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Understanding of Small, Minimum and Large Sample Size and Its Clinical Implications

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A basic important question under planning of any study including randomized controlled clinical trial (RCT), especially of phase III, is the required sample size [1, 2]. My experience of working in the field of epidemiological research for more than two decades shows that most of the time meaning of small, minimum and large sample size is misunderstood and quoted in a wrong sense knowingly and/or unknowingly. Hence, clarifying this issue through a reputed journal/ Bulletins becomes essential in view of the need of better epidemiological understanding. To make the communication more effective among the clinical colleagues, who are quite often responsible to plan the study (e.g., as Student/ Principal Investigator), this issue may be explained taking RCT as a case that is familiar topic for them.

In general, RCT involves a problem of testing of hypothesis-comparison of proportions or means [3] between treatment groups (including placebo group, if any). In view of specific objective of the trial, using best available probable information (e.g., group specific cure rate) on the topic under investigation, the required sample size is calculated at considered level of confidence (e.g., 95%), power of the study (e.g., 90%) and relative precision (e.g., 10%). Further, again on account of objective under study, a case of one-tail (one-sided) or two-tail (two-sided) test is considered. These basic issues involved in sample size calculation will be explained in future communication.

In developing countries like India, without knowing clinical implications, an investigator may purposefully try to consider a small sample size taking into account all or some of the considerations like higher levels of group specific cure rate, broader differences in cure rates between groups, lower confidence level, lower power of the study, higher relative precision, and one-sided test. While doing so,(s)he may think of that small sample size is enough for his study to answer the question under study. Further, to justify his consideration, he may quote statistical theory that a large sample size will show a small difference in cure rates between the groups as a significant result. Why should he unnecessarily consider large sample size which is just wastage of time, money etc.? This type of practice or thinking itself comes mainly because of misconceptions like misunderstanding of meanings of small, minimum and large sample size.

As a matter of fact, in general practice, required sample size calculated with all valid scientific considerations (inputs) is referred as a minimum sample size. It is known as a minimum sample size required to answer that specific question under used considerations. Most of the time, as reported earlier, attempt is made to consider a small sample size that is smaller than the required minimum sample size. It is very rare that a large sample size is considered, which means consideration of sample larger than the required minimum sample size. Hence, on account of the need of appropriate clinical practice, there is need to communicate reminders from time to time to ensure use of at least minimum sample size if one really wants to conclude the study.

To support his stand in favor of a small sample size, an investigator may argue that a little difference between cure rates may be shown as significant under large sample size. Accordingly, consideration of a large sample size may be just wastage of time, money etc. without much clinical use. However, he forgets the fact that : it is very rare that a large sample size, more than required minimum sample size, is considered. Sometimes, a large sample size being quoted by him may be even less than required minimum sample size to answer a specific question under investigation. He may be doing so only because of a sample size which involves much time and money; consideration of a small sample size, less than required

minimum sample size, may result in lower power of the study which may give the message that new drug is as good as old drug. As a result of this, use of new drug will come into clinical practice that may not be appropriate in real sense. Further, as an availability of new drug, the physicians may get tempted to prescribe this more frequently. In reality, new drug may not be appropriate, but wrong perception/ practice about sample size may result into bad clinical practice; and consideration of even large sample size, more than required minimum sample size, may not have bad clinical implications. If we get significant result, either old drug may be better than new one or new drug may be better than old drug. In first case, old drug will continue to be used in clinical practice. In second case, use of new drug may not be that much dangerous because result being based on a large sample size will have more precision (accuracy). In this case, we may feel more comfortable using new drug.

Taking into account above-mentioned brief facts, it is necessary to consider at least minimum sample size in a RCT/ other studies making us able to conclude the results without much distortion in clinical practice. There is no dispute in a study based on larger sample size in real sense, which will obviously provide more precise and stable results. Otherwise, if minimum sample size is not considered, the study may be reported as a pilot study. In this case, one should not try to conclude the study that may result into wrong clinical practice.

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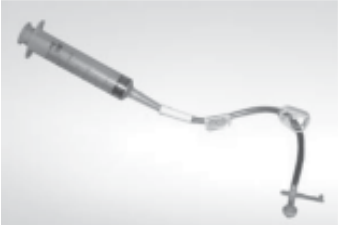
Percutaneous Endoscopic Gastrostomy, 1979



When patients have difficulty swallowing, as a result of disease or injury, a feeding tube can be inserted to provide the nutrients to sustain life. In 1979, Micheal Gauderer, a pediatrician from University Hospitals of Cleveland, and Jeffrey Ponsky, a University Hospitals endoscopist, devised Percutaneous Endoscopic Gastronomy (PEG) to insert these feeding tubes that was both inexpensive and low risk. This procedure comprised an attractive alternative to laparotomy, a surgical incision of the abdomen, and soon became a widespread indication for therapeutic endoscopy. The placement of a PEG tube involves but a few ingenious steps. First, a cannula containing a suture is inserted through the skin into the abdomen of the patient. An endoscope is inserted down the esophagus to the stomach and the endoscopist snares the suture from the cannula. The suture is then pulled up through the esophagus and out of the mouth where it is tied to the enteral feeding tube. The tube is then pulled back down through the hole in the stomach wall and skin until it is partly out of the body. The mushroom tip on the internal end of the tube keeps it in the stomach. After the tube is inserted, nutrients may be fed directly into the stomach via syringe after twenty-four hours. PEG could be performed either as an inpatient or outpatient surgery. The procedure eliminated risks associated with laparotomy, including anesthesia complications, infection, and organ rupture. In their review of 150 cases published in the *Archives of Surgery* (August,1983), Gauderer and Ponsky found no deaths as a result of the procedure, and complications (in only ten percent of cases) were minor and easily treated. The apparatus seen here is the PEG feeding tube and a syringe that would be used to administer the nutrients.

Facing the challenge of tobacco in India - National Tobacco Control Programme

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Tobacco is the foremost cause of preventable death and disease in the world today. Globally approximately 5.4 million people die each year as result of diseases resulting from tobacco consumption. More than 80% of these deaths occur in the developing countries. Tobacco is a risk factor for six of the eight leading causes of death i.e. IHD, cerebrovascular diseases, lower respiratory infections, COPD, tuberculosis, and trachea/ bronchi/lung cancer (World Health Statistics, 2008). India is the second largest consumer and third largest producer of tobacco in the world. As per National Family Health Survey -III, 2005-06, the prevalence of tobacco consumption in India is on the rise, with 57% males and 10.9% females reportedly consuming tobacco in some form (NSS, 52nd Round, 1995-96 showed 51.3% prevalence among males and 10.3% among females). The Global Youth Tobacco Survey (GYTS), 2006 also indicates that 14.1% children in the age group of 13-15 years are consuming tobacco in some form. Compared to GYTS, 2003 findings, prevalence of current use of any tobacco product had not changed significantly over three years at the national level, but had increased in the central region of the country. And during this period, ever smoking of cigarettes had significantly increased in the central, southern and north-eastern regions. More than 0.8 million people die due to tobacco consumption every year (Report on Tobacco Control in India, 2004). There are studies to indicate that approximately 40% of the overall disease burden in the country is associated with tobacco use and almost 50% of all cancer deaths in the country occur due to tobacco related cancers. The majority of the cardio vascular diseases and lung disorders are directly attributable to tobacco consumption. Studies have indicated that incidence of impotence is 85% higher in smokers. Tobacco use by pregnant women leads to low birth weight babies and birth defects.The second hand smoke (SHS) or environmental tobacco smoke (ETS) contains more than 4000 chemicals, many of which are carcinogens. Recent research has shown that SHS causes lung cancer in adults and SIDS (Sudden Infant Death Syndrome), exacerbation of asthma and other respiratory ailments in children (The Health Consequences of involuntary exposure to tobacco smoke – Report of the Surgeon General, CDC, US Dept of Health and Human Services, 2006).

