.

This study will provide insight into the role to functional foods and medicines in transitional diets and enable the development of culturally specific strategies for preventative modes of therapy.

THE PLACENTAL MORPHOLOGY OF MELANESIAN WOMEN IN RELATION TO MATURITY AND COMMON MEDICAL CONDITIONS IN PAPUA NEW GUINEA

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Introduction:
Pre maturity, post maturity and low birth weight infants imposes greater burden on both the obstetrician and neonatologist There is well-documented literature on increased morbidity and mortality in association with pre and post maturity and the low birth weight infants. Studies have further demonstrated strong relationships between Medical and socio-economic factors on pre maturity, post maturity and low birth weight infants. The fact that there had been observed correlation between premature placental calcification in maternal cigarette smokers; and defective placental function resulting in pre term babies in hypertensive mother (to mention a few), do strongly suggest the significant role that placenta plays in relation to pre maturity, post maturity and low birth weight

Placenta plays a crucial role in supporting the fetus in utero. It acts as a barrier, regulating the transfer of the important macro and micro molecules in between the mother and the unborn fetus. The other important role of the placenta is hormonal productions, which are essential for the maintenance of pregnancy. These are some of the many significant roles placenta plays. The placenta is the only organ derived from two different individuals. These are from the trophoblast tissue and partly from the maternal decidual tissue.

The objectives of this study are, to document normal variation in placental morphology among the Melanesians. To correlate morphological changes in placenta with placenta from pre mature, post mature and low birth weight infants. To explore possible variation in vascular pattern of placenta in relation to pre maturity, post maturity and low birth weight infants. To identify and document changes in placental morphology in relation to common medical condition in Papua New Guinea;

Material & Methods:
Those Mothers attending antenatal care with in the Port Moresby area and presenting to the Port Moresby General Hospital labour ward for delivery were followed in this longitudinal study.

Inclusion Criteria:
Mothers attending the antenatal clinic up to the time of delivery at PMGH; Referred patient from other centers with in central province was included in this study; Mothers with obstetric complication was noted and studied as well; Mothers in which labor was induced for medical reasons was included in the study. Multiple pregnancies and placenta previa type 2&3 patient were excluded from the study Enrolment & Sample Size

Eligible cases were enrolled until pre determined sample size has been obtained.

- One thousand and twenty one (1021) cases were studied.

Data Sources: Patient antenatal clinic visits record, Delivery record information. Mothers after delivery Investigations/Variables:

A standardized structured questionnaire was used and the non-laboratory variables to be measured are in the questionnaire. The placental tissue was subjected to examination in the labour ward within one-hour post delivery. The structural abnormalities and morphometric parameters noted on the placenta was studied and documented accordingly.

Required information on the fetal size and maternal health were recorded accordingly. An adequate sample size of the placenta was obtained for histological examination. The raw data collected was subjected to compute entry and analyzed using epi-info 6.0.

Observations and Discussions:
The study showed that the majority of mothers were in the age group of 20 – 24 and 25 – 29, which accounted for 68.5% of the mothers who delivered. Only 8.9% and 1.9% of the mothers were in the age groups of 15-19 and 40-44 years respectively, and the mode was 25 years.

Most placentas were within the normal range of 12 – 20 cm, which accounts for 70.3 % of all the placentas studied. It also shows that only 0.6 were below the normal range while 29.1% were above the normal range.

Most of the placentas were greater than the normal weight of 500, which accounts for 45.9%. Thirty three per cent (33%) of them were less than the normal value while only 21 % of them were equal to the normal value. Most of the placentas were within the normal range, which accounts for 87.1% of all the placentas studied. It shows that 9.0% were above the normal range and only 3.9% of them were below the normal range.

Most of the placentas were below the normal value that accounts for 52.7% of the placentas studied and the rest were equal to and above the normal placental area value, which accounted for 47.3 % of the placentas. Majority of the placentas studied were discoidal in shape, which accounts for 92%. Only 6.8% were oval, and 1.3 % was bi-lobed and 98.4% of all the placentas studied do not have accessory lobes, while 1.6% of them did have accessory lobes. Only 2.5% of the placentas studied were circummargiante and the 1.2% was of the circumvallate type. The rest of the placentas that accounts for 96.3%, were neither circummarginate nor circumvallate.

Of all the placentas studied, 99.6% had the disperse type of chorionic vessels, whilst 0.4% had the margistral type and 24.6% found to be calcified, whilst 75.4% were not calcified. Nearly 51% of the umbilical cords were inserted eccentrically, 27.6% of them were centrally inserted while the rest 21.2% were marginally inserted. Only 1.0% of the total cords examined had velmentous insertion of the cord. The rest of the cords did not have velamentous cord of insertion.

There were 49 smoking mothers with placenta weights more than average, compared to only 50 with weights less than the average. This was shown to be significant (p 0.0385.). There were 290 anemic mothers with placental weights more than average compared to only 100 with weights less than average. This was shown to be significant ($p < 0.01$).

There was no significance between betel nut chewing (p 0.186), pre-eclampsia (p 0.345) & Essential hypertension (p 7595), malaria (p 0.2095) and the weight of the placenta. It was found that there is a significant relationship between the between anemia, pre-eclampsia, malaria and the thickness of the placenta.

There were 30 pre-eclamptic & hypertensive mothers with placental thickness of more than average. This was shown to be significant (p=0.023). There were 24 mothers with malaria, who had placental thickness less than average compared to nine with more than the average. This was shown to be significant (p 0.0021

There was no significance between smoking (p =0.9922) and the thickness of placenta.

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VISION AMONG SCHOOL CHILDREN IN CENTRAL PROVINCE AND NCD

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Introduction

Vision, one of the five senses is vital for general perception of the external environment. This starts right in the eye. The light rays that enter the eyes are converted to impulses by the retina and mainly transmitted to the Lateral Geniculate Nucleus, and then directed to the primary visual cortex, and secondary visual cortex for processing. Only then, perception is complete. Surprisingly, more than half of all the sensory receptors in human body are found in this system, and the largest portion of the cerebral cortex is devoted to processing visual information (3). Since it is worth having vision, it is worth evaluating its status in every individual in a population as visual status in an individual changes from infant stage to old age. In addition, it is not always the same all across the different persons (1).

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Therefore, to distinguish and document any existence of differences, a survey was conducted. This survey does not appear new as Pasons (8) did a similar survey in 1982 in Madang Province, and Loschdorfer and Mann in Port Moresby General Hospital in 1955 (7). They considered the parameters of vision such as acuity and colour vision, but had their focus on some diseases of the eyes. Since Mann and Loschdorfer, nothing has been documented about vision in Southern Region. Hence, the current survey was only a pilot survey to document something about vision in part of the Region.

Unlike the two, the current survey employed few children with only healthy eyes on inspection to discriminate the visual status. There were two main objectives for the survey.
To discriminate vision of the different age groups of the same environment,
To discriminate vision of the same age groups but from different environments (i.e. rural and urban areas);

Materials and Methods

Population Sample, 200 children from four Primary Schools were included in the survey. Two were rural schools from Central Province, and the other two were urban schools from NCD. From these, 50 grade 3s were from rural schools and the other 50 grade 3s from urban schools. The first 50 grade 7s were from rural schools and the other 50 grade 7s were from urban schools. The younger children's age range was from 9 to 11 years old, and the older children's from 14 to 16 years old. To exclude any error that may exist, the numbers of sexes were equalized for each grade and location

Materials Used. The other materials used were; Snellen Chart, a torch, a tape measure, ophthalmoscope, small card board with letters, small red ball (size of a marble) attached to the tip of a small short stick, and Ishihara colour chart.

Methods:
Visual Acuity, it was measured with Snellen's Chart. When a subject with each eye could not read up to more than 30% of the letters on a particular row, his/her acuity was recorded for that row. *Near Point of Vision*, The small cardboard was moved towards each eye until the nearest point where focus was very clear before becoming blurry. *Visual Fields* was tested by doing confrontation test. Eye Movements; the subject was moving the eyes to all the cardinal positions of gaze. *Colour Vision* was tested with Ishihara colour chart and Smooth Pursuit Eye Movement test for presence or absence of *Saccadic Eye Movement* and *Nystagmus*.

Those children found to have severe visual problems were reported to the Headmaster for rearrangement in the classroom and other assistances wherever necessary, and then referred to PMGH for further examination by the ophthalmologists.

Results and Discussion:
Initials used
VFD = Visual Field Defect, EMD = Eye Movement Defect, CVD = Colour Vision Defect, SEM = Saccadic Eye movement, NPOV = Near Point of Vision

Many younger children had some degree of myopia, and significantly shorter near point of vision. This was contradictory to what was expected. However, some possible explanations have been suggested. Firstly the eyeballs may have been abnormally longer than usual, for a perfect focus on the retina. Secondly, the eyes of the younger children were not fully matured to focus or interpret clearly (9, 10). Thus, it's convincing to say that the immaturity here was detected as degree of myopia. Myopia starts to develop in children between the ages 6 to 9 years, and increases with the greatest at puberty. These children either acquire or inherit the condition. Perhaps majority of the younger children surveyed could have been in this latter category. Surprisingly toward the end of the survey, some children still in grade 3 revealed illiteracy of certain letters of the alphabet. The near point of vision was significantly shorter for the younger children. This reveals the fact that as age increases, the plasticity of the lens decreases. Thus, most young children could focus clearly on very near objects as well as far.

Many older urban children had some degree of myopia. This appears reasonable as age increases, the elasticity of the lens decreases, and at around 13 to 14 years, the visual status begins to change to that of adults (4). Daniel, Paul and Taylor, say that between 6 and 9 years myopia develops and increases, with the greatest at the time of puberty (1). This is in correlation with increase in the axial length of the eye – uncompensated by correlated growth of the cornea and lens – is related to the greater and more rapid general growth of the children due to better nutrition and health (10). The near point of vision was significantly shorter in the younger children. Explanation for the latter finding is otherwise is the same as for the rural case discussed.

The near point of vision was significantly shorter for the rural children compared to that of urban children. The acuity showed no good difference, but one may be surprised to find many urban with decreased acuity when working on a bigger sample. This may mean that the vision of the urban schoolchildren develop/or damage more quickly than the rural schoolchildren. The first possible reason is that most urban children are exposed to screens that are bad for the eye. The radiation from the screen cause the lens to lose its transparency, and further more there is possibility that the fluid in the lens might be drastically withdrawn (4). The latter mechanism gradually causes the lens to lose their plasticity, and thus greatly reduced accommodative power. Another reason is due to better nutrition and health as discussed. Still another explanation put forward by FA Young (2) states that a person is more prone to developing myopia when exposed to a confined area for over a considerable amount of time. Generally saying most urban children

are always in their houses or in other confined areas, whereas the rural children are not. Exposure to books may also contribute to the problems, but this may not be supported.

In the older age group, there were many children of the urban area with some degree of myopia. Their near point of vision was significantly longer than those of the rural children of the same age range. The possible explanation is otherwise the same as the explanation given for the younger age groups, except that the muscles of accommodation are well developed to accommodate and focus by ages 13 to 14.

Of the 200 children, colour vision defects were seen only in males, with red-green colour defect. The condition is not very common in females because one normal X chromosome can take over the function of the other X chromosome that has defects and cannot function. Therefore, since gene for colour vision is located on the X-chromosome, and males have one X-chromosome, the defect was obvious in them.

Saccades and nystagmus reveal maturity, interconnections and well-being of the CNS. Many children with uncontrolled nystagmus and saccadic eye movement could mean early manifestation of some pathology in the control centers, or of the nerves supplying the different extra ocular muscles. John Allen and Attah Johnson (5) say that saccadic eye movement in adults means they are vulnerable to schizophrenia later in life.

According to the data for this survey, a trend appears to be revealed. It shows that many rural children may have better visual acuity when comparing between the respective age groups, and when comparing between the older and the younger children, the younger children may have better acuity. The near point of vision may be longer for the urban children, and between the younger and older children, the younger children may have significantly shorter near point of vision. Nystagmus and Saccadic eye movement may be quite common in the older children and children of the rural areas. The other parameters otherwise, may generally be same, or good for the urban children. However, the sample collected for the survey was not big enough, and thus, a better conclusion could not be made about the visual status of younger children against the older children, and between the rural and the urban children of the same age groups.