The tobacco epidemic has four stages, based on the percentage of adult male/female smokers and percentage of deaths caused by smoking. As the prevalence of use as well as deaths due to tobacco are on the rise, India is in the second stage of tobacco epidemic, whereas, most of the developed countries have a decrease in prevalence as well as deaths due to tobacco and are in the fourth stage of tobacco epidemic. In addition to the disease and death burden resulting from tobacco use, it has other implications also in the form of social, economic and ecological or environmental effects. approximately 0.27% of irrigated land is under tobacco crop in India. More than 10 million farmers, farm workers, tendu leaf pluckers, bidi rollers, middlemen, agents, retailers constitute tobacco workforce. (ILO 2002 estimates- 5.5 million bidi hand rollers, 85% of whom are women and children). Tobacco farmers suffer from "Green Tobacco sickness", due to absorption of nicotine through skin. Bidi rollers are one of the lowest paid workers in the country and are trapped in a vicious cycle of poverty. They are exposed to absorption of nicotine through skin and inhalation of tobacco dust, making them vulnerable to many diseases. Tobacco

contributes to deforestation in three ways: forests cleared for cultivation of tobacco, fuel wood stripped from forests for curing of tobacco and forest resources used for packaging of tobacco, tobacco leaves, cigarettes, etc. Tobacco growing depletes soil nutrients at a much faster rate than many other crops, thus rapidly decreasing the fertility of the soil. Tobacco is a sensitive plant and therefore, requires huge chemical inputs and fertilizers. Such chemicals may run off into water bodies, contaminating local water supplies, causing excessive leeching etc. Frequent contact with and spraying of chemicals, and storage of tobacco in the residential premises of farmers have adverse health effects.A Health Cost Study conducted by ICMR/AIIMS in 1998-99 showed that cost of treatment of just three diseases caused by tobacco use i.e. cancers, lung disease and cardiovascular diseases far exceeded the economic benefits from tobacco. It was estimated that the economic estimate/health cost of these three diseases was Rs. 30,833 crores (extrapolated to rates of 2002-03), which far exceeded the revenue collected (approx. Rs. 27,000 crore) for the same year. According to another study, the total economic cost of tobacco use amounted to US $ 1.7 billion for the year 2004. The study took into account four major categories of tobacco related diseases – tuberculosis, respiratory diseases, cardiovascular diseases and neoplasms. This was 16% more than the total tax revenue from tobacco.

Tobacco Control legislation

Government of India enacted "Cigarettes and other Tobacco Products (Prohibition of Advertisement and Regulation of Trade and Commerce, Production, Supply and Distribution) Act (COTPA), 2003" to discourage the consumption of tobacco in the country. The specific provisions of this Act include:

- Prohibition of smoking public places.
- Prohibition of direct and indirect form of advertising, promotion and sponsorship of cigarettes and other tobacco products.
- Prohibition on sale of cigarette or other tobacco products to minors (<18 years of age) and within 100 yards of educational institutions.
- Mandatory depiction of pictorial warnings on all tobacco products packs.

International Obligations

India also ratified the WHO-Framework Convention on Tobacco Control (FCTC) in 2005. FCTC provides a key set of recommendations for reduction in demand as well as reduction in supply of tobacco products.The demand reduction strategies include

- Price and tax measures
- Non price measures (statutory health warnings; comprehensive ban on advertisement, promotion and sponsorship; cessation facilities, tobacco product regulation etc.).

The supply reduction strategies include :

- Combating illicit trade in tobacco
- Providing alternate livelihoods to tobacco farmers and workers.

In 2008, WHO came out with a policy package to reverse the tobacco epidemic, namely, MPOWER package. Specific interventions for the countries, listed in the package are :

M-Monitor tobacco use

P-Protect people from tobacco smoke

O-Offer help to quit tobacco use

W-Warn about the dangers of tobacco

E-Enforce ban on tobacco advertisement and promotion

R-Raise taxes on tobacco products

National Tobacco Control Program

National Tobacco Control Program (NTCP) was conceived keeping in view the provisions under "Cigarettes and other Tobacco Products (Prohibition of Advertisement and Regulation of Trade and Commerce, Production, Supply and Distribution) Act (COTPA), 2003" and spirit of FCTC, by bringing together appropriate and effective tobacco control strategies to tackle the tobacco problem in the country. The main objective is to bring about greater awareness about the harm effects of tobacco, and institute a regulatory mechanism including laboratory facility for effective monitoring and implementation of anti tobacco initiatives at State/

District level. The pilot phase of the NTCP was launched in 2007-08 in 18 Districts of 9 States (two districts in each state) i.e. Assam, West Bengal, Madhya Pradesh, Tamil Nadu, Karnataka, Gujarat, Rajasthan, Delhi, Uttar Pradesh. The main components of the programme were :

- Setting up of State Tobacco Control Cells
- District Tobacco Control Programme with components of training, school programme, cessation facilities, IEC and monitoring, evaluation and reporting of tobacco control laws.
- IEC campaign
- Setting up of tobacco testing labs
- Research
- Monitoring and Evaluation, including Global Adult Tobacco Survey – India (GATS)

District Tobacco Control Programme was expanded to cover 24 new districts (in 12 states) during 2008-09.

Budget for the Pilot phase of NTCP during 2007-08 was 30 crores and it was 39 crores for 2008-09.The Government is required under FCTC to provide alternate livelihoods to tobacco farmers and tobacco workers including bidi rollers. Tobacco farmers are encouraged to shift to alternate crops and for this Ministry of Health & Family Welfare supported Central Tobacco Research Institute (CTRI), for a pilot project on alternate cropping strategies.

For the 11th Five year plan, Ministry of Finance approved the following components of NTCP :

- Capacity building of states/ districts for promoting awareness and for monitoring/enforcement of COTPA will form a part of the state health delivery mechanism under the overall framework of National Rural Health Mission (NRHM).
- Establishment of one apex research lab and five tobacco testing labs.
- National public awareness campaign.
- Research in alternate crops for tobacco will be undertaken by ICAR/DARE (Indian Council for Agricultural Research). Research projects for alternate livelihoods to persons engaged in tobacco sector will be taken up by Ministry of Rural Development through their various ongoing schemes.
- Global Adult Tobacco Survey.

Challenges in implementation of NTCP

- Low priority to tobacco control initiatives by the policy makers.
- Low awareness regarding tobacco laws and harm effects of tobacco, including, health, socioeconomic and ecological effects.
- Limited capacity of states to undertake implementation of tobacco laws and tobacco control activities.
- Limited availability of resources to fund tobacco control initiatives.
- Opposition of tobacco control initiatives by tobacco industry.
- Providing alternative livelihoods to large number of workers engaged in tobacco farming, manufacturing and sale.
- Lack of inter-sectoral coordination- various stakeholder departments work in isolation.
- Lack of regulatory mechanism at the national level to spearhead the tobacco control activities and monitor the implementation of tobacco laws and tobacco control programme.

The way forward

India Global Health Professional Student Survey (GHPS), 2006, carried out amongst third year medical and dental students, reported the lifetime prevalence of cigarette smoking (ever smoked a cigarette, even one or two puffs) and use of other tobacco products as 28.2% and 22% respectively. Over 70% of these students wanted to quit tobacco. Nearly 91% students expressed the need for specific training on cessation techniques. COTPA is a public health act. Awareness regarding various provisions under it, which safeguards against harm effects of tobacco, needs to be raised. As far as hospitals, health facilities, health educational institutions are concerned, strict compliance with smoke free rules shall be ensured. The undergraduate medical, dental, nursing and other paramedical curricula and postgraduate curriculum for medicine, community medicine,

psychiatry, and surgery need to include tobacco control strategies, with special focus on formal tobacco cessation techniques. A tobacco cessation facility shall be available at all levels of health care delivery system. Training on tobacco cessation for medical, dental, nursing students and existing staff may be carried out at these cessation facilities. The tobacco control initiatives need to be synergised with National Rural Health Mission and integrated with ongoing national health programmes e.g. National Cancer Control programme, National programme for prevention and control of CVD/DM/Stroke, RNTCP and also state initiatives such as school health programme, training of health professionals and IEC/BCC campaigns etc.The awareness campaigns regarding harm effects of tobacco and SHS need to be intensified with focus on BCC strategies as nicotine contained in tobacco is highly addictive and requires behaviour change and treatment.

Pain relief during labor

Music -Historical records reveal that the ancient Greeks played soothing instrumental music to women in labour. Music can have a relaxing effect in labour due to its ability to alter mood, reduce stress and promote positive thoughts. It can be used as a trigger for a breathing response or as a cue for relaxation. It may also be used as a distraction although this is a less effective use for music in labour. Music can be comforting not only for you, but also for your supporters

Heat and cold-Two further simple ways of easing pain and assisting relaxation during labour are through the application of heat and cold. They provide a source of counter-stimulation.Heat can be applied in several ways:

- by taking a hot shower or bath
- via a hot water bottle or hot wet towel over the abdomen
- by applying a hot compress over the perineum

Instead of applying heat to the skin, some women find that cold is more soothing. A cool, damp face-cloth is always refreshing, while an ice pack can easily be applied to the lower back.

Imagery -Creative mental activity, known as imagery, can also be used to encourage relaxation and help women manage their pain during labour. Many people use imagery in everyday situations. For example, when we feel hungry we can often 'see' (visual imagery) and 'taste' (taste imagery) an imagined meal in front of us - even to the extent of making our mouths water. The word imagery (or visualisation) implies that only the visual sense is used. However, all senses (vision, touch, hearing, taste and smell) can be included in this mental activity.

Rhythmical movements-Many women find that rhythmical movement helps to ease pain during labour. This is not surprising because the movement is a common response in other painful circumstances. Likewise, during labour, many women instinctively have a strong urge to be active. Movement provides a source of counter-stimulation and may stimulate the release of endorphins within the nervous system. For example, rocking the pelvis backwards and forwards during contractions is often found to be soothing. This can be performed while standing, sitting, kneeling, lying down or on hands and knees.Other rhythmical movements include tapping your fingers, rubbing your abdomen, breathing rhythmically and stamping your feet. Some women find it helps to count, sing, shout or howl at the same time!. Whichever manoeuvre appeals to you, the action should be rhythmical and repetitive, and make you feel better.

TENS-Transcutaneous Electrical Nerve Stimulation (TENS) provides yet another form of counter-stimulation and has been used for several years in the management of postoperative and cancer pain. It has been postulated that TENS helps to relieve pain by stimulating the release of endorphins. The TENS equipment consists of a small, battery driven pulse generator, connected to one or two pairs of electrodes which are attached to the skin with adhesive tape. When it is turned on, the TENS machine causes a tingling sensation underneath the electrodes - the strength of which

can be adjusted at the generator controls. TENS is most useful during labour in helping to relieve pain. Consequently, the electrodes are usually placed on each side of the lower spine. A back-ground stimulation is set and the hand control unit is used to increase the intensity of the current during a contraction. In order to be of benefit, it is necessary to turn the control to a setting which is 'almost painful'. The most effective time to begin using TENS is early in labour before the pain becomes too intense. TENS is non-invasive and simple to use. It does not have any side effects (apart from irritating the skin) and is controlled by the mother herself. TENS is also portable and does not interfere with the mother's ability to move around. (Sometimes, TENS can interfere with the signal from an electronic fetal monitor. In this event, TENS may have to be abandoned). Women differ considerably in their opinions about the effectiveness of TENS in labour. In practice, additional analgesia is often needed - although it is possible that drug dose requirements may be less with the aid of TENS. Not everyone finds TENS effective and some dislike the tingling sensation.

Massage-Touch has been associated with the power of healing since the beginning of civilisation. During labour, many women find comfort through being touched, stroked and massaged. touch reinforces the fact that someone cares for you and that you are not alone. Moreover, by providing a source of counter-stimulation touch and massage can sooth pain. Therapeutic massage (eg: shiatsu) has been recommended as a means of preventing and treating many of the ailments associated with pregnancy and as a means of easing the pain of labour. Perineal massage (the area between the vagina and anus) during the last six weeks of pregnancy may reduces tearing or the need for an episiotomy during delivery. Touch and massage can be provided in several ways:

- lightly stroking the abdomen;
- vigorously firm stroking where it hurts most;
- firm circular massage using the palm of the hand over the centre of the back or sacrum. This is most useful when the pain is being felt mainly in the back;
- rhythmical squeezing and letting go of the shoulder muscle;
- a long stroke down the length of the back, buttocks and down the back of the legs; stroking across the forehead, down the neck and down the arms;
- simply holding hands!

Shiatsu- Shiatsu is a Japanese form of therapeutic massage. Shiatsu means 'finger pressure'. The basis and application of Shiatsu is similar to that of acupuncture. For example, when using shiatsu to relieve labour pain, pain-relieving pressure points ('tsubo') are stimulated which are similar to pressure points used in acupuncture *but without the use of needles.*

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Tele-ophthalmology: A New Initiative of National Programme for Control of Blindness (NPCB)

Commentary

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E-Health is a relatively recent term for healthcare practice that describes the application of information and communications technologies across the whole range of functions that affect the health sector from the health personnel to hospital manager, via nurses, data processing specialists, social security administrators and-of course-the patients. In a broader sense, the term characterizes not only a technical development, but also a state-of-mind, a way of thinking, an attitude, and a commitment for inter-linked global thinking, to improve health care locally, regionally, and worldwide. This brief provides an overview of e-health, current scenario of telemedicine in India and initiatives taken by National Programme for Control of Blindness [NPCB], Government of India with regard to Tele-ophthalmology in the Eleventh five-year plan.

The term E-Health encompass range of services in health sciences, namely

- **Electronic Medical Records [EMR]**: enable easy communication of patient data between different healthcare professionals (general physician, specialists, nursing care team, pharmacy) and the accounting team.
- **Evidence Based Medicine and Health Knowledge Management**: entails a system that provides information on appropriate treatment under certain patient conditions. A healthcare professional can look up whether his/her diagnosis is in line with upto date scientific research, overview of latest medical journals, best practice guidelines or epidemiological tracking
- **Consumer Health Informatics**: Empowered healthy individuals and patients want to be informed on health issues.
- **Medical research**: uses e-Health Grids that provide powerful computing and management capabilities to handle large amount of data.
- **Telemedicine**: Telemedicine, as the name suggests, is the application of communication and information technology for remote consultation and diagnosis of diseases by medical professionals. It is a procedure through which medical services are made available remotely, through a combination of telecommunications, multimedia technologies and medical expertise. It also includes health professionals who collaborate and share information on patients through digital equipment like mobile on real-time monitoring of patient vitals, and direct provision of care (via mobile telemedicine).