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REVIEW PAPERS

Alcohol Dehydrogenase-Update - *Journal Article Review*

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Alcohol remains a widely abuse substance relative to other type of substances of abuse. It is also the single most prevalent contributing factor in serious road crashes worldwide. For this reason, numerous research articles have been devoted to the study of its metabolism, and the consequential biochemical and physiological effects of its metabolites. This paper (1) is one such work that looked at the activity of alcohol dehydrogenase in a homogenous population group (Caucasian). It investigated the physicochemical properties of the enzyme that is specific to the gastric mucosa in humans. The enzyme is important in the catalytic oxidation of ethanol (and other higher alcohols) to acetaldehyde and NADH. The reaction also involves the coenzyme-oxidised nicotinamide adenine dinucleotide (NAD^+) as the oxidising agent. Acetaldehyde is further oxidised by a cytosolic acetaldehyde dehydrogenase to acetate and NADH. NADH generated by this step can be used directly by the mitochondrial electron transport chain.

Alcohol dehydrogenase is a ubiquitous enzyme, and the distribution of several of its isoforms in different tissues amongst different populations is believed to contribute to the varying degree of alcohol tolerance. In particular, the vast difference in the level of the enzyme in the stomach and liver is believed to account for the way different gender and ethic grouping are more prone to intoxication. Given the vast data differences with respect to gender and ethnicity in ADH activity levels, the article seek out to address the anomalies in this comprehensive study. It has been widely reported that the reason females are more susceptible to alcohol is due to their diminished capacity to affect the biochemical oxidation of ethanol. Several studies have unravelled the biochemical basis of this difference being to the levels of ADH in the gastric mucosa where ADH levels are much lower in females than in males. The consequence of this is that the bioavailability of ethanol in females is greater than in male because ADH is involved in first-pass metabolism of alcohol in humans.

The authors assessed a number of parameters and their possible effect on gastric ADH activity. These include the effect of smoking, alcohol and drug intake, gender and age differences in the Caucasian population. The inclusion criteria employed in the study were that the study population was exclusively Caucasian, and those having had Oesophago-gastro-duodenoscopy, i.e., those with upper abdominal complaint, e.g. bloatedness, pain, or heartburn. Those excluded from study were:
(i) Any type of acute illness or had operation last 2 weeks
(ii) Chronic diseases e.g. chronic liver disease, renal insufficiency (Serum creatinine > 2 mg/dl) or malignancies; (iii) Gastroduodenal ulcer or gastritis; (iv) Endocrine disorders; (v) Severe heart insufficiency
The total sample size of the study was 142 initially then reduced to 111 due to 31 developing ulcers and gastritis. ADH activity was assessed in endoscopic gastric biopsy specimens in 111 subjects between 20-80 years old by a coupled assay system, and protein determination was according the method of Lowry. Of those studied, 51 were females. There were questionnaires given prior to endoscopy to gauge the social habits of the study population, such as (i) Frequency of alcohol consumption; (ii) Serving size (medium glass or bottle of wine, cans, or bottles of beers or shots hard liquor); (iii) All subjects were asked about smoking habits (how many sticks/packets daily); (iv) Intake of drugs 2 weeks prior study

Their results showed that the highest ADH activity was obtained at ethanol concentrations 150 – 500mM. The mean ADH activity was high in antral specimens than those in gastric corpus of the same subjects. In addition, ADH activity decreased with increasing age in males while the ADH levels in females between 41-60 years were greater than females 20-40 or 61-80 years old. In men between the ages of 20 to 40 years,

the consumption of larger quantities of alcohol (0.8 g/Kg body weight/day) was associated with a reduced ADH activity. The patients treated with H_2-receptor antagonists, known ADH inhibitors, also displayed decreased levels of gastric ADH activity. Thus, the authors concluded that the ADH activity in human gastric mucosa is negatively associated with consumption of larger quantities of alcohol. Furthermore, whether ADH activity in males was higher than in female, as initially thought can only be answered with respect to AGE. In addition, gastric ADH activity in young men was distinctly higher compared to young women but interestingly the gastric ADH activity in middle-aged men was lower than in middle-aged women.
Overall, the study presented a comprehensive research finding demonstrating for the first time age and gender influenced ADH activity in stomach of Caucasian subjects. It confirmed prior findings of decreasing gastric ADH activity with increasing age. It noted that smoking does not affect gastric ADH with respect to age, gender, and alcohol consumption. The influences of drugs (cimetidine & ranitidine) greatly diminished gastric ADH activity.

Whilst the study was comprehensive in its findings, a number of assertions made did not include the relevant data. This include the pH profile to demonstrate pH optimum of gastric ADH at pH 9.0, the increase in pH of buffer not to alter ADH activity over pH range 6.8 – 10.0, the activity profile of ADH under the storage conditions described (-80^{o}C). It did not indicate what storage medium were employed at –80^{o}C, and it did not furnish data showing smoking had no effect on gastric ADH with respect to age, gender, and alcohol consumption. Moreover, the study employed high substrate concentrations (100-500mM Ethanol) although the Michaelis constant (Km) of gastric ADH was much lower at about 41mM. In addition, it was curious NADH formation was followed at 334 nm rather than absorbance maximum (Abs_{max}) of 340 nm. It is also speculative whether the claim four (4) weeks freezing without lost of ADH activity is plausible, whether physiological pH (7-7.5) should have been employed in the study, and whether 25^{o}C was optimal for assay conditions. In terms of sample size, whether 51 female subjects were statistically significant for the conclusions drawn with respect to the gender, even though sample size overall (female and male) was sufficient.

In summary, this paper adds to the myriad of others detailing the confounding factors into the understanding of alcohol dehydrogenase and its important role in alcohol metabolism. An important study may enlighten and further generate interest into understanding alcohol abuse and toxicity in different populations.

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CHANGING PHYSIOLOGICAL PARAMETERS - GENETIC AND ENVIRONMENTAL FACTORS

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It has been reported that Africans have lower white blood cell count compared with Caucasians (1,2) These authors also documented that the Neutrophil/lymphocyte ratio of Africans indicates absolute neutropaenia. The reason for these phenomena remains evasive. Shaper and Lewis (1) suggested genetic and racial factors; while Hawgood (2) reported that, it was due to environmental factor such as altitude.

In series of studies conducted by Ezeilo (3 – 5), the followings were concluded: There exist non-genetic neutropaenia in healthy Africans. The neutropaenia is acquired, thus it and should not be described as absolute. Dietary factors were implicated for the emergence of the neutropaenia. African diet was found to impair the production of a hormone responsible for neutrophil production. Exact dietary factor was responsible for the neutropaenia.

We conducted series of studies in an attempt to identify the nutritional factor (6-8). We tried to answer the following questions: Is protein calorie malnutrition (PCM) a neutropaenic factor? Are high carbohydrate diets a neutropaenic factor? Is fat deficiency in diet a neutropaenic factor?

We examined whether the neutrophil/lymphocyte ratio in an animal model could respond to PCM, High carbohydrate diets, or Fat deficiency.

Materials and Methods

Albino rats of Wistar strain weighing 200-300g were used. They were divided into 6 groups & fed with the following diet for 60 days, Protein-depleted (PD), High-protein (HP), High carbohydrate (HC), Fat-free (FF), Normal and control rats were fed rat chow.

Rats in the control group were sacrificed at the beginning of the study and their lymphoid organs – spleen, thymus & liver were removed & weighed. Total and differential WBC counts were taken. These values were used as the reference values.

The experimental rats were weighed daily and on day 60, the rats were sacrificed, their spleen, thymus and liver were weighed.

Total WBC and differential leucocyte counts were determined; using the Coultier counter Model S. Serum protein levels were also estimated. All results are expressed as means $\pm$ S.D. Statistically comparisons between various experimental groups were performed using Student's two-tailed t-test for unpaired data.

Results

Results from our initial study showed the following. Rats on PD (3.2% protein) diet had indications of malnourishment, with gradual weight loss, Gross emaciation, loss of hair, and stoop in the shoulder. These rats also had cirrhosis of the liver; PD, HC and FF did not change the granulocyte pool substantially. There was no difference in the distribution of differential WBC in all the experimental groups. The neutropaenic factor was therefore absent or not adequately present in our dietary formulations.

We concluded that neither HC nor absence of fat, nor HP, nor PCM is responsible for neutropaenia in Africans. This study did not identify the dietary factor responsible for neutropaenia in Africans.

We therefore conducted further studies that looked into The Effect of Cholesterol on Neutrophil Production. 250 adult male Wistar strain rats (250-300gm) were used and they were divided into the following groups Gr.1 – Control, Rats fed with normal rat pellets. Gr.2, rats fed on 95% carbohydrates, low protein (3%) and fat (1.5%) and vitamin – a modified formulation of Rogers and Harper (9); Gr.3, rats fed on peanut containing mainly polyunsaturated fatty acids. Gr.4, rats fed on diet containing cholesterol and saturated fatty acids – a modified formulation of Agbedanna (10); Gr. 5, rats fed on rat pellets + 0.042gm.b.wt per rat/day cholesterol powder in normal saline, intraperitoneally for 60 days.

The following initial determinations were made: Total mean serum cholesterol, Total leucocyte count; Differential leucocyte count after 60 days, same parameters were determined to ascertain the effect of the diets.

Results and Discussion

The results showed the followings: Rats fed on low cholesterol diet had lower leucocyte count. Low cholesterol diet cause lower neutrophil count, but higher lymphocyte count. High cholesterol diet caused preponderance of neutrophils over lymphocytes – inverting the neutrophil/lymphocyte ratio. Only free circulating granulocytes are estimated in blood cell counts in the present study. Marginated granulocytes were not counted.

The result therefore showed that Cholesterol is a mobilizer of marginated leucocytes. It would be reasonable to assert that a dietary factor, cholesterol, in our study is responsible for higher granulocyte pool. High cholesterol aided by saturated fatty acids is a neutrophilia factor. Contrary to the previous findings, there is probably no absolute neutropaenia. Saturated fatty acids in large quantities may assist cholesterol in mobilizing leucocytes, causing neutropaenia. The neutrophil count in circulating blood depends on the level of dietary cholesterol and thus the serum level.

We are presently studying the mechanism of action of cholesterol in mobilizing marginated neutrophils into circulation.

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HEALTH OF PNG WOMEN IN 21st CENTURY: A CLINICAL PHYSIOLOGIST'S POINT OF VIEW

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Introduction:

It is surprising that in the whole of South Pacific islands, PNG's statistics of infant mortality rate and the under-five mortality rate are the highest and maternal mortality rate is the second highest, only next to Solomon Islands (7).

These statistics are interrelated to women's health, as women are the pivots of the families. She is the mother, wife, sister and daughter, who convert a simple house into a home. A healthy mother can provide a healthy home for all its members. If any society has to progress, the focus should be on the physical, mental and social welfare of its women.

Few important observations on women's health studies show that in spite of more pregnancy-related deaths in women, their life expectancy is more than men in every society (1,6,7). Mortality and morbidity are comparatively less in women than in men (6,14).

A positive health of women could be economical for the total healthcare system of any country, because a healthy mother with positive physical and mental health can manage the health of the whole family better. She provides better nutrition for the children and husband along with other members in the family.

A good mother can provide the best education to the children, which can go a long way in life. In the long run, improvement of women's health will make happy, long, healthy life for the whole Nation.

Discussion:
PNG women health at different age groups:
(A) Childhood to puberty: there is not much difference in male and female health from childhood to puberty in PNG statistics (7), though more emphasis should be given on vaccination, education and nutrition of all the children irrespective of their sexes.

In schools, nutrition should be taught as a major subject to make a foundation of improved health status, in the long run. More natural food should be introduced in diet instead of processed expensive food or the so-called 'junk food'.

Reproductive anatomy, physiology and ethics should be taught at a school level, to prevent the sexually transmitted diseases and make a new generation of responsible citizens, which will cut down the health care cost considerably.

(B) Health in female reproductive age groups: the reports of NDOH (7) show that the fertility rate of PNG women is the highest in the South Pacific islands and 2.4 % of all deaths are due to obstetric causes. The reports of 1995 to 1999 indicate that only 66 % of all pregnant women had antenatal coverage and only 44% of them had supervised deliveries.

During 1993 to 1997, number of deaths due to perinatal conditions was 12.2% and 10% of all the newborn were of less than 2.5 Kg birth weight. These figures indicate the worst scenario of PNG women's health status in their prime reproductive age group. This fact is reflected in the highest infant mortality and under five mortality rates in children of PNG.

Other contributing factors in the alarming maternal and infant mortality rates are the lowest expenditure on Health per head (less than $ 25.00) and the percentage of GNP spent on Health is less than 2.5%, which are the lowest in the whole of South Pacific Islands (7). To decrease the rate of maternal mortality, care should be taken in educating women about the importance of proper balanced nutrition during pregnancy. Sever anemia during pregnancy is preventable easily by iron, folic acid and calcium supplementation from the early stage of pregnancy.

Antenatal care should reach the doorstep to prevent maternal mortality rate and low birth weight babies. Stillbirth and obstructed labor should be prevented by good antenatal care. Prolonged labor leading to postpartum complications should be minimized by prior prediction through regular antenatal check-up. Health workers should be trained properly to assess a difficult pregnancy.