Types of Telemedicine:

Telemedicine could be broadly grouped into [1] based on specialty: Tele-radiology, pathology, psychiatry, cardiology, ophthalmology, dermatology and surgery [2] based on interventions : Tele-consultation, diagnosis, treatment, monitoring [3] based on time frame: store & forward, real time, and collaborative.

Current Scenario of Telemedicine[1, 2, 3]

- Telemedicine implementation has outgrown from its infancy stage as interest and activity have grown phenomenally during this decade e.g. a day after the earthquake in Gujarat during 2001, Ahmedabad-based Online Telemedicine Research Institute (OTRI) came to the rescue and established the first communication link from Bhuj, which was close to the epicenter of the quake. Specialists were able to provide consultations from far-off places, For example, after the telemedicine center was set up at Bhuj hospital, an X-ray facility was provided

to the people, whereby a specialist provided online consultation from Ahmedabad. During the subsequent days, quake victims could get medical advice from other doctors, based at Ahmedabad and Bangalore. Over 750 sessions were conducted in a period of 30 days, thus saving many lives/limbs.

- The major support and thrust provided by Department of Information Technology [DIT] has been through various projects and system development; organizations like ISRO, reputed academic medical institutions like SGPGI, AIIMS, PGIMER, AIMS, SRMC, C-DAC, Arvind, Shankar nethralaya and corporate hospitals like Asia Heart Foundation, Apollo Hospitals, SGRH, Fortis, Max etc. have taken and continue to take significant initiatives for installation of telemedicine systems in different parts of the country.
- The Department of Information Technology has taken a pivotal role in defining and shaping the future of Telemedicine application in India. DIT has been involved at multiple levels including development of technology, initiation of pilot schemes and standardization of Telemedicine in the country. Some of the other policy initiatives have been development of standardi-zation guidelines, national broadband policy, dedicated satellite for education and health, & revision of medical curriculum is under process.
- Ministry of Health and Family Welfare has set up a National Task Force to address various issues to promote telemedicine in the country and has launched a major country wide network of district hospitals and medical colleges under the Integrated Disease Surveillance Project [IDSP]. National Cancer Care Network, Tele-ophthalmology network, National Digital Medical Library Consortium and Medical College network are going to be implemented in the near future. Other international projects in the pipeline are SAARC telemedicine network and Pan-African e-network
- While there are over 20,000 PHC's providing primary care services in the rural areas, and more than 500 district hospitals, Telemedicine has reached to about 100 centers however more than 50% of them are in the urban areas only. Integrated information on agriculture, health, education, natural resources are initially being made available in the Andaman and Nicobar Islands and some parts of Kerela & North East States.
- One of the key factors to success of Telemedicine in India is going to be the reliability of telecommunication link. Fiber optic network across the country has been laid down by public sector and private telecommunication service providers paving the way for availability of high bandwidth terrestrial connectivity to build ubiquitous health network for telemedicine country wide with competing price. Some of the other challenges and concerns are sustained funding, availability of trained manpower, level appropriate infrastructure/facility development, confidentiality, ethical & legal practices. What started as application of science and technology in the field of telemedicine has now got a significant attention as an important national programme.

Tele-ophthalmology

Under the Telemedicine programme, National Progra-mme for Control of Blindness [NPCB], Government of India initiated Tele-ophthalmology project on pilot basis in Apr 2007 with the objective of making eye care services available to the people across the country especially rural/tribal/hilly and other hardcore/un served areas. Based on the encouraging results and on approval of Eleventh five-year plan [2007-12] period under NPCB, tele-ophthalmology since then has up-scaled and extended to need based areas. Till date, 20 Tele-ophthalmology projects have been assisted by NPCB.

Financial assistance for Tele-ophthalmology under NPCB

In the approved Eleventh plan under NPCB, financial assistance upto Rs. 60 lakhs is being provided to government/voluntary organization for initiating/strengthening tele-ophthalmology projects in the

country.[4] The financial assistance can be spent towards procurement of approved list of equipment/instrument/vehicle and adjusted for extending service on Cataract surgery, treatment of Diabetic retinopathy, glaucoma, low vision, dispensing of glasses, corneal blindnes. The grantee institute based on the recommendation of State/UT government gives its commitment by signing a bond to bear all recurring expenditure, to provide free services to the poor and to abide by guidelines of programme as announced from time to time.

Conclusion

Healthcare is increasingly becoming technology driven to make it accessible, interactive, interoperable, intelligent, transparent and paper-less. Telemedicine, Tele-health, Hospital & Health information system, Picture Archiving and Communication Systems [PACS] is the future of India and Government of India is committed for advancement of health objectives & development of E-health by ensuring favorable, supportive and sustainable environment.

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Childbirth techniques

Childbirth has been associated with pain since the beginning of time, and throughout history measures have been introduced to help relieve it. Various exorcisms can be found in the records from the ancient civilisations of Babylon, Egypt, China and Palestine. Primitive attempts to help relieve pain were based mainly on suggestion and distraction. The former embraced the use of rings, necklaces, amulets and other magical charms; while the latter included counter-stimulation i.e. the infliction of a painful stimulus sufficient to detract from a natural one. In the Middle Ages various herbal concoctions based on extract of poppy, mandragora, henbane and hemp were introduced. There is evidence that alcohol was also used in labour. At the beginning of the nineteenth century other 'remedies' were introduced. In 1806 a thesis by Miller, entitled "Means of Lessening Pain of Parturition", recommended vigorous exercise, bloodletting and a variety of medications designed to induce vomiting. One can imagine that treatments such as these would have been quite effective in distracting women from their pain!

Medical history abounds with episodes where new treatments have been embraced with well-intended but misplaced enthusiasm. The introduction of anaesthesia and pain relief in childbirth in the nineteenth and early twentieth centuries was no exception. Some practitioners were so seduced with the powerful effects of the new drugs available to them (chloroform, opioids, 'Twilight Sleep'), that they used them indiscriminately. However, when revolutionary new remedies are promoted uncritically, they invariably lead to counter-revolution. The excessive use of sedative and analgesic drugs used during labour at the beginning of this century was a prelude to the so-called Natural Childbirth Movement. The origins of this movement go back to 1914 when Behan wrote: "Like menstruation, childbirth should be a painless process. It is only as culture advances that the labour becomes painful, for in women of primitive races pain is absent.".Dr Grantly Dick-Read proposed the same argument in 1933.