More GNP should be allocated in the Health issues including proper health education to women. More money should be allocated in training more number of health workers from the local area population. Any difficult case should be explained to the expectant mother in proper and clear terms. Care should be taken, so that she complies with referral to the nearest big hospital, where better facilities are available for ultrasound and caesarian section.

Due to difficult road conditions of PNG, not every woman can reach the hospital or health centre for their antenatal check-up or deliveries. Health extension officers or Community Health Workers (CHW) should be

properly trained. To avoid too frequent un-planned pregnancies causing maternal morbidity and mortality, early marriage and child bearing before the age of 20 should be discouraged.

Family planning methods should be practiced to prevent too many pregnancies at short intervals. Condoms should be promoted to prevent sexually transmitted diseases, cervical carcinoma and unplanned pregnancies. Intrauterine contraceptive devices should be promoted more, to give pregnancy as a choice to women. Various church groups should play a vital role in promoting the cause of contraception and planned pregnancies, instead of just promotion of the practice of 'safe period' method of contraception

Sexually transmitted diseases (STD) and HIV in PNG: during 1995 to 1999, there were average 1545/ year reported cases of syphilis for both sexes. Out of them 49% were women. There is a trend of increase in NCD, MBP, Morobe and Southern Highlands (7). Women suffering from gonorrhea shows 46% out of average 5588 cases/year from 1995 -1999 (7). However, many cases of STD remain unreported in women, as very few contact health workers for their sexual problems.

Globally more than 43 million women are suffering from HIV/AIDS and a majority of them is from the developing countries (1, 2). The rate of spread of HIV/AIDS in PNG is alarming. Suggestions to control STD include regular screening of sex workers, to diagnose the cases of gonorrhea and syphilis as early as possible and treat them adequately. Proper follow-up should be there to see that the diseases are under control. For HIV/ AIDS, prevention should be the top priority, as the treatment is very expensive, prolonged and inadequate at present.

To prevent STD, routine use of condoms should be promoted and society should have more reality approach towards the sex workers, instead of denying the realities. There should be more emphasis on sex education and understanding of STD from early age. Various church groups should play a vital role to curb sexual promiscuity and unsafe sex.

Other conditions affecting women's health: there are some gender differences in prevalence of certain diseases like hypertension, ischemic heart disease, diabetes mellitus, cancer, autoimmune diseases, osteoporosis and Alzheimer's disease during reproductive age group of women (1,9,10,12,14). There is little data available regarding the abovementioned in PNG.

Diabetes mellitus (DM) in women: estrogens enhance the insulin sensitivity in women. In spite of estrogen protection women suffer from DM due to higher prevalence of obesity. DM in women counteracts the protective action of estrogen and makes women more prone to Ischemic heart disease (IHD) (1,3,6,12,16). Other contributing factors for IHD are associated decreased HDL, high LDL cholesterol and total cholesterol: triglycerides ratio more than 4.

All these factors make a woman prone to hypertension, coronary artery diseases which may lead to renal diseases, in spite of their hormonal protection (1,3,6, 10). In PNG the number of DM cases, are increasing . Regular exercise, proper nutrition by natural food selection with unsaturated low-fat, high-fiber diet, avoidance of smoking and control on alcohol consumption would not only control obesity but it would improve the health conditions and morbidity of women and her families. Too much consumption of refined and processed food liked tinned fish beef etc should be discouraged.

Autoimmune diseases: women have more powerful immune system, which to large extent protect them from infections. The immuno-protective mechanisms are mainly hormonal. Estrogen increases both cellular and humoral immune mechanisms (1). Some immunocytes contain estrogen, progesterone and androgen receptors (1,14). Uterus also produces a variety of cytokines (1). There is a complex interaction between estrogen, progesterone and immune system (1).

However, after menopause these protective immune responses, becomes less effective (1,6,9,10). The powerful immune mechanisms in women make them more prone to autoimmune diseases like, Rheumatoid arthritis, Systemic lupus erythematosus (SLE), Multiple sclerosis (MS), Grave's disease and Thyroiditis (1,14). The exact data is not available in PNG.

Cancer: male to female ratio of cancer data available show that cancer in women is less prevalent than in men. The raw data (Source Prof Sims of SMHS of UPNG) shows that male to female ratio in oral cancer 3.4:1, liver cancer 4:1, colon cancer 2.6:1, stomach cancer 2.5:1and others 1.5:1. Gynecological Malignancy in PNG shows approximately: Cervical carcinoma 700-1000 per year (age group 35-40+), Ovarian carcinoma 50 per year (age group 50+), Uterine carcinoma 100-200 cases per year (age group 40-50+), Choriocarcinoma 100-200 cases per year (age group 20-45).

Breast cancer data is not available. Though it is presumed that gynecological malignancy is a small problem in PNG, most probably, it is not true, as most of the cases in rural areas are not reported and many women die due to other reasons before the cancer kills them.

To minimize the morbidity and mortality from these diseases, an early diagnosis is the key to success. Regular breast self-examination can lead to early diagnosis of breast cancer. Any change in menstrual history should be reported early to help early detection of cervical malignancy.

Promotion of condoms could not only decrease the chances of pregnancy or prevent HIV or STDs, but it would also decrease the number of cancer cervix cases, which is the 2nd most common cancer in women. Cigarette smoking, Alcohol and drug abuse are not major issues in women of PNG. Lung cancer cases are few. Betel nut chewing is common but the prevalence of oral cancer is lower in female (M: F 3.4:1). Violence against women and its impact on PNG women's health is a major issue. These include domestic violence, discrimination, sexual abuse and emotional torture. Though domestic violence is rampant in PNG society (1,3,4,7), discrimination and emotional torture are less prevalent.

Education and good family values can make a lot of difference. 'Wantok' system can play a positive role in prevention of violence. Education and job opportunities among youth and mixing of different cultures from different provinces would help to respect each other. In the long run it would prevent 'gang rape' and payback sexual violence to women considerably.

(C) Health of postmenopausal women: include hypertension and ischemic heart diseases, as women in reproductive age group are protected from these conditions by their high level of estrogen and progesterone. However, after menopause that protective hormonal armor is lost, and they become equally prone to these conditions (1,6,914).

In Afro-American women these conditions are more prevalent than their counterpart in white women (1,16). No such data is available for Melanesian women. Regular exercise, prevention of obesity, low fat balanced diet and prevention of DM can contribute to curb the incidences of hypertension considerably. Relaxation techniques also decrease stress or tension, which is one of the major contributory factors in hypertension.

Other conditions like osteoporosis and Alzheimer's disease are not major problems in PNG women, unlike their Western counterparts, probably due to lower life expectancy, which averages 54.6 years (7). Majority of women in PNG die at a younger age, due to other causes, before suffering from morbidity of osteoporosis or Alzheimer's disease.

In western countries follow up on post menopausal women health were carried out in 200,000 women from many countries for more than 22 years and funded by NIH and Women's Health Initiative (WHI) (10, 3). The

results show, the impacts of smoking, diet, physical activity etc on the risk of morbidity and mortality due to IHD, breast cancer, stroke, DM and fracture due to osteoporosis.

These studies also showed the value of regular screening for cervical cancer and breast cancer, proper medication and psychosocial changes relaxation. A change of food habit with regular intake of low-fat diet, antioxidants and calcium supplementation along with exercise and control of obesity were shown to prevent these conditions.

There was also indication of the positive role of HRT or hormone replacement therapy (3,8,10,12,17) to prevent hypertension and coronary artery diseases . However, all the latest studies indicated that HRT is not a panacea as it could make menopausal women more prone to breast cancer and other malignant conditions (5, 13). Such studies should be taken up on menopausal women on PNG. Improving women's health will make happy, long, healthy life for the whole Nation. There is a hope and enough scope to improve women's health in PNG.

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HOMOCYSTEINE: A RISK FACTOR FOR CORONARY ARTERY DISEASE – *Review Article*

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Introduction:

Cardiovascular disease remains the leading cause of mortality in developed countries and the same trend is now being experienced by the developing countries. Although tremendous gains in our understanding of coronary artery disease (CAD) have been made over the past several decades, traditionally recognized risk factors, such as cholesterol levels, blood pressure, and smoking, do not fully account for the high incidence of CAD. Mounting evidence is now pointing to homocysteine as an important part of the cardiovascular risk puzzle (1). McCully first suspected the role of elevated homocysteine in vascular diseases 30 years ago after observing people with a rare condition called homocysteinuria. These patients were prone to develop severe cardiovascular disease in their teens and early twenties (2,3). Despite early resistance to this

theory, recent studies suggest that elevated serum homocysteine levels are as important as cholesterol levels but that homocysteine is independent from cholesterol, smoking and high blood pressure.
Speculations are that approximately 10 to 20 percent of cases of coronary heart disease have been linked to elevated homocysteine levels. Both hereditary and dietary factors may be involved in bringing about elevated serum homocysteine levels (4).

Metabolism of Homocysteine:
Homocysteine is produced by the demethylation of Methionine and is an intermediate in the biosynthesis of Cysteine from Methionine via Cystathione. It may also undergo remethylation to Methionine. Increases in homocysteine concentrations often result from the decreased activity of the key enzyme Methionine synthase (which require vitamin B12 as cofactor) or betaine-homocysteine methyl transferase, which is involved, in these metabolic pathways. Cysteine is formed from homocysteine through the transsulfuration pathway via the Cystathionine as shown in Fig 1.

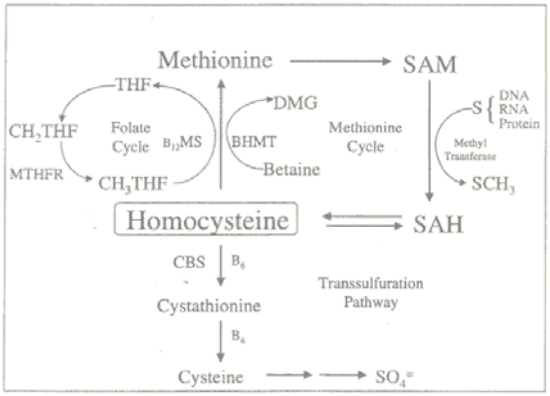

Fig. 1 *Homocysteine, an intermediary between Methionine & Cysteine(1)*

Role of Folic acid, Vitamins B6 and B12
Plasma hyper-homocysteinaemia is normally associated with premature arterial diseases and may reflect dietary deficiencies of Folate, vitamin B12 or vitamin B6 or of certain essential enzymes especially the methylhydrofolate Reductase (5). These substances are essential components for homocysteine metabolism as they are cofactors for methylation and demethylation of methionine and the enzymic reaction of methylhydrofolate reductase as illustrated in Fig. 1 (1,5).

Increased folic acid intake is needed to decrease plasma homocysteine concentrations and to prevent complications of coronary artery disease. Demonstration of this effect was more noticeable in a study by Malinow et al where they observed that when folic acid was fortified in breakfast cereal and the subjects who had CAD had their homocysteine levels reduced accordingly (6).

Vitamins also play the similar role as the folate, they act as cofactors for the enzymic degradation of homocysteine. Vitamin B12 is essential for the cobalamin cycle, which is the folate cycle of the homocysteine metabolism (Fig 1). Elevated homocysteine can also be caused by a genetic defect that block the transsulfuration pathway by inducing a deficiency of the B6 dependent cystathionin β-synthase (1,7).
Homocysteine and Vascular DamageSeveral potential hypotheses have emerged as to the relationship between homocysteine levels, heart disease, and other vascular diseases. Abnormal homocysteine levels appear to contribute to atherosclerosis in at least three ways: The first theory asserts that homocysteine may exhibit a direct toxic effect on the endothelial lining. Some researchers also believe that homocysteine may interfere with the clotting cascade and increase thrombosis. Clots can block blood flow, causing a

heart attack or stroke. High levels of homocysteine may be involved with atherosclerosis resulting in a gradual build up of fatty substances in the arteries, which may make blood vessels less flexible and so less able to widen to increase blood flow. Finally, it is contended that homocysteine may interact with lipids by oxidizing LDL cholesterol, making it a more significant risk factor for CAD, (7). Among these mechanisms, it is not sure which is the most viable, or if they work in combination.

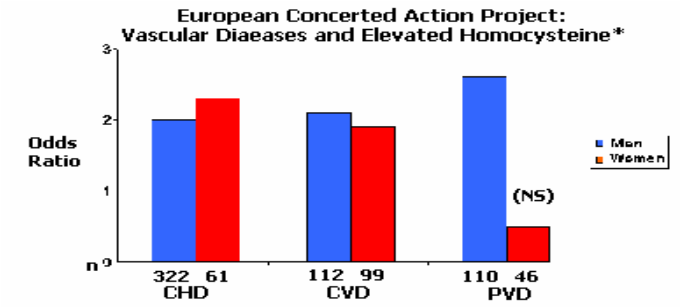

Fig. 2 - Top quintile [homocysteine < 12 μmol/l] compared to remainder (controls, n = 800) *Adapted from Graham JM, et al JAMA 1997;277:1775-1801*

Correlation between homocysteine and CAD

Studies done elsewhere have shown that there is some relationship between the increased homocysteine levels and CAD. In one of these studies, The European Concerted Action Project, (8) looked at 750 cases of athrosclerotic vascular disease and 800 control cases in man & woman less than 60yrs. (Fig. 2) They found that hyperhomocysteinaemia was the about 2.2 times higher than overall risk of CAD and was also a sole risk factor (8). In a similar Norwegian study, Nygard et al. (1997), they noted that the risk of death was proportional to total homocsyteine levels in 587 patients studied (9). Their findings indicated 3.8% with lowest levels (9 μmol/L) were able to survive up to five years longer as opposed to 24.7% with highest levels (>15 μmol/L) who did not survive beyond five years (Fig 3). The Framingham Study (US) prior to these studies, (10), noted that there was positive relationship between the blockages and the levels of homocysteine. Of the 418 men and 623 women between 67-97 yrs followed, dangerous obstructions of the carotid artery were noted in 43% men and 34% women (10).

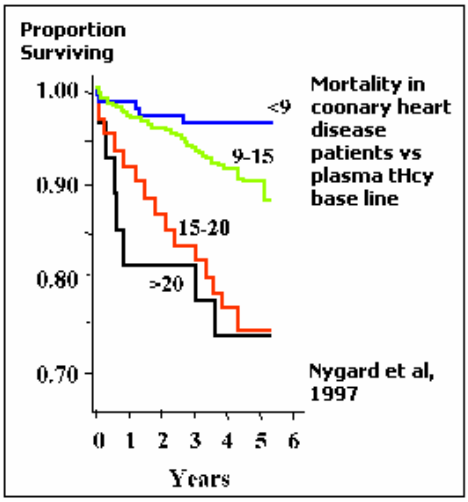

Fig.3 -Proportion of survival rate compared to homocysteine levels

At a recent seminar for the European Society of Cardiologists, Stockholm 2001 several papers were discussed on consequences of hyperhomocysteinaemia. Among them was a paper submitted by Schnyder et. al. who followed 549 patients for a year with successful coronary angioplasty. Their findings were consistent with other research papers presented and to the earlier studies undertaken by other researchers (11,12,13).
It was found that elevated homocysteine was significantly associated with cardiac deaths, target lesion revascularisation and major adverse cardiac events. They established that "total plasma homocysteine is a strong predictor of outcome after successful coronary angioplasty"

Laboratory Investigations
In a normal person, the level of homocysteine is within the range of 5 – 15μmol/L. At levels above 15 μmol/L it is considered hyperhomocysteinaemic. However, the CAD risk may begin to rise at levels as low as 10μmol/L (14).

The methionine-loading test is used to determine the homocysteine status by giving an oral dose of 0.1 g/kg L-methionine to a fasting subject and the blood drawn again at 6 hours. The difference between the basal and the 6-hour homocysteine level is referred to as the increase in total homocysteine (5). The laboratory methods in detection of homocysteine have developed quite dramatically. Earlier methods were quite laborious (15,16) until the development of radioenzymic methods (17,18,19). Recent methods developed by Frantez et al (20) now use enzyme conversion immunoassays for total homoeysteine. These methods use mouse monoclonal antibody directed against S-adenosylhomocysteine (SAH), which is formed after reductive cleavage of disulfide, and is allowed to react with adenosine in the presence of S-adenosylhomocysteine hydrolase, an enzyme-linked immunoassay. The method is rapid and precise and does not require the use of radioisotopes and chromatographic separation (20).

Treatment
Hyperhomocysteinaemia is a treatable disorder and in most cases, simple and cheap. In order to go onto a treatment the secondary causes have to be ruled out. The aim of the treatment is to reduce the concentration of homocysteine in the body and therefore the potential for further systemic damage. The first line of therapy may involve a multivitamin tablets containing 400 mg of folic acid. If the plasma homocysteine level is still elevated after 4-8 weeks of therapy, the patient is than given a daily regimen of 1-2 mg of folic acid, 1 mg of vitamin B12, and 100 mg of vitamin B6 as recommended. However, some cases may not be responsive to this therapy, especially renal failure patients, and the therapy may need to be assessed again (21).

Conclusion
Hyperhomocysteinaemia could be the missing link that could fit in the puzzle that most researchers are trying to equate with the unknown causes of CAD deaths. The continued interest in hyperhomocysteinaemia and with lots of papers being published recently, it is now quite evident that hyperhomocysteinaemia has significant association with the risk of cardiovascular events. Like other known risk factors, Homocysteine is now considered an independent risk factor and a strong predictor of CAD mortality.

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IODINE DEFICIENCY DISORDERS (IDD): FOCUS ON THE PROCESS AND SIGNIFICANCE OF MONITORING IN PNG

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Why the Need for Iodine:
Iodine is a micronutrient that is essential for the biosynthesis of the thyroid hormones Thyroxine (T_4) and Triiodothyronine (T_3). Adequate dietary intake of iodine is required for normal thyroid hormones production and for the maintenance of euthyroid state. On the other hand inadequate intake of iodine leads to insufficient production of thyroid hormones, causing adverse effects on tissue metabolism in adults and infants, more specifically it can affect crucial stages of prenatal and postnatal brain development (1; 2).

What Is Iodine Deficiency Disorders (Clinical And Subclinical)?
Inadequate production of thyroid hormones caused by abnormalities in the intake and proper utilization of iodine results in a spectrum of diseases collectively referred to as Iodine Deficiency Disorders (IDD) (3; 4; 5). In addition, concurrent exposure to naturally occurring thyroid anti-metabolites (Goitrogens) in the diet of susceptible individuals can enhance the expression of the IDD. {Goitrogens are substances, such as Thioglucosides, Goitrin, Thiocyanates, Isothiocyanates, Cyanogenic glucosides, Aliphatic disulphides, Phenolic compounds, Polycyclic Aromatic hydrocarbons, Flavonoids, Phthalate Esters, Inorganic salts, etc. that either interfere with iodine uptake, or alter the regulatory mechanisms of thyroid hormone synthesis and release, or alter the peripheral metabolism and excretion of the thyroid hormones (6)}. Some of these compounds are found in foodstuffs such as cabbage, broccoli, cauliflower, and soybeans, cassava used in tapioca, sweet potatoes, lima beans, maize, and millet while others are environmental pollutants (6).

The Clinical consequences of iodine deficiency are manifold. Iodine deficiency has been called the world's major cause of preventable mental retardation (1; 2; 5). The severity of IDD can vary from mild intellectual blunting to frank cretinism, a condition that includes gross mental retardation, deaf mutism, short stature, and various other defects. Fortunately, in most countries, the occurrence of severe iodine deficiency that leads to endemic cretinism has been reduced because of dietary iodine supplementation programs (2, 5). However, mild to moderate iodine deficiency persists in many countries (1, 7). In adults low intake of iodine can cause hypothyroidism, which is characterized by any or some of the following: low energy levels, dry, scaly or yellowish skin, tingling and numbness in extremities, weight gain, forgetfulness, personality changes, depression, anaemia, high blood cholesterol, and prolonged heavy periods in women (1, 2, 5). Low to moderate dietary iodine deficiency in the pregnant female may have even more serious consequences, because maternal iodine deficiency can severely compromise the thyroid status of the

foetus and the newborn child (1; 2). The frequency distribution of IQ in apparently normal children of iodine-deficient mothers is shifted towards low values as compared to matched controls, (i.e., children that were not exposed to iodine deficiency during the critical period of brain development, because of correction of the deficiency in the mothers before or during early gestation) (1; 2).

Subclinical Consequences of IDD:

Subclinical consequences of IDD are of great significance because of the more subtle degrees of mental impairment, which occur in apparently normal children with low dietary intake of iodine (7). Their manifestations include poor performance in school, reduced intellectual ability, and impaired work capacity (7). Investigations conducted in areas where moderate iodine deficiency is common, have demonstrated the presence of definite abnormalities in the Psychoneuromotor and intellectual development of children and adults who are clinically euthyroid and have no clinical signs or symptoms of iodine deficiency (1; 2; 5).

Prevalence of Goitre:

The size of the thyroid gland changes inversely in response to alteration in iodine intake, with a lag interval that can vary from a few months to several years. The prevalence of goitre is an index of the degree of long standing iodine deficiency and therefore is less sensitive, than urinary iodine in the evaluation of a recent change in the status of iodine nutrition in a population (2).

Prevention and Control of IDD:

In 1990, the World Health Assembly recognized that iodine deficiency is the world's greatest single cause of preventable mental retardation, and established the goal of eliminating this public health problem by the year 2000 (7). Universal salt iodization (USI), a policy of iodizing all salt used in households, catering, food processing and agriculture, is the agreed strategy for achieving this goal. During the past decade, USI has resulted in an unprecedented public health success in the field of non-communicable diseases (1; 7; 8). WHO, in collaboration with UNICEF, the International Council for the Control of Iodine Deficiency Disorders (ICCIDD) and other international organizations has played a crucial role in supporting national governments in their efforts to achieve this goal. Despite the achievements of the past decade, some problems remain. These problems include the following (8), Iodized salt is not reaching all target communities, in particular the most disadvantaged. Some salt producers are either unwilling to use the recommended iodization agent, potassium iodate (KIO_3) altogether, or they use less than the required amount; There is frequently unacceptable variation in the quality of iodized salt; Many salt iodization programs are not being adequately monitored; Lack of laboratory facilities in many countries impede monitoring of salt and urinary iodine levels.

The USI Policy, its significance and the process of monitoring:

Dietary Iodine:

Until recently the amount of iodine to be added to salt for a given population, was determined by a number of factors. The basis of the severity of IDD; the average per capita consumption of salt in the region; and the anticipated loss of iodine content in the salt that occurs between the time of production (or importation) and the time when the salt is actually consumed (7, 8).

According to WHO/UNICEF/ICCIDD expert committee, the main objective of any salt iodization program is to ensure that salt contains the recommended amount of iodine at the time of consumption (5, 7, 8, 9). In order to ensure this objective a regular system of salt monitoring must be instituted to periodically check the concentration of iodine in salt at various points in the distribution system, from production (or importation) to the point of consumption. Continuous monitoring of iodine levels in salt is one of the best and simplest ways of monitoring the entire IDD elimination program when USI is the intervention strategy (5, 8). Failure to monitor properly has been the major cause of breakdown of IDD control programs in a number of developing countries. In addition, poorly monitored programs of salt iodization in some countries have resulted in largely excessive iodine intake associated with risks of adverse health consequences such as Iodine-Induced Hyperthyroidism (IIH). Iodine concentration in salt at various points in the distribution system

can be monitored primarily by using reliable test kits (including recheck solutions) for iodine (iodate); a more accurate titration method can subsequently be used in a properly equipped biochemical laboratory (10, 11).

Urinary Iodine:
A distinction must be made, however, between the intake of iodine and the status of a population's iodine nutrition. The concentration of iodine in the urine (Urinary Iodine concentration UI, also called Urinary Iodine Excretion UIE) is an important indicator of the status of iodine nutrition of an individual. It is the prime biochemical variable used to measure the success of iodine supplementation in a population (4, 5, 8, 11). UI is the key biochemical marker of the very recent dietary intake of iodine, because under normal physiological conditions about 85% of ingested iodine is excreted in the urine (5, 8).

UI concentrations are useful when used in cross-sectional, epidemiological surveys in population samples of appropriate size (5, 8, 9). It is the biochemical index of choice for evaluating the degree of iodine deficiency and for developing strategies aimed at IDD elimination (5, 7, 8, 9).

The overall goal in measuring UI is to monitor and correct any existing iodine deficiency in a given population, using casual/random urine samples (5, 7, 11).

According to current WHO/UNICEF/ICCIDD expert committee recommendations, the iodine status of a given population can be accurately determined by assessing the average UI concentrations (5, 7, 9). The UI values obtained can be conveniently expressed either as a range with a median, or as proportions, using a series of cut-off points to indicate the severity of iodine deficiency.

In most cases, these values accurately reflect the extent of required intervention (3, 5, 9, 10).
The suggested cut-off points are as follows:
Median UI < 2 ug/dl, indicates severe iodine deficiency;
Median UI 2 – 4.9ug/dl indicates moderate iodine deficiency;
Median UI 5 – 9.9ug/dl indicates mild iodine deficiency;
Median 10 – 19.9ug/dl this is the optimal value;
Median 20 – 30ug/dl indicates risk of iodine-induced hyperthyroidism (IIH) within 5 – 10 years following introduction of iodized salt in susceptible individuals.