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Paradigm Shift in Pathology Education In India

Commentary

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Medicine is an ever-changing science. The earlier one to one physician patient relationship which traditionally characterized the practice of medicine is changed as the setting in which the medicine is being practiced is changing. Now in India, 136 medical schools admit more than 6000 trainees into postgraduate programs[1]. Almost all of them have either postgraduate diploma and or degree in pathology. The paradigm shift in pathology education is parallel to the change in the practice of medicine. Some of the important reasons include – one, the increasing reliance on technologic advances and computerization for many aspects of diagnosis and treatment. two, increasing mobility of both patients and physicians and three, the need for more than one single physician to be involved in the case of most patients who are seriously ill. The objective of this paper is to trace the shift through last 30 years.*If you want to build a ship, don't drum up the man to go to forest to gather wood. Instead teach them the desire for the sea. Antoine Se Saint exupery, WWII fighter and a poet.*A pathological diagnosis requires both aspects of logic – analysis and synthesis and the more difficult the problem, the more important is the logical approach to it. The primary objective of pathology training program is to encourage a logical approach to the diagnosis by training in different aspects of pathology and to provide adequate hands on experience to establish or run a laboratory. So a pathology postgraduate is expected to achieve at the end of the training for three years, core competency in clinical pathology including hematology, histopathology and cytology and adequate exposure to microbiology and biochemistry. Though essentially the goal has remained the same, the entry, course content and the evaluation has been changing over the years.The post graduate degrees in pathology established by Medical council of India are MD, a three year course and Diploma in Clinical Pathology, a two year course. Though the Medical council of India, which is the premier policy making Institution was established in 1934, by the Indian medical council act (1933) before independence, the increase in number of colleges with postgraduate programs was only after 1980s[2]. The competition was always high for the clinical subjects and pathology was not generally a primary choice for many of the aspirants of the postgraduate course. So many a times , the seats were vacant ,especially the seats for the diploma course. The introduction of the competitive exams for admission in 1990s did not change the scenario much. With the awareness about the private labs and increase in the lucrative practice of laboratory medicine, the scenario changed. National Board of examinations (NBE) was established in 1975, as a response to the demand for increase in postgraduate programs and the need to establish an all India examination of high and uniform standard. There are 55 seats in pathology across the country, in different institutions recognized by NBE. In addition, introduction of DM and Ph.D program, has changed the perception in the academic scenario. Recently with the concept of integration of different disciplines, a postdoctoral fellowship in laboratory medicine has been instituted by NBE.

Course and Evaluation- In the 1970s, the emphasis was on anatomic pathology. The post graduate program was loosely structured. Day in and out, the student worked in the same department and had hands on experience. The relationship between the mentor and the student was more one to one basis. The evaluation consisted of mainly essay questions and the grueling practical exam which lasted for three days. There was no dearth of autopsy material. As both theory and the practical valuation were together, the result was totally dependent on the examiners. In traditional autopsy and slide and viva examination, the examiners have liberty to ask

whatever questions they wish around any one slide or specimen. Although the reliability is generally acceptable in this format, the difficulty is that if one examines the correlation across session or cases, the reliability drops to unacceptable low around of 0.35. It is also compromised by lack of standardization of examiners, cases and questions[3,4,5].The syllabus of Diploma in clinical Pathology was variable in different universities across the country. Some universities like Mumbai (earlier referred as Bombay) included microbiology as part of the course. Some of them allowed a student who entered the degree course to take the exam at the end of two years E.g. Madras University (Now the medical and dental disciplines are referred under MGR university of Health sciences). This was possible as the curriculum was loosely structured. Later at the end of 80s, this practice stopped and the takers for the DCP also declined. The other reason was probably in an academic set up, a person with DCP could not go beyond the level of lecturer, as for further promotion a post graduate degree was required.As the National Board of examinations set up a parallel postgraduate program, a shift in the evaluation system started. The diploma course in clinical pathology which is for two years, gained popularity as after the DCP, students were able to take the final DNBE exam which was offered by National board of examination. This helped in students not to waste many years in waiting to get into postgraduate training. The All India nature of the examination gave an edge in the quality over the degree course by the Medical council of India. But the success rate in DNBE was low which was a deterrent to the postgraduate aspirants. A major shift happened in the 90s and the policy decisions were taken in 2000. The reasons are probably,

- An increase in the number and application of laboratory tests
- Decreasing rate of autopsy
- Setting up of autonomous institutions and
- 4. the most important, the emergence of subspecialties of pathology as major disciplines like Hematology, transfusion medicine, Clinical pathology and cytopathology. These disciplines were advancing very rapidly and an exposure to all these disciplines required a structured curriculum.

Seeping corruption in few of the major organizations also led to this shift. The stress was now laid on practice based learning and improvement exercises for learning by reflective practices by the post graduates, as they enter postgraduate training with different prior experience, knowledge and skill. They have different intellectual ability, starting points and learning rates are highly variable. The introduction of log book and internal assessment by some of the universities are in that direction .If effectively used during the training period, these tools of formative assessment can achieve more reliability .They also can provide fair direction as to the future of assessment in post graduate evaluation. The examination pattern also changed with constructed autopsies, Instrumentation, interpretation and clinical utilization of laboratory tests and the number of days decreasing from three to two days. In some of the centers, part of the viva was conducted as OSPE (objective structured practical examination) introducing more objectivity in to the evaluation. However, the pattern of evaluation is not uniform, irrespective of whether it is the degree by the university or by National board of examinations. The careers which student takes up after the training has also changed. In the 1970s, once they finish, they entered either into an academic setup or setup private laboratories. Now the career options include administration, informatics, scientific advisers for instrumentation, research officers for clinical research organizations which conduct clinical trials and pharmaceutical companies. But research as the primary option, remains poor unlike in the west. The responsibility for the training of pathologist is an obligation of the faculty and the ultimate success of medical curriculum reforms is largely dependent upon the faculty's ability to adopt and sustain new attitude and behavior. The reforms are prompted by reconsideration of the expanding knowledge base and professional competencies that are most essential in training the pathologists for the future. The concept of faculty development is catching up and is already in practice in some of the institutions. However, the need for internal quality control, external review and accreditation

system to ensure uniformity across the country still remains. For that , policy makers at the highest level should make policies that will encourage and drive such changes and the personnel responsible for implementation should design tools needed for effective implementation, so that student and finally public will reap the reward.

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Obstetrics forceps

To Arthur H. Bill (1877-1961), obstetrics in the early 20th century confronted a two-fold challenge. First, obstetrical procedures required substantial improvement and second, individuals needed to be trained in the application of these methods. As Bill noted at the end of his career, "instead of bringing our art down to the level of general practitioners, let us bring our art up to a higher level and educate those who do obstetrics to that point." Bill promoted the methods of the "new obstetrics" pioneered by Joseph Bolivar De Lee of Chicago. As Bill observed, "the old plan [which] allowed nature to take its course, even in the face of abnormalities with the hope that eventually the abnormalities might correct themselves, has given way to far more scientific and humane methods of correcting abnormal conditions and thus assisting natural forces." The approach endorsed by De Lee, Bill, and their adherents revolved around such procedures as the use of scopolamine or "twilight sleep," prophylactic forceps delivery, and episiotomy. The "new obstetrics' was highly interventionist in character. When entering the field of obstetrics, Arthur Bill was alarmed that many physicians lacked adequate training in the proper use of forceps. The consequence: damage to both mother and child. He worked to remedy this by carefully teaching his students the technique. Bill structured the obstetrics training program at Case Western Reserve University so that students did not simply witness confinements, but helped deliver as many as 40 babies and attend innumerable labors. By his retirement in 1948, Bill had trained over 2,000 obstetricians-gynecologists in this manner. Bill also developed the Bill Axis Traction Handle, which further reduced the chance of damage to the child and lacerations to the cervix of the mother. This attachment was placed over the front of the forceps handles and made the instrument more accurate in delivery by reducing and determining the force needed for a forceps delivery. Arthur Bill employed the forceps and axis traction handle seen here during his tenure at MacDonald House, the maternity hospital of University Hospitals of Cleveland. For obstetricians, the choice of forceps could be overwhelming; some six hundred variants had been devised since the introduction of the instrument by the Chamberlen family in early-17th century England. For most forceps assisted deliveries, Bill preferred the Tucker McLane forceps, introduced around 1880-85: They were especially appropriate for outlet and low forceps deliveries, where the head is less than 45 degrees rotation from the occiput anterior position. The Tucker-McLane is distinguished from other forceps by its solid or non-fenestrated blades, prominent pelvic curve, and overlapping shanks, and articulating lock.