Median > 30ug/dl indicates risk of adverse health consequences, such as IIH, autoimmune thyroid disease.

It is important to note however, that the selection of samples for survey, and adequate sample size, are critical features in using UI as a reliable marker of iodine status in a given population (3; 5; 10).

Significance of IDD monitoring in PNG
IDD was identified in PNG as far back as 1957 (12). The first ever trials of iodized oil injections for the treatment of severe forms of IDD were conducted in PNG (13). Data obtained from schools on the Costal belt in Sogeri, Central Province, the Highlands, and Island areas show goitre rates ranging from 12.6% to 44% (12). This led to the conclusion that IDD is a public health problem in PNG. Between 1991 and 1993, limited surveys conducted among schoolchildren in the Highlands and costal, as well as Island provinces, concluded that goitre is not only common in the mountainous areas, but also in flat areas near the sea: 13% in Kimbe (New Britain Island) and 35% in Baiyer River Valley (WHP). In one district in Morobe mild IDD was reported in children between 8 – 10 years in 1997 (12; 13; 14).

In an attempt to eliminate IDD, and to comply with the international goal of USI, the Government of PNG amended the Pure Foods Act in June 1995, to prohibit the importation and/or sale of non-iodized salt in PNG (12). According to the Act, importation and sale of non-iodized salt in PNG was banned; all salt should

be iodized with potassium iodate (KIO_3); the recommended iodine content for all salt in PNG should be 20ppm (20 mg of iodine per kilogram of salt).

However, the estimated daily per capita salt consumption in PNG was not indicated. At the time of implementation of the Act, all iodized salt (20ppm) sold in PNG was imported from Australia. The Consumer Affairs Council (CAC) was empowered to promote and monitor the implementation of the Act (12, 13, 14).

How successfully this salt legislation (Act) has been implemented, and what its impact on the elimination of IDD in PNG has been, can be judged using two criteria (8): The major criterion is the achievement of the objectives in terms of process (i.e., universal salt iodization). The major indicator of process is the proportion of salt that is iodized and consumed, as measured, for example, by the proportion of households consuming iodized salt and by the Median urinary iodine (UI) concentration in the population.

The second criterion is the assessment of the impact of the strategy, i.e., the actual reduction in IDD. Impact indicators measure the reduction in the signs of iodine deficiency, such as reduced prevalence of goitre, improved function of the thyroid gland, or improved intelligence, and hence, improved educability of children.

Eight years after the enactment of the salt legislation in PNG, and Three years after the proposed date for the elimination of IDD as envisaged by the WHO/UNICEF/ICCIDD (7), only scanty scientific data are available on the status of the IDD program in PNG. A limited survey on the iodine content of salt in Lae city of PNG was carried out by Betty Amoa et.al (14) between, 1996 and 1997. There are no other scientific publications on the iodine content of salt in PNG, and absolutely no information on UI concentration among PNG population is currently available in scientific literature.

According to the information published in the “IDD prevalence and control program data” (15), there are no published scientific data to indicate systematic monitoring of the implementation of the salt legislation and the progress of the IDD program in PNG.

Some of the Nutritional objectives indicated in the PNG National Health Plan 2001 – 2010 HEALTH VISION 2010 are (16): To eliminate Iodine Deficiency Disorder by 2010; Maintain surveillance of and Monitor Iodine Deficiency Disorders and the Iodine content of Iodized Salts at the National level, Monitor the availability and utilization of iodized salt at the Provincial level.

In view of the lack of adequate scientific data on the progress and monitoring of the USI strategy for the elimination of IDD in PNG, and in line with the nutritional objective in the National Health Plan (Health Vision 2010), a multidisciplinary research project to be carried out in selected areas in PNG with the following aims and objectives is proposed.

To study the status of IDD as measured by goitre prevalence and median urinary iodine excretion (UIE) in primary school children aged 6 to 12 years. To determine the proportion of households using adequately iodized salt (i.e., iodine content of salt in ppm by titration method). To determine the average per capita consumption of salt in households; To determine proportion of retail shops selling adequately iodized salt

The laboratory facilities and the appropriate quality control used in this project will serve as the focal point for a national cross-sectional survey to access the progress of the IDD program. It will be used for systematic monitoring of urinary iodine concentration, (which is the key indicator recommended for assessing the impact of iodine deficiency control measures) and for monitoring the iodine content of salts in PNG.

Methods and Experimental Approach:
Study population
Schoolchildren in the age group 6 – 12 years will be enrolled in the study.

Collection of samples and methods of analysis:
The different brands of salt available in PNG and samples of salt used for preparing household meals will be collected from randomly selected households. Analysis of the iodine content in each salt sample will be carried out, using the standard Iodometric titration procedure recommended by the ICCIDD (17).

Urine samples: Casual urine sample will be used. Urinary Iodine concentration will be estimated by the sensitive colorimetric method of Sandell-Kolthoff reaction after digesting the urine with Ammonium Persulfate (5; 11).

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MONITORING THE DRUG THERAPY

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A. Introduction: Drugs are poisons in small doses (William Withering). Therapeutics is not just matching the name of a disease with the name of a disease. It involves application of rational knowledge, judgment, skill and wisdom in order to provide Individualized optimum therapy for the patients. When the drug is given, 4 BASIC questions need to be answered:
Is the Drug –
1. Getting into the body? → Pharmaceutical aspects
2. Getting to the site of action? → Pharmacokinetics of drug
3. Producing the desired Pharmacological Effect? → Pharmacodynamics

4. Effect being translated to Therapeutic effect ? →Therapeutic aspects
Answering these Qs. involves MONITORING OF THE DRUG THERAPY.
B. Monitoring Drug Therapy: What has to be monitored?
? Pharmacokinetics ? Pharmacodynamics ? Therapeutics (Therapeutic Efficacy)

B.I. MONITORING THERAPEUTIC EFFICACY OF DRUGS
1. Therapeutic Efficacy in Individuals: Many clinical 'indicators' can be easily monitored e.g.-
Improvement in Muscle Power after Anti-ChE therapy, Frequency of Anginal attacks and Decrease in rescue GTN tablets intake, Fall in body Weight after Diuretic therapy, etc.

2. Therapeutic Efficacy in Population: Population Health Indices indicate the success of any therapy, e.g. Immunization, Popular preventive measures e.g. Reduced Smoking & IHD, Lung Cancer, Respiratory Diseases, Weight Reduction & Diabetes, Hypertension, Ischemic Heart Disease, Arthritis, High Fiber diet & Diverticular diseases, Irritable Bowel Syndrome, and Hypocholesterolemic diet in Ischemic Heart Disease. Long Term Prophylactic measures e.g. Oral Contraceptives & Population Growth Rate; Secondary prophylaxis in MI by Aspirin/ β-Blockers; Anti-hypertensive therapy & Hypertensive sequelae, Antidiabetic therapy & Diabetic sequelae

B.II. MONITORING PHARMACODYNAMIC EFFECTS OF DRUGS
Some Pharmacological Effects of drugs are Easily Measurable e.g. Blood glucose levels (Diabetes); Prothrombin Time for anticoagulants, FEV_1 in asthma therapy, Serum Uric Acid levels in antigout therapy. However, monitoring pharmacological effect is not always easy e.g. in Mental Illnesses the pharmacodynamic end-point is not precise and calibrable. In such cases, Pharmacokinetics of the drug can be monitored.

B.III: MONITORING THE PHARMACOKINETICS OF DRUGS
Best option is to Monitor Drug Concentration at the Site of Action (in the tissue involved) as it correlates best with the Pharmacological / Clinical response. More often, it is not possible to measure them e.g. Digoxin levels in Heart, or the Phenytoin levels in Brain.
Next Best Option is to Monitor Plasma Drug Concentration because Plasma Drug Level is in Equilibrium with Drug Concentration at the site of action
Definition:
Therefore THERAPEUTIC DRUG MONITORING [TDM] is the assessment of drug response to plasma drug levels vis-à-vis the disease process leading to –→ Adjusting dose of drug in Clinically Rational manner & → Obtaining "a predictable response in each individual patient" →→ i.e. INDIVIDUALIZE the THERAPY

C. ALL CLINICAL SITUATIONS DO NOT BENEFIT FROM TDM – example
1. PLASMA CONCENTRATION "NOT WORTH the trouble of measuring": Because the clinical response can beeasily & finely calibrated, Therefore, the Dose Adjustment is very easy, e.g. Blood Pressure & Antihypertensives; Prothrombin Time & Anticoagulants; Blood Sugar & Antidiabetics; Bronchodilators in Asthma & FEV_1.

2. PLASMA CONCENTRATION DOES NOT CORRELATE WITH DRUG EFFECT: Effect persists though drug has been eliminated. The Target molecule [receptor/enzyme] is irreversibly destroyed as in 'HIT & RUN' drugs e.g. - Aspirin on platelets; Anticancer drugs; Irreversible Anti-Cholinesterases.

3. PLASMA CONCENTRATION MAY CORRELATE POORLY WITH EFFECT: as in following conditions- Inflammatory states lead to acute phase proteins leading to more binding of basic drugs (Lignocaine, Disopyramide). Total Plasma Drug Levels rise but free levels do not rise. Therefore, NO CONTROL of symptom is seen. Drug Metabolites: Assay method may not measure active metabolites e.g.

Benzodiazepines; or conversely, Inactive Metabolites are also estimated. In such cases, there is no use of monitoring Total Blood-Drug Level. Further, the estimation of Free Drug / Metabolites is more difficult.

Situations always benefited because plasma drug levels correlate well with clinical effects –

1. When aim of therapy is Prophylactic/Suppressive because Clinical episode is too infrequent to be useful for monitoring, Also clinical episode, even if rare, is harmful and, therefore, undesirable. Therefore, the Aim of Rx is to prevent occurrence [Prophylaxis] e.g. in Epilepsy, Cardiac Arrhythmia.

2. When Patients' Response cannot be easily quantitated: The end is not discrete and easily quantitable – e.g. Response to Antidepressants; or Therapeutic response declines beyond optimal plasma ranges [e.g. 50-110 μg/L of Nortryptyline (Therapeutic Window) & "Inverted U effect curve"].

3. When Drugs have Narrow Margin of Safety or Therapeutic Index (T.I.): Drugs like Digoxin, Phenytoin, Lithium, Gentamicin, etc. have Narrow Margin of Safety or Therapeutic Index (T.I.)

4. When Drugs have Non-Linear (Zero-order) Kinetics: Most drugs follow linear (First Order or Exponential) kinetics i.e. A fixed-fraction of drug in body is eliminated per unit time, and the (log) Dose-Concentration curve is linear over most part. However, some drugs follow Non-linear (Zero Order) kinetics i.e. Metabolizing "enzyme is in limited supply, which gets saturated early". Therefore, a fixed-amount of drug is eliminated per unit time. Therefore, further increase in dose causes prolongation of T ½. The '(log) Dose – plasma concentration' curve is linear only at low dose, and 'STEEPS' disproportionately thereafter, causing increase in response / toxicity un-predictably. PHENYTOIN is most important clinical example of this kind. NOMOGRAMS are used for dose titration in patients based on the plasma concentration estimates. Other examples of Zero order / Saturation kinetics are Ethanol and Salicylates.

5. When Inter-individual variation in pharmacokinetics is too HIGH: Variations in drug responses, and in plasma concentrations after same dose of a drug, are always expected phenomenon. However, Unusually High "Extent of Variation" warrants TDM of drugs concerned, e.g. Phenytoin, Warfarin, Theophylline.

6. When Physiological / Pathological variables are present:
Children require higher dose (mg/kg wt) than adults in case of some Antiepileptics e.g. Phenobarbitone. Pregnancy alters drug kinetics due to dilutional effect (increased body water content), Biotransformation of drugs by fetus, and Decreased plasma proteins causing more free drug levels and toxicity.Hepatic / Renal disease will decrease drug elimination and plasma drug levels would rise, leading to toxicity, e.g. Phenytoin in liver damage, Gentamicin in renal disease.

7. When Drug- Interaction is suspected due to Multi-Drug Therapy: Drug interactions alter drug response by Pharmaco-dynamic or Pharmaco-kinetic reasons; With 'Low Therapeutic Index drug', toxicity can result e.g. Lithium (by Thiazides), Digoxin (by Quinidine, Amiodarone), and Phenytoin which interacts with large number of drugs

8. When Therapeutic efficacy and Toxicity is difficult to distinguish example
Digoxin and some Antiarrhythmic drugs can both treat, and cause, some arrhythmias.
Phenytoin Toxicity itself can increase seizure frequency.
Gm –ve septicemia, OR Gentamicin used to treat it can both cause Renal Failure.

9. When Standard Drug Regimen fails & Non-Compliance by the Patient is suspected:
Noncompliance is a major cause of Therapeutic Failure. Factors leading to Noncompliance are -
ADRs leading to 'Intelligent Noncompliance'; Dissatisfaction (Poor Patient-Doctor relationship);
Forgetfulness (Old age, Psychiatric disorders); Complex frequent dosing schedule;
Inappropriate Health Beliefs; Family Instability, Poverty, Homelessness, etc

10. When Drug-Overdose Treatment & Monitoring is needed: To confirm a suspected overdose (poisoning), and to monitor the progress of overdosed patients;

D. Examples of Drugs with Proven Value from TDM:
Aminoglycoside Antibiotics (Gentamicin, Amikacin); Cardiac Glycosides (Digoxin, Digitoxin); Antiepileptics (Carbamazepine, Phenytoin); Cyclosporin, Lithium, Theophylline

E. Examples of Drugs where TDM is not yet proven clearly useful:
•Anti-arrhythmic Drugs •Methotrexate •Other Anticonvulsants •Tricyclic Antidepressants

F. INTERPRETING TDM DATA -
Plasma Therapeutic Concentration is a range, a statistical concept, & to be used only as a general guide.Some Patients will always be on Two Extreme Ends of the Frequency Distribution Curve (of plasma drug levels & drug responses). Therefore, some patients will show desired effect at plasma drug levels below average therapeutic range [~20 % Epilepsy patients are well controlled at Phenytoin levels below 10 μg/ml]. Some patients need plasma levels Above average Therapeutic Range [3-5 % Epilepsy patients need phenytoin levels >20 μg/ml for control], yet show no toxiciy at all. PATIENTS in above two situations DO NOT NEED DOSE ADJUSTMENTS to bring them inside the 'average / standard' therapeutic range]. Therefore, plasma drug levels must be interpreted in the backdrop of clinical response in each patient. Dose Increments: In case of Zero-Order drugs, dose increment must be very small [e.g. ¼ or ½ tab (25-50 mg) Phenytoin at weekly interval]. Compliance: If drug levels are sub-therapeutic repeatedly, must suspect non-compliance. Check compliance before increasing the dose. Success of TDM: most useful in Epilepsy control – more than 70% patients benefited on Monotherapy

G. TIME FOR SAMPLING
Monitor drug levels only after drug reaches steady state level i.e. Drug was taken for ~ 4-5 half lives.Some drugs lower own levels by auto-enzyme induction – e.g. Carbamazepine, Phenytoin → In such cases monitor 2-4 weeks after onset of therapy [levels will have stabilized]. If drug has short t ½, it is desirable to know both Peak (15-30 min after i.v. infusion) & Trough levels (just before next dose). For drugs with longer t½, it is sufficient to monitor just before next dose.

H. SOME DRUG ESTIMATION METHODS
IMMUNOASSAYS: FPIA (Fluorescence Polarization Immuno Assay) on TDx, AXSYM (Abbott), EMIT (Enzyme Multiplied Immunochemical Technique), RIA (Radio-Immuno Assay).
CHROMATOGRAPHIC ASSAYS: GLC (Gas Liquid Chromatography), HPLC (High Pressure Liquid Chromatography)

J. Concluding Remarks:
TDM is a powerful tool to ensure an individualized therapy with problematic drugs. The antiepileptic therapy has been revolutionized due the TDM concept. TDM is not same thing as getting the routine lab tests done (FBE, Urine -routine & Microscopic, etc). TDM requires a bridging specialist who can devote more time to deliberate on issues related to pharmacokinetics and pharmacodynamics of these special drugs, as well as understand the clinical response pattern developing in the specific individual over the preceding period of therapy. A hybrid of clinician and pharmacologist is the 'entity' one looks for such task.

Some like to call such a person as a "Clinical Pharmacologist".Traditionally (basic) pharmacology has been viewed as one discipline 'doing experiments on animals' but teaching theory of 'Human Pharmacology' – yet having nothing to do with the "human bedside therapeutics". This makes the discipline as neither here (animal / veterinary) nor there (human). In the developed countries, Clinical Pharmacology specialty as

separate from the Basic (? Pre-clinical / ? Non-clinical) Pharmacology has evolved. Developing countries have usually not been able to afford this luxury so far.

Like the Clinical Pharmacology unit in the Department of Pharmacology, SGS Medical College, Mumbai, India, which proved their value to the clinicians for 2-3 decades from within the traditional pharmacology environments, and then became first fully functional independent department of Clinical Pharmacology in India, still working with HPLC (instead of highly expensive automated equipments). The Pharmacology discipline in any university of developing country should strive to achieve a status of becoming useful in the patient service, in addition to the usual student teaching / learning activities.

THE MODERN APPROACH TO THE CARE OF DENTAL CARIES

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Introduction

Dental caries: It is a process that affects mineralised tissues of the teeth namely Enamel, Dentin and Cementum and is caused by the action of microorganisms on fermentable carbohydrates in the diet. It can ultimately result in demineralisation of the mineral portion of these tissues followed by disintegration of the minimal portion of these tissues followed by disintegration of the organic maternal. At the crystal level, initiation of the caries process may be inevitable but progression of a microscopic lesion to a clinically detectable lesion is not a certainty because in its early stages, the process can be arrested and a carious lesion would become inactive. However, the progression of the lesion into dentine can ultimately result in bacterial invasion and death of the pulp and spread of infection into the periapical tissues, causing pain. For Dental Caries to normally occurs, it takes about 3 years. Therefore, time is on the side of the patient to prevent it from forming “holes” in teeth.

In the past Dental Caries was considered an irreversible process but modern understanding of dental caries shows that it is reversible process. A person may suffer this disease and get filling done or even root canal treatment or crowns or bridges or even implants done in modern care. This seminar is mainly focussing on showing the effects of fluoride on enabling enamel caries to be healed.

Epidemiology

Dental Caries in the whole world is on the decline, in the industrialized countries, the caries was very high in the 1960’s, but then there was a sudden drop from the mid 70’s in the industrialized countries. In developing countries, caries has been not as high as in the industrialized countries. Fluoride toothpaste was introduced to the world in mid 70’s and most believe that this has resulted in the fall of dental caries both in the Industrialized and in Developing Countries.

In the few surveys done in Papua New Guinea, Dental Caries is not very high it is in fact low. In the last Dental survey done by Professor G. Davis and Dr. B. Gwale in 1990, shows a clear picture that in Papua New Guinea caries is high in the Highlands but low in the Islands. This may be due to the people in the Islands eating a lot of seafood, which has fluoride. In the Highlands where Tea Estates are found, people should be made aware that the tea plant in peculiar that it selectively absorbs fluoride from the soil and in fact plain tea could be used in a fluoride rinse. In fact, if one were to drink between 5-9 cups of plain tea or one would be obtaining the same benefits as living in a town having fluoridated water.

It must be mentioned that water fluoridation, which confers equal benefits to all who have access to the reticulated water supply. This was stopped in Port Moresby once the dental school was closed. This is one way where the fluoride benefits could be equitably distributed whether a person is in a settlement or living in a wealthy part of the town the benefits are the same as they drink the same water containing the proper amount of fluoride.

Aetiology of Dental Caries
For dental caries to occur microorganisms should act on fermentable carbohydrate to produce acids to demineralize the enamel, dentine and cementum.

1. Possible Interventions - reduce intake cariogenic sugar (primarily sucrose, glucose & fracture)
2. Possible Interventions reduce strep mutans numbers by: reduction of sugar intake, active or passive immunization
3. Possible Interventions, avoid frequent sucrose intake (snacking) stimulate salivary flow and sugar clearance

Possible Interventions, water and other types of fluoridation, prevention and post eruptive maturation, fissure sealing, remineralizing solutions, properly contured restoration

Importance of Early Detection of Dental Caries
In the modern approach to the care of dental caries, one of the important skills taught to a dentist is this. The dentist is able to detect a surface discoloration – white/brown spot on the surface of a tooth. This demineralised portion could be remineralised, in fact the remineralised portion is more resistant to dental decay (fluorapatite) than normal hydroxyapatite crystals observed in normal enamel.
This preventive approach to combating the disease is the modern approach it has resulted in emphasis of dental care being extended to antenatal clinics and well baby clinics since caries is an infectious disease.

For detection of dental caries there should be, good visualization, constant source of light contrast, be able to direct light to one point, tooth should be dried well, and the dental probe should be used as a single tufted wire brush to remove debris and plaque use of x-rays.

Today apart from x-rays even electronic caries monitors propriety kits etc. are being utilized to monitor carious lesions. This skill by the modern dentist is being utilized to detect early enamel lesion and treat by use of fluoride etc. Dentistry presently is moving away from surgery and moving towards medicine

Polarising electronic microscopic studies have shown that the early enamel caries lesion consists of four different regions namely an outer enamel zone, inner body of the lesion and a still inner portion that appears dark and the innermost Zone, which is the translucent zone. The refractive index of enamel is 1.66 and that of water is 1.33 and air 1.0. When air is blown on to the tooth, the air blow out the water and due to scatting of light lesion appears white. The new modern approach encourages patients who have such lesions to make use of fluoride to remineralise this portion of tooth. If caries results in a cavity, the approach has been to use mechanical, rotary – handpieces and burs. Mechanical, non-rotary – hand excavator, air abrasion, air polishing, ultrasonics, sono-abrassion. Chemo- mechanical – carisolv, enzymes photo – ablation – lasers

In this country, we have been able to convince the authorities that fluoride toothpaste is not a cosmetic product but a medical product as a result we have been able to remove the tax on toothpaste and thus the cost of toothpaste has been brought down. We have also started teaching the new biological aspect to cavity preparation this is as the modern approach to do filling. In addition, we have started a program to cover the entire country of Papua New Guinea to get benefits of modern technology and materials to villages. This has been done in the Islands region and the Momase region. – The ART Technique; The

importance of dietary counseling, and stressing the use of fluoride has resulted in helping to bring down dental caries all over the world.
Molecular diagnosis for caries detection; Better remineralising solutions; Better ways to introduce fluoride; Better adhesive materials

Summary
The modern dentist owing to a better understanding of dental caries process has now embarked on newer approaches to control dental caries by utilizing ones eyes, wearing loupes, etc. Once caries is detected the patient is shown region of teeth where white spot lesion is. He too by his own activities helps to heal the lesion.

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THE THREE PHASES OF HIV: HAVE WE BEEN ASKING THE RIGHT QUESTIONS?

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Introduction
The seminar reflected on the HIV/AIDS pandemic, which is still rising at exponential rate. The leading question was considered based on a two-point working premise presented as If a proposed solution to a problem does not adequately address all facets either of the problem then it is the wrong solution being applied, the problem algorithms have not been rigorously defined, or there is lack of resolve to implement the solution. He who does not learn from history is condemned to repeat.

The problem definition consisted of review data that indicated globally that by 2002 the number of people living with HIV/AIDS had reached 42 million of whom 5 million were newly infected and that 3.1 million had already died (1). It was further revealed that the global statistics indicated that the epidemic was growing at the rate of 14,000 infections per day, which implied 5 million per year. The majority of the new infection was occurring in the developing world (1). For countries in the Western Pacific region where PNG is (excluding Australia) the statistics of the epidemic show an exponential rise (2).

In order to tackle the question: how well have we coped with the control of this epidemic? Hence, the leading question. Have we been asking the correct questions and hence seeking the right answers? Primarily it was noted that HIV/AIDS is not the first epidemic disease in the world to threaten a large

segment of society! There have been others. Therefore, it was important to examine the current epidemic in relation to past epidemics in order to assess how well the current epidemic has been tackled. Societal responses to previous epidemics were reviewed in detail* and are summarized here.

The simplest disease/epidemic control examined were the ancient Hebrews who were a small deeply religious group whose culture dictated that appearance of eruptions (e.g. leprosy) on the body was a manifestation of sinfulness. The sufferer was segregated until he was cleansed. If the disease were contagious, other people would thus be spared.

By far the most important epidemic in history was the bubonic plague that affected Europe from the middle of the 14th century, killed 25 million people (or 1/3 population) and lasted for 150 years (3). A number of factors in the preceding 200 years had facilitated the rise of epidemic; these included:

i. Between the 11th and 12th centuries Europe was politically stable.
ii. Diseases were at minimal level.
iii. The weather was good and food production rose several folds.
iv. Population grew sharply from 25 million in 950 to 75 million by 1250.
v. At about 1300 the mean temperature in Europe dropped followed by widespread crop failures.
vi. Due to famine unchecked urban migration ensued, giving rise to serious poverty and overcrowding.
vii. With the poor hygiene that prevailed huge rat populations thrived.
viii. By mid-14th century overland travel was efficient enough to carry the disease westward to Europe from Asia where it was already established.
ix. Poor understanding of cause and transmission of the disease enabled recurrent episodes of the epidemic in the next 150 years to hold European population at about 50 million.