Occupational Health and Safety

Commentary

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"What is your occupation?" a very pertinent question with a potential implication on the health of an individual was first raised by Bernardino Ramazzini, father of Occupational Medicine some 3 centuries ago.[1] He is credited for his profound study on work-related sickness. Workplace fatalities, injuries and illnesses remain at unacceptably high levels and involve an enormous and unnecessary health burden, suffering, and economic loss amounting to 4–5% of gross national product [GNP].[2] No doubt that Industrial development is a barometer of nation prosperity & progress leading to attenuating the problem of growing unemployment, however, it is no more viewed as a simplistic and harmless tool for progress. Proliferation of human settlement surroundings such industrial nuclei cause serious concern not only for human safety, protection of other life, property but also the environment. The damage is considered to be acute in the area of safety, chronic in the area of occupational health and persistent in the case of environment. OHS comprises many diverse but inter-related issues and through this article an attempt is made to provide an overview of burden of occupational morbidity & mortality, institutional framework & legislation in India, present status, challenges and solutions.

Need [3,4,5,6]

- Workers are exposed to a wide range of safety and health hazards on the job. Exposure differs from trade to trade, from job to job, by the day and even by the hour. Exposure to any one hazard is typically intermittent and of short duration but is likely to recur. The severity of each hazard depends on the concentration and duration of exposure for that particular job.
- Today, many people work for longer hours, hold multiple jobs, do shift work, work from home, have reduced job security, and perform part-time, contractual or temporary work. It is estimated that of the total 3 billion workers in the world over 80% work and live without having access to occupational health services. The coverage today is diminishing rather than expanding.
- In the 21st century, Multi National Enterprises [MNEs] are significant source of economic growth and employment around the world. Estimated 65,000 MNEs and their 800,000 subsidiaries employ upward of 90 million people worldwide or 5.0% of global workforce.
- There is growing need to study the health status among employees at Information Technology Enabled Services [ITES], since the number of workers is rapidly growing and will touch 1.2 million in the next three years in India from a figure of 2,50,000 in March 2004, according to National Association of Software and Service Companies. Similarly, there are upcoming developmental issues like Nanotechnology, robotics etc which may also have an effect on occupational health and safety.
- In medical sciences, health care professionals are exposed to variety of dangers like infections [HAI], cuts and needle stick injuries, exposure to anesthetic gases, radiation, dermatitis causing substances, vaccines & serums and experiences severe stressful situations with little time to spare for personnel & social activities. Most of the paramedical staff is exposed to HAI and repetitive strain injuries (mainly lower backache) due to patient lifting, transportation, long-standing duties and bad work postures.

Burden of occupational morbidity and mortality: World

- There is 30%-50% of the world's population at work-

related risks i.e. exposed to physical, chemical, biological, psychosocial and/or ergonomic hazards. Globally, there were 337 million occupational accidents causing 4 or more days of absence from work; 358,000 work related fatal accidents, 1.95 million works related fatal diseases and 2.31 million total fatalities.[7] According to estimate for the year 2000 there are 2.0 million work-related deaths per year [WHO/ILO].

- United States [USA] labour department recorded a total of 5,488 & 5,840 fatal work injuries in 2007 & 2006 respectively for the country. This figure represented the smallest annual preliminary total since the Census of Fatal Occupational Injuries (CFOI) program was first conducted in 1992. Based on these counts, the rate of fatal injury for U.S. workers in 2007 was 3.7 fatal work injuries per 100,000 workers, down from the rate of 4.0 per 100,000 workers in 2006.[8]

Burden of problem statement in India

- The major occupational morbidity of concern in India include silicosis, musculoskeletal injuries, coal workers' pneumoconiosis, chronic obstructive lung diseases, asbestosis, byssinosis, pesticide poisoning and noise-induced hearing loss. In India, occupational health is more than simply a health issue, which includes child labour, poor industrial legislation, vast informal sector, less attention to industrial hygiene and poor surveillance data.[9]
- There are figures from various studies/estimates to provide an insight to the burden of problem as reported figure do not reflect the true magnitude. Some of these are, Leigh et al. estimated the annual incidence of occupational disease between 924,700 and 1,902,300, leading to over 121,000 deaths in India.[10] According to a survey of injury incidence in agriculture conducted in Northern India, an annual incidence of 17 million injuries per year (2 million moderate to serious events) and 53,000 deaths per year was estimated.[11] Nearly 50,000 to 60,000 accidents are occurring annually in the manufacturing sector. These accidents results in injuries of varied severity and about 1000 people die every year. The frequency rate has not come down significantly over the years.[12]
- Another source has mentioned the estimate of burden of occupational diseases (1.83 million) and occupational injury (18.3 million) in India, the figure indicate that as a nation, India is contributing nearly 20% of the global burden in respective areas. Prevalence studies on occupational disease in many parts of the world have shown such burden to vary from 5 to 20%.[1]
- Agnihotram through his paper based on review of literature on occupational health research in India has also reflected high burden of morbidity at workplace.[13] C Kesavachandran et al in their review article concluded that musculo-skeletal, ocular disorders and psycho-social problems were some of the key health problems observed among Information Technology [IT] professionals.[14]

Definitions[15]

Before going further we should be clear with certain terminologies that are encountered in context of occupational health and safety.

- Hazard: The inherent potential to cause injury or damage to people's health.
- Risk: A combination of the likelihood of an occurrence of a hazardous event and the severity of injury or damage to the health of people caused by this event.
- Occupational injury or illness: An injury or illness is considered to be **work-related** if an event or exposure in the work environment either caused or contributed to the resulting condition or significantly aggravated a pre-existing condition.[16]
- Conventions: are international treaties and are instruments that create legally binding obligations on the countries ratifying them.
- Recommendations: are non-binding guidelines, which orient national policies and actions.

- Occupational Health: is the promotion and maintenance of the highest degree of physical, mental and social well-being of workers in all occupations by preventing departures from health, controlling risks and the adaptation of work to people, and people to their jobs. (ILO/WHO 1950]
- Occupational Safety Health [OSH] management system: includes organizational structure, planning of activities, assigning responsibilities, detailing procedures, processes and mobilizing resources for implementing, reviewing and updating occupational health & safety policy to manage the risk associated with the business of the organization.[17]

What is Occupational and Health Safety Administration [OSHA] Act[18, 19]

The OSHA act was created on December 29, 1970 by United States of America to provide US workers with a safe working environment. OSHA is administered through the department of labour but many states have their own OSHA laws. Its statutory authority extends to most workplaces where there are employees and staff. Despite early difficulties, over time, manufacturers of industrial equipment have included OSHA-compliant safety features in new machinery, enforcement has become more consistent across jurisdictions, inspection, recording & reporting is regular and some of the more unpopular rules have been repealed. OSHA now has over 1000 inspectors across more than 200 offices, and Health services in USA. However, 40% of the workforce of some 130 million people in US does not have access to adequate occupational health services.[2]

Institutional framework for OHS[20]

- The Constitution of India has specified provisions for ensuring occupational health and safety for workers in the form of three Articles i.e. 24, 39 (e and f) and 42. The regulation of labour and safety in mines and oil fields is under the Union list while the welfare of labour including conditions of work, provident funds, employers' invalidity, old age pension and maternity benefit are in the Concurrent list.
- The Ministry of Labour, Government of India, nodal agency for employment & labour-related statistics along with labour departments of the States/Union Territories are responsible for safety and health of workers. Directorate General of Mines Safety (DGMS) and Directorate General Factory Advice Services & Labour Institutes (DGFASLI) assist the Ministry in technical aspects of occupational safety and health in mines and factories & ports sectors, respectively.