The major impact of this epidemic was four fold. It killed over 25 million people, caused medicine of the time to be questioned as well as enabling herbal remedies of unproven efficacy to be adopted. It led to new scientifically based-thinking leading to formulation of theories of contagion as well as developing quarantine rules and in part influenced the Reformation, as the accepted practices of the Christian church were perceived as a failure during the epidemic.

Next came, the Influenza a pandemic of 1918-19, which started in US, spread to Europe then to the rest of the world. By the time it petered out in 1919, it had killed 40 million people worldwide. This epidemic was by comparison a short-lived one with no lasting impact.

The next significant epidemic was a cholera outbreak in USA, which occurred in three successive waves in 1832, 1849 and 1866. Because of cholera, the New York Legislature enacted laws to set up the NY City Board of Health to enforce quarantine regulations and public food hygiene.

Syphilis is another disease that reached epidemic proportions. Even though by the turn of the 19th century syphilis was declining (because of improved hygiene), doctors feared that its spread to all human species was unavoidable (4)

Results / Discussion

Faced with an epidemic, almost invariably the first reaction of virtually all governments is a denial that the disease was occurring. When the fist six cases of cholera were announced on 26th June 1832, New Yorkers attacked the announcement as being premature or unwarranted and thus refused to be concerned with it. It took six weeks to accept the fact by which time the epidemic was raging out of control (3).

After the influenza outbreak in the USA, the epidemic spread to Europe. First, each affected country in Europe denied there was influenza within its borders. Later the French blamed the Spaniards for the epidemic while England described it as a disease of the French (3).

Once an epidemic is established in a given country a scapegoat is quickly found to pin blame on. In the 14th century, the Jews were blamed for causing the bubonic plague by poisoning wells though it was killing them too! The cholera epidemic of USA was seen as God's punishment of the poor for their idleness and the prostitutes as it was deemed that moral failing was the cause of the disease even though cholera is not a venereal disease. The Spaniards were picked as the culprits by the French for the influenza epidemic while England saw it as a disease of the French. However, the truth of the matter remains that:

> Epidemics occur in part because old diseases are not yet understood or new diseases have arisen. In either case, physicians do not have the knowledge either to prevent the epidemic or to treat its victims efficiently. As a result, society views the physicians and medicine of the time as having failed. Many alternate therapies of dubious efficacies arise and get adopted (3).

Epidemics also spawn many laws aimed at arresting the epidemic fast but then linger on long after the cause for which they were enacted is removed.

Syphilis and gonorrhea are two venereal diseases that may result in mental illness and sterility respectively. During the time when they raged at epidemic levels it was recognized that sex education was required to stem their spread, yet remnants of 'Victorian respectability' made it impossible to discuss venereal diseases publicly. *It was socially a greater sin to mention venereal diseases in public than to privately contract it.*

In response to the complaints about a large number of middle class-wives infected by their husbands who had contracted the diseases from prostitutes, physicians actively disseminated falsehood by promoting the idea of casual nonsexual transmission of syphilis and gonorrhea. It was thus more important to protect the 'reputation' of middle-class men than to elucidate the truth about these diseases (4).

With the foregoing brief review of past epidemics and their control responses, let us now examine the rise and spread of HIV/AIDS and gauge societal response to the control efforts of this epidemic.

The rise and spread of HIV/AIDS

As with plague the rise and spread of HIV/AIDS throughout the world needed a number of factors to be in place to facilitate its spread and these included:

i. Development of rapid, frequent and inexpensive air travel among nations
ii. Introduction of HIV/AIDS into a smaller closed community of homosexual males at the time when sexual activity and promiscuity was running rampant. This served to amplify this disease by widely spreading it in that community.
iii. Presence of a large population of bisexual intravenous drug users sharing poorly sterilized needles to provide a bridge for the disease to cross to the rest of the society.
iv. Increased societal tolerance of promiscuity permeating entire populations
v. Persistence of socio-cultural and moral contempt for sex education of any form at all
vi. Confusion between sexuality and sex education

As with other epidemics, at the beginning it was denied that there was a major epidemic underway. The homosexuals and intravenous drug users were blamed by Americans for starting and spreading the epidemic. The rest of the world blamed Africa for conjuring up the disease.

These attitudes are reminiscent of the 19th century view that poverty was a moral failing and therefore cholera was God's wrath on the poor and prostitutes because of their idleness or moral failing. However, those views were fundamentally flaw and would be laughable if present day views of HIV/AIDS were radically different in nature (and no stigmatization of the victims existed). Furthermore, as with other epidemics medicine has been criticized for failing to stop the HIV/AIDS epidemic; and following hard on this 'failure' is the rise and propagation of alternate remedies of even more dubious efficacy.

HIV/AIDS Epidemic in PNG: In this country, the first six cases of HIV/AIDS were reported in 1987 in NCD. From that time on the epidemic spread to all provinces and its increase has been exponential reaching 914 and341 HIV and AIDS cases respectively by 1997and by 2002 those infected passed the 6000 mark (2) with projections of over 15,000. Many factors fan and exacerbate the epidemic. The most important being resistance by people to attitude change linked to the perception that open discussion of sex matters is not in the Melanesian culture. Moreover, cultural practices such as polygamy, wife inheritance and other vices that allow youngsters to be sexually active at an early age add to the problem. Rape, alcohol abuse, and prostitution, as frequently reported in the media (5-12) are other conspicuous factors promoting the epidemic.

The three 'phases' of HIV/AIDS Epidemic

Every disease that develops into an epidemic passes through a number of phases whose length varies with the intensity of hysteria it whips up in the affected community. For HIV/AIDS, there are three identifiable characteristic phases; namely (a) Denial and Blame Casting, (b) Hysteria and Frustration and (c) Institutionalization or internalization and incorporation into folklore. The last of these phases usually represents the settling-in of the disease and represents the worst form scenario. For an epidemic that kills or disables many this final phase must be prevented from being established.

Bell the Dragon: controlling the epidemic

Of necessity, control of HIV/AIDS will be multifaceted, arduous, and protracted. Great strides have been made to bring awareness to most people but a lot needs to done to change people's attitudes and their habits. Is it possible to do so? The answer is yes! An insight of this possibility is seen from the latest figures of global infection rates. It shows a decline in all developed countries and exemplified by the eleven-year data on reported HIV cases in Australia (1) where a halving of the figure of 1600 in 1989 and a decline of AIDS figures from 1000 in 1994 to about 200 by 2000.

How did they do it?

In Australia, like other developed countries, the success is attributed to a highly literate society (except for Aborigines) reinforced by well-developed communication infrastructure where the society was able to evaluate and utilize available protective measures. A similar decline for Uganda was due to the active role of its president in the control programs. The political leader was seen as a respected source for the people.

The response and attitude of governments play a crucial role in the control and shaping of the attitudes of people towards any epidemic. If this is not done effectively, the government may be entangled in a web of contradiction and ineffective control activity. All epidemics are accompanied by exaggerated societal fear, which Swenson (3) neatly sums up thus:

> *In fact, this paralysing fear is the single major obstacle to instituting reasonable, rational public policies*.

Many governments found it convenient to accept WHO control measures, which they then delegated to National AIDS Control Programs (ACP) and stopped there. The use of the condoms should and was meant to be a temporary phase while, more permanent rational solutions, were developed and implemented; instead, these temporary measures have become permanent solutions. There is a good reason for doubting this easy solution. Data from condom-use in family planning (13) show effectiveness of about 88-94%. Meaning there is an inherent failure rate of 6-12%. Translated into a permanent solution for HIV/AIDS control this will mean a window of opportunity of 6-12% for the virus. Thus this ambivalent, almost non-committal attitude by governments creates doubts and uncertainty in the minds of the citizens about the seriousness of the problem.

In developing countries, HIV/AIDS is mainly transmitted by sexual intercourse. It does not require a lot of imagination to see that the only way to control and tame HIV/AIDS is to educate the people about this by

speaking specifically and directly about sex and sexual transmission of HIV/AIDS. Here then lies the solution, and paradoxically, the problem to implement it. Current control policies rely heavily on the model of broadcasting information and counselling identified victims. Unfortunately, this approach needs sums of money beyond the budgetary allocations of most ACPs. So how can the coverage are made more effective with limited resources? An unprecedented openness in handling the epidemic involving all political and other public role models is required. In the opinion of the author, there is an urgent need to address the following:-

- There remains a lingering 'Victorian prudence' that direct and explicit discussion of the sexual transmission of HIV/AIDS is not in the culture of the affected society. However, how could it have been when the epidemic appeared only some twenty years ago? It is in response to this crisis that the very culture being defended must be enlisted to deal with the crisis.
- Hesitance to come to grips with the HIV/AIDS crisis led to use of disguised and vague messages that have not served the purpose fully just as the Victorian sex education discussed sexual aspects of insects, animals and even flowers but not human sexual transmission of syphilis and gonorrhea with the result that these two disease became internalized in every society
- It is important to tap and harness cultural perspective of the target communities in the fight against HIV/AIDS. The culture has to adapt rather than 'be protected' as it will not survive if its entire people succumb to HIV/AIDS.
- Most people of different social and education level respect public figures that in turn influence their lives. These leaders represent a huge resource for fighting the epidemic.
- HIV/AIDS is far too important to be solely left in the hands of multidisciplinary councils. The 'wantok' system and religious leaders should be involved to extend the fight into the grassroots once the crucial message about the current epidemic is made known to them.

HIV/AIDS Policy and Planning Unit

Given the foregoing discussion it is a matter of urgency that an HIV/AIDS Policy and Planning Unit be formed in the school with the following express functions:-

- Innovation, development, and appraisal of new culturally sensitive technologies for the control of the HIV/AIDS epidemic
- Impact assessment of technologies that are currently in use
- Continuous reinforcement of technologies found to be effective.
- Instituting, running and maintaining a continuous dialogue with mass communicators: politicians, Religious and wantok leaders, 'big men' and chiefs.

Through this unit the motto "learning from history" shall be met and avoid being "condemned to repeat previous mistakes". It must be remembered that fact that if a proposed solution to a problem does not adequately address all the facets of the problem then either the wrong solution is applied or the problem algorithms have not been rigorously defined or we simply lack the resolve to implement the solution. Time is not on our side.

Conclusion

It has been shown that present day societal response to an epidemic, despite a higher level of general emancipation and greater technological development, is not much different from that of the 'black death' era. The creation of nation-states with transparent borders to international travel has, in some cases aided the epidemic. It has also been demonstrated that the HIV/AIDS pandemic can be controlled if tenacious adherence to customs, which are ill prepared to handle the new crisis are opened to visualize the danger. Allowing different role models to participate actively in the fight against the epidemic will speed up its control. A Policy and Planning unit should be set up spearhead a culturally adoptive fight against the pandemic. (* For a more complete discussion see the full review available in the Medical Library)

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ZINC: THE CONTROVERSIAL TRACE ELEMENT

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Introduction:
Malnutrition among children in developing countries is thought to be the underlying cause of a least half of the deaths and a substantial portion of the infectious disease morbidity (1).

Recent scientific evidence has modified the idea that Protein-Calorie deficiency is the major course of malnutrition in developing countries (1, 2). Deficiencies of specific micronutrients have been recognized to be partly responsible for the severity of the infectious disease morbidity in malnourished children (2). For example, Supplementation with iron and Vitamin A reduces child mortality (2, 3). This is considered one of the most cost-effective health interventions in the developing countries (3). A number of recent studies have demonstrated that Zn supplementation reduce the duration and severity of diarrhea, respiratory infections, including pneumonia, and malaria, while improving immunocompetence in children (2, 3). The results of these studies indicate that Zinc may be another specific micronutrient for which there is widespread deficiency in developing countries and that great benefit can be achieved by supplementation.