Occupational and Safety legislation in India[20, 21, 22]

- There are various work-related statutes in the country concerning safety, health and environment [Table 1]. These statutes could be broadly divided into three domains i.e. statutes for safety at workplaces, statutes for safety of substances and statutes for safety of activities.
- The acts and set of rules framed there under have taken into consideration the articles under different ILO Conventions and Recommendations. The practice followed by India so far has been that a Convention is ratified only when the national laws and practices are in conformity with the provisions of the Convention in question. India has so far ratified 41 ILO Conventions out of 182 conventions and 190 recommendations.
- Three schedules include list of 20 industries involving hazardous processes, the permissible levels of certain chemical substances in work environment and the list of 29 notifiable diseases.

Status in India[2, 23, 24]

- Industries were established in India as early as 1850's. After Independence in 1947, country had about 31,000 factories employing about 2.5 million workmen. This figure rose to 01 lakh factories and 07 million workers during 1981 and by 2005 India had more than 2.3 lakh factories employing 08 million workers. The major chunk of our workforce belonged to agriculture sector [69%], construction [16%] followed by manufacturing [11%] and

then sector. According to Ministry of Labour, approximately 92% of the workforce is in the unorganized or informal sector.

- Though there are number of laws relating to occupational safety and health enforced by different enforcing agencies. Some of them also contain requirement which are not consistent with one another. On the other side, the requirements under the Factories Act 1948 are so detailed and exhaustive that small factories are unable to comply with procedural requirement. There is no legislation which covers the OHS aspect of agricultural operations. The Building and other Construction Workers [Regulation of employment and condition of services] Rules are notified by 09 states only. As such, the benefit of protection is not extended to construction workers in other states. Minor, intermediate ports, inland containers depots and container freight stations are out of the scope of any statue relating to safety and health.
- There is no single authority to address the OHS requirements of various sectors and there is little coordination amongst different players with poor implementation. There is no penalty for non-compliance and often, statutory procedures are such that there are more penalties for disclosure than for non-reporting.
- The Factories Act and factory rules cover 5% of the workforce. Occupational health services are mandatory only for factories with hazardous processes, which encompass 1% of the Indian workforce. There are numerous units employing less than 10 workers which handle hazardous chemicals and undertake dangerous operations. The workers employed in these units are not protected against hazards.
- The major hindrance of occupational health development in India is that the subject was never given proper attention in presence of other pressing issues like malnutrition, communicable diseases & unemployment etc. Most of the state governments have inadequate staff to statutorily inspect the establishments, compared to 3000 factory inspectors in a small country like Japan, we have no more than 500 inspectors. The deficiency is further compounded by absence of basic infrastructural and communication support system.

Teaching and Training[25, 26, 27]

- The dedicated occupation health personnel that can play a critical role in ensuring occupational health & safety services in the country are Occupational health physician and nurses; physiotherapist; Ergonomists; Occupational or industrial hygienists; Safety engineers; Occupational psychologists, Managers of OHS units or organization and audiologist.
- Inspite of 'need' for the personnel there is neither 'demand' nor any well defined carrier progression path. For medical graduates there are handful of medical colleges that offer post-graduate course on occupational health. Physicians, chemists, physicists, safety officers often perform some of the functions of occupational hygienists.
- National Safety Council [NSC] set up by Labour Ministry in 1966 has grown into a well-organized national body with an all India network of 14 State Chapters and 31 Action Centres with members from industry, trade unions and professional bodies and emerged as a National Resource Centre on Safety Health and Environment.
- Short orientation & specialized training courses, symposia, seminars, conferences and educational campaigns are conducted regularly on occupational hygiene in India by various institutes such as National Institute of Occupational Health (NIOH), Ahmedabad; central & regional labour institute at Mumbai, Chennai, Kolkata, & Kanpur; All India Institute of Hygiene and Public Health [AIIH&PH], Kolkata; Industrial Toxicology Research Centre [ITRC], Lucknow;

Regional institutes in Calcutta and Bangalore under Indian Council of Medical Research (ICMR), Lok Manya Medical Research Centre, Pune and Centre for Occupational and Environmental Health (COEH), MAMC, New Delhi and a professional bodies like Indian Association of Occupational Health [IAOH].

- There are few others national level disability prevention and rehabilitation institutes in New Delhi, Deharadun, Mumbai, Secunderabad, Kolkata, Cuttak, Chennai and Mysore, which offer such courses. The Master of Industrial Hygiene (MIH) course being conducted by Sardar Patel University, Vallabh Vidyanagar, Anand, in collaboration with Cincinnatti University, USA.

Solutions[27, 28, 29, 30]

- The requirement is to have a single point responsibility with adequate authority to address needs, ensure compliance and disseminate OHS information to all concern. In the countries like Australia and even in USA separate OH & S act has been made. However it also needs to be ensured that implementation of legislation does not remain confine to papers. Therefore public sector manpower strengthening, infrastructural and commun-ication support is required for improving compliance of statutes, monitoring & supervision at hazardous workplace.
- Till few years ago, safety management has been to a great extent, the concern of Government agencies limited to the compliance with the laws relating to this domain. Even in situations involving safety and health problems, which are not specifically covered by the statutes, the response to the management was only reactive.
- India had adopted a self-regulatory [voluntary, self-compliance, certification, or accreditation] approach since 1987 through amendments to the factory act 1987. The vast majority of the sector should be encouraged to develop, adopt and/or adapt quality safe work practices by fostering a conducive environment of teaching, training, sensitizing and advocacy opportunities for owning & empowering stakeholders on the issue of health and safety.
- Over the year, occupational health and safety [OHS] issues have improved considerably in India due to intense advocacy by media, activist, professional bodies, public interest litigation's [PIL], and societal demand due to occurrence of national disasters that have spurred management to change its approach towards OHS. Organizations have started attaching importance to occupational safety & health through adoption of a structured approach for the identification of hazards, their evaluation, control of risks and ensuring basic health needs.
- Bureau of Indian Standard [BIS] formulated an Indian Standard of OHS management system based on voluntary adoption for a comprehensive framework & specification with guidance for OHS. It is called as the IS 18001:2000 Occupational Health and Safety [OHS] Management Systems with the following revised edition IS 18001:2007. This standard prescribes the requirements for an OH&S Management Systems, to enable an organization to formulate a policy, taking into account the legislative requirements. It also provides information about significant hazards and risks to be analyzed & evaluated at workplace, which the organization can control in order to protect its employees and others, whose health and safety may be affected by the activities of the organization.

Conclusion

Occupational health and safety is an important strategy not only to ensure health of workers, but also to contribute positively to the national economies through improved productivity, quality of products, reduced absenteeism, work motivation and job satisfaction. Accident prevention has to be perceived not as a separate and independent discipline but rather interwoven philosophy of any management function.