Why Is Zn A Significant Trace Element?
Zinc is present in over 300 Metalloproteins with wide range of biochemical functions (4, 5):
Some of the Metalloproteins that require Zinc for normal functioning include the following (2, 4, 5, 6, 7): Carbonic Anhydrase (low Zn may affect the regulation of HCO_3^- ion); Alcohol Dehydrogenase (low Zn affect metabolism of alcohol. NB; alcohol increases loss of Zn in the urine). Nucleoside Phosphorylase (low Zn may affect the Salvage pathway and may also result in accumulation of toxic levels of Nucleotides, leading to impaired cell division or cell death). Lactate Dehydrogenase (low Zn may adversely affect CHO metabolism in mature red cells and muscle tissue); Glutamine Synthetase and Glutamate Dehydrogenase (low Zn may lead to accumulation of NH_3 in plasma); Prolyl Hydroxylase (low Zn may affect post-translational modification of Collagen); Porphobilinogen (PBG) Synthase (low Zn may affect biosynthesis of Haem); Phospholipase C (low Zn affect activation of this enzyme and therefore affect the formation of Inositol Triphosphate and Diacylglycerol – two important second messengers that controls release of

intracellular Ca^{+} ions and stimulation of Protein Kinase C, respectively thus affecting a large number of cellular reactions)

A number of Regulatory and transport proteins that require zinc include (6, 7): Gustin, which is a Zn-dependent polypeptide found in saliva. Gustin is essential for normal development of taste buds and normal taste acuity. The loss of taste acuity is usually linked to decreased salivary Zn concentration (thus the decreased taste acuity in Zn deficient individuals). Metallothioneins (Zn induces biosynthesis of MT in the intestine, liver and kidney. MT is involved in the uptake and regulation of Zn and Cu). Gene-regulatory proteins (e.g., "Zinc finger motif" – involved in sequence-specific DNA recognition and Gene expression)

How Does Zn Influence Cell Replication and Thus Growth And Maturation?
Zn influences the activity of multiple enzymes at the basic levels of replication and transcription (5, 6, 7). These include DNA Polymerase (the major enzyme regulating DNA replication), Thymidine Kinase (the enzyme that catalyzes the phosphorylation of Thymidine to form dTMP), DNA –dependent RNA Polymerase, Terminal Deoxyribonucleotidyl Transferase, Aminoacyl transferase RNA synthetase, and a family of Transcriptional regulators known as Zinc-Finger DNA binding proteins. Zn is required for expression of multiple genes regulating mitosis. Thus the requirement of Zn for normal cellular growth and differentiation may underlie the impairment of physical growth that is the hallmark of Zn deficiency in childhood and may also contribute to impaired function of the developing brain of the Zn-deficient infant for which evidence continue to accumulate (5).

Modulates Metabolism Of Vitamin A:
Zn regulates vitamin A absorption and is required for the biosynthesis of retinol-binding protein in the liver. The transportation of retinol from the liver, to other organs is possible only if hepatocellular secretion can take place via zinc accumulation on the so-called Retinol-binding protein (5, 6, 7). Zn is required for the biosynthesis of Retinol dehydrogenase, an enzyme that catalyzes the oxidative conversion of Retinol to Retinaldehyde in the intestine, liver, testes, and other tissues, including the retina of eye where this Zn-dependent enzyme participates in the visual cycle (a process that is necessary for vision, thus the impaired dark adaptation in Zn deficient individuals). It is well known that Vitamin A deficiency in infants is associated with increased morbidity and mortality, which may be due to increased severity of infections. This situation is made more severe in infants with low/moderate intake of Zn (8, 9).

Dietary Patterns That May Result In Inadequate Zn Intake:
Cereal and legume-based diets, which are not fermented are potentially high in Phytate, a potent inhibitor of Zn absorption, and thus reduce the amount of absorbable Zinc from the diet (5, 10). (A simple remedy is by germination and fermentation of the cereal and legumes to reduce the Phytate content via the action of Phytase. Soaking also removes the water-soluble phytate from cereals and legumes). A number of nutritional studies (2, 5, 10) have shown that Diets based on starchy roots and tubers with a low content of flesh foods have a low Zinc content. Diets based exclusively or predominantly on plant products have relatively low Zinc contents and poor absorption of Zinc. (Zinc absorption can be enhanced by Citrate, Vitamin C, High dietary protein, and Lactose). Consumption of colored drinks containing the yellow food dye "Tartrazine" may contribute to reduce plasma Zn in young children. The yellow food dye binds Zn in the blood, as a chelating agent, thus reducing plasma Zn level (5).

Zinc Nutriture in Infants:
The first six months of life are a period of rapid growth, and Zn intake varies with the mode of feeding (2). The relatively high Zinc requirements during this period can be met satisfactory from breast-milk alone for most healthy infants. The infant is able to utilize Zn from hepatic Zn thionein for several weeks postpartum to supplement Zn derived from breast-milk (2, 5). The bioavailability of Zinc in breast milk is very high (80%) compared to whey adjusted cow's milk (35%), even thought the concentration of Zn in breast milk is lower than in cow's milk (2, 3). The difference in bioavailability is due to higher levels of Citrate and the present of

Lactoferin in Human breast milk, compared to the high levels of Phytate, Calcium and Casein in cow's milk (2, 5). Healthy infants fed exclusively on breast milk for 4 to 6 months usually do not develop Zinc deficiency (2, 3, 5). Several researchers (2, 4, 5) have suggested the possibility of suboptimal Zn status in infants after six months breast-feeding.

It is well known that Zn content of breast milk falls with the duration of lactation. From six months to two years of age, adequacy of Zinc intake becomes highly dependent on the amount and bioavailability of Zinc from Complementary foods. Thus, prolonged breast-feeding without adequately prepared Complementary foods may reduce an infant's Zn intake, thereby increasing the risk of Zn deficiency (2, 4, 5, 11). The breast-fed, low birth weight infant is usually at risk of developing Zn deficiency because of increased requirements, potentially lower intake, and/or lower absorption efficiency.

Zn deficiency may also occur in infants fed with cow's milk, because of the high levels of Phytate, Calcium and Casein in cow's milk that impairs Zn absorption. The same holds true for Soymilk, which contains high Phytate level (2). Thus, from the nutritional and biochemical point of view, the following recommendations can be made (2, 5). Promote (exclusive) breast-feeding for about four to six months (a standard UNICEF concept); Identify Complementary foods that ensure improved intake of Zn (and other Micronutrients) from six months onwards, and explore ways to enhance adequate intake and absorption of Zn, other micronutrients, energy and protein by infants. (Note that Zinc supplementation enhances linear growth and significantly reduces the incidence of anaemia. Stunted children benefit more than non-stunted children; children of up to 24 months of age benefit more than older children.)

Clinical and Subclinical Features of Zn Deficiency:

The biochemical correlates of the clinical features of Zn deficiency still lack adequate definitions (2, 4, 5). This includes the non-specific nature of the deleterious effects of Zn deficiency on human health and development. For example, it is now clear that lesser degree of Zn deficiency are more common than was appreciated and that the subclinical deficiency of Zn contributes to an increased incidence and severity of common but important infections such as diarrhea and pneumonia in children (2, 3, 4, 5, 9). Hence, clinical features of Zn deficiency do not give the same strong clue to the existence of this deficiency as, for example does hypochromic anemia to iron deficiency (2, 5).

It is much more probable that zinc deficiency would be encountered when it presents with a subtle non-specific effect such as, jitteriness, tremor, weight loss, failure to thrive in infants or decreased taste acuity in adults (2, 5). Other features of zinc deficiency include, poor appetite, taste/smell dysfunction, impaired wound healing, immunodeficiency, abnormal secondary sexual development and hypogonadism in juvenile males, infertility in adult males, delayed onset of menstruation in juvenile females, amenorrhea in adult females, defective visual dark adaptation, etc. (2, 3, 4, 5, 9).

Assessment Of Zn Status – The Controversies!:

It is difficult to assess Zn status because Zn has a dynamic metabolic state – plasma Zn turns over 150 times a day in normal individuals, and when Zn is low in the diet, the body reduces the excretion of Zn in order to preserve Zn store (2, 4, 5). Plasma Zn concentration are decreased during the acute phase of illness (4). Thus, the observation by several researchers (2, 4, 5, 6) that plasma Zn concentration may be less useful as an indicator of Zn status in individuals and populations in low-income countries, where high prevalence rates of infections are common.

A number of recent community-based assessments of Zn status in children found no association between the presence of infection and plasma Zn concentration (12, 13). The reasons for such controversial results may be due to a number of factors: Reduced severity of infections typically encountered in community settings; Plasma level of albumin; Time of sampling in relation to meals; Diurnal variations – time of day

sampling was done; Non-specific decrease as a result of an acute phase response following infection, etc. These factors have been reported to have greater effect on plasma Zn concentration than common childhood infections (5, 12).

It is well documented that most microorganisms require Zn for basic cellular processes (4, 5, 14). During the acute phase response, Zn is redistributed from plasma to the liver and lymphocytes (4, 14). An adaptive response by the host intended to deprive invading pathogens of Zn. This statement itself is controversial because high concentration of Zn has been shown to be microbicidal (4, 6, 14). For example, the relatively low frequency of urinary tract infections in men is said to be partly due to the very high Zn concentration in semen (6). However, with regards to Zn assessment, available data suggests that the mean plasma Zn concentration may be a useful indicator of population Zn status in developing countries, despite the elevated rates of infection that are frequently observed.

How can Zn Status in Children be assessed?
There are some basic steps recommended (if you intend to contribute to the ongoing debate in terms of research. Determine the amount and sources of Zn in the diet; Determine the amount of phytate and fiber in the diet; Calculate the diet Zn/phytate molar ratio (A ratio greater than 15 indicates poor bioavailability); Measure plasma Zn concentration (value less than 9.2 μmol/dl indicates possible Subclinical deficiency); Zn status can also be indicated by measuring whether growth rate of a child is affected by Zn supplementation (2).

Effect of Zn on Diarrhoea:
A number of research studies (2, 4, 12, 13, 14) have show that most children with acute diarrhoea had low levels of plasma Zn. These low Zn levels were associated with longer diarrhoeal episodes (12, 13). Diarrhea is associated with an increased loss of Zn in faeces, thus putting affected infants at an increased risk of Zn deficiency (4, 12, 13). Daily Zn supplements resulted in a marked reduction in duration of diarrhoea and frequency of stool passage, regardless of the presence of viral enteropathogens (12, 13).

Effect of Zn on Malaria:
Cross-section studies among school-age children in Papua New Guinea and in pregnant women in Malawi showed inverse association between Zn status and P. falciparum parasitemia (14, 15). Anuraj Shankar (15) a scientist at the John Hopkins University School of Hygiene and Public Health recently carried out a placebo-controlled trial of Zn supplementation of preschool children in Papua New Guinea.

The study shows that Zn supplementation reduced the frequency of health center attendance due to P. falciparum malaria by 38%. Moreover, a 69% reduction was observed for malaria episodes accompanied by high levels of parasitemia (> 100, 000 parasites/μL), suggesting that Zn may preferentially protect against more severe malaria episodes. According to Shankar (15), Zn does not reduce the incidence of malaria but reduces the number of parasites that cause illness and thus its severity.

According to Ananda Prasad, (the first scientist to link Zn to human growth in the 1960s) this may be due to insufficient Zn levels, which affect the development and functioning of most immunological cells and inhibit cell-mediated immune responses (14). The general opinion was that if these findings are confirmed by other studies in different countries it could provide a much, needed weapon in the fight against malaria. The department of Tropical Hygiene and Public Health in Ruprechi Karls University, Germany design a study to check the findings of Anuraj (16).

A randomized double blind placebo controlled trial was carried out in West African children (in Bokina Faso). – According to the results of this study, “No evidence for Zn supplementation being effective against falciparum malaria in a population of West African children with a high prevalence of malnutrition and Zn deficiency was found”. Recipients of Zn were no different for number of episodes of falciparum malaria or

any other malarimetric measurements from the recipients of placebo. The finding was for all age groups and was consistently seen during both the longitudinal study and the cross sectional surveys (16).

Is this a controversy or is it due to different response to Zn because of the endemic nature of malaria in the different communities studied? So far, however, it is two against one. More research is need in this area.

Possible Effects of Excess Intake of Zinc:
Despite the fact that Zn is considered the least toxic trace element, over consumption can have toxic effects (2, 5, 6). Toxicity can occur when approximately 10 times the daily dose is ingested (over 50 mg for infant, between 150 to 200 mg for adults). Unnecessary intake of supplemented Zn can contribute to nutrient imbalances by interfering with the absorption of other trace elements such as iron and copper. Most people can meet their daily Zn requirements by choosing variety of Zn-rich foods as part of a balanced diet. Adverse effects associated with chronic use of supplemented Zn include suppression of immune responses and decrease in HDL-Cholesterol (5, 6). Long-term toxicity can result in anaemia, depressed growth, haemorrhages in the bone joints, iron and copper deficiency, etc (5, 6).

Laboratory Assessment:
While Zn status can be assessed, there are no good clinical tests for Zn deficiency. However, serum Zinc concentrations persistently below 5umol/L is suggestive of impending clinical deficiency and requires further investigation.

Conclusion:
It is important to indicate at this point that policy makers should identify opportunities to integrate Zinc intervention into ongoing primary health care programs and/or existing nutrition and public health programs. This is because single-element micronutrient deficiencies are usually the exception rather than the rule, thus, it is logical to develop multi-micronutrient interventions. It is however necessary to evaluate the Zinc status of the population before developing suitable intervention programs.

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