Table-1, Various legislative acts & rules drafted there under concerning Occupational health & safety and social aspect, India*

The Explosives Act, 1884	The Radiological Protection Rules, 1971
The Indian Electricity Act, 1910	The Dangerous Machines (Regulations) Act, 1983
Workman compensation act, 1912	The Dock workers (safety, health and welfare) Act, 1986
The Indian Boilers Act, 1923	Environment Protection Act, 1986
The Petroleum Act, 1934	The Manufacture, Storage and Import of Hazardous Chemicals [MSIHC] Rules, 1989, amended in 1990, 1994
The Factories Act 1948, amended 1954, 1970, 1976, 1987	Chemical Accidents [Emergency Planning, Preparedness and Response] Rules, 1996
Employee State Insurance [ESI] Act, 1948	The Building and other construction workers [Regulation of Employment and Conditions of Labourers] Act, 1996
The Plantation Labour Act, 1951	Biomedical Waste Management and Handling Rules, 1998, 2003
The Mines Act, 1952	
The Indian Atomic Energy Act, 1962	
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Review Article

Preeclampsia and Associated Risk Factors

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Preeclampsia contributes about 8 to 10% of maternal deaths in India and 5 to 10% of maternal deaths in western countries.[1] The incidence varies about three fold in various geographical areas with different ethnic and social characteristics. Globally, the hypertensive disorders of pregnancy together are responsible for up to 50,000 maternal deaths and as many as 9, 00,000 perinatal deaths annually . Prompt diagnosis and intervention is of vital importance in reducing maternal mortality. This has guided the development of antenatal care preventive management strategies such as regular monitoring of maternal blood pressure and early detection of proteinuria. Preeclampsia resolves postpartumly, that is why presently premature delivery of the baby is followed as an optimal strategy to save the mother's life. Consequently, many of the infants born to preeclamptic mothers require expensive therapeutic support in the form of NICUs. The burden of preeclampsia on health care settings is therefore substantial. Progress in the prevention and treatment of this condition requires an in-depth analysis of the risk factors. The National Institute for Clinical Excellence (NICE) guidelines on antenatal care have reduced the number of antenatal visits recommended for healthy woman at low risk.[2] It is important to define risk of preeclampsia at the beginning of pregnancy, as reflected in few reported randomised controlled trials on which this recommendation was based. These trials could not identify important outcomes such as mortality, which may be due to the lack of awareness and thus identification of existing risk factors at the time of registration. A comprehensive knowledge gained from systemic review of published literature will provide an evidence base from which healthcare professionals can assess each pregnant woman's risk of pre-eclampsia at her first antenatal visit or the time of registration and tailor her antenatal care accordingly.

Clinical Symptoms-Hypertension and proteinuria are considered as the cardinal features of preeclampsia. Hypertension in preeclampsia is defined as an elevation of more than 30 mm Hg systolic pressure or more than 15 mm Hg diastolic pressure above the patient's baseline blood pressure. This definition proved to be a poor indicator of outcome and was redefined by the National High Blood Pressure Education Program[3] in 2000. The criteria defined hypertension as a systolic blood pressure more than 140 mmHg or a diastolic level (Korottkoff V) more than 90 mmHg on two or more occasions, at least 4 - 6 hours (but not more than 7 days) apart after 20 weeks of gestation in a woman with previously normal blood pressure. For most healthy nulliparous women, the factor that differentiates preeclampsia from other gestational hypertensive disorders is *concomitant proteinuria*, which is defined as the excretion of 30 mg/dl of protein in a random urine specimen or more than 0.3g/l protein or more than 1+ on a dipstick test strip in a 24 hour urine specimen, with loss of serum protein, increased creatinine, alanine amino-transferase, aspartate amino transferase, lipids, triglycerides, low platelets count and increased urea. Preeclampsia can be associated with edema, visual disturbances, headache, epigastric or upper right quadrant pain with nausea and vomiting. Its life threatening complications include seizures, cerebral hemorrhage, disseminated intrav-ascular coagulation, and renal failure. The clinical diagnosis of edema is made when swelling is evident, however fluid retention may also manifest as a rapid increase in the body weight without evident swelling. Kidney function is dependent on adequate glomerular blood flow and selective permeability of glomerular capillaries. The renal dysfunction may manifest as a vascular irregularity, decline in renal blood flow and glomerular filtration rate and clinically significant proteinuria . Oliguria or anuria can occur in patients with severe preeclampsia as a result of low cardiac output and high

systemic vascular resistance. Preeclampsia can rapidly progress to a convulsive phase termed eclampsia, especially if untreated. Impaired uteroplacental blood flow or placental infarction can affect the feto-placental unit, causing intra uterine growth restriction, intrauterine fetal demise, oligohydramnios, or placental abruption. Generally, maternal and perinatal outcomes are better in mild preeclampsia that develops after 36 weeks of gestation than in cases that are symptomatic before 33 weeks of gestation.The duration between the first detection of hypertension and proteinuria and the subsequent development of these complications can be extremely short in many cases. Maternal death is more likely in the presence of severe hypertension and eclampsia. So far no effective intervention for prevention of preeclampsia is available globally. The only known cure is delivery of the placenta.[4] If maternal signs develop before the fetus is mature, the risk of neonatal morbidity and mortality due to premature delivery is markedly increased.[4]

Risk factors associated with preeclampsia (Table-1)- Preeclampsia is primarily regarded as a disease of first pregnancy. The risk of preeclampsia is at least twice as high during first pregnancies as during second or later pregnancies. Recent studies have suggested that the risk may decrease with a second pregnancy only if the mother's partner is the same. The hypothesis is that the risk of preeclampsia may be reduced with repeated maternal exposure and adaptation to specific foreign antigens of the partner. According to this hypothesis, a new partner presents new antigens, which results in a risk of preeclampsia that is similar to the risk during a first pregnancy. The evidence from the Medical Birth registry of Norway indicates that the protective effect of multiple pregnancies is confounded by the time interval between the births.[5] The association between risk of pre-eclampsia and interval was more significant than the association between risk and change of partner. The risk in a second or third pregnancy was directly related to the time elapsed since the previous delivery. A cross sectional study from Uruguay found that women having time interval with more than 59 months between pregnancies had significantly increased risks of pre-eclampsia (relative risk 1.83, 95% confidence interval 1.72 to 1.94) compared to women with intervals of 18-23 months.[6] A Danish cohort study found that a long interval between pregnancies was associated with a significantly higher risk of pre-eclampsia in a second pregnancy when pre-eclampsia did not exist in the first pregnancy and paternity had not changed.[7] The data obtained from more than 1.8 million births over 31 years, showed that when the birth interval was more than 10 years, a multiparous woman had the same risk of developing preeclampsia as a primiparous woman. Women aged e" 40 had twice the risk of developing pre-eclampsia, whether they were primiparous (relative risk 1.68, 95% confidence interval 1.23 to 2.29) or multiparous (relative risk 1.96, 95% confidence interval 1.34 to 2.87).[8] Nulliparity almost triples the risk for pre-eclampsia (relative risk 2.91, 95% confidence interval 1.28 to 6.61) (three cohort studies).[9,10,11] Women with pre-eclampsia are twice as likely to be nulliparous as women without pre-eclampsia (relative risk 2.35, 95% confidence interval 1.80 to 3.06) (six case-control studies).[9,12,13,14,15,16] Women who have pre-eclampsia in the first pregnancy have seven times the risk of pre-eclampsia in a second pregnancy (relative risk 7.19, 95% confidence interval 5.85 to 8.83) (five cohort studies).[11,17,18,19,20] A family history of pre-eclampsia nearly triples the risk of pre-eclampsia (relative risk 2.90, 95% confidence interval 1.70 to 4.93) (two cohort studies).[21,22] When a woman is pregnant with twins, her risk of pre-eclampsia nearly triples (five cohort studies, relative risk 2.93, 95% confidence interval 2.04 to 4.21).[9,11,15,23,24] Neither the chorionicity nor zygosity of the pregnancies alters this increased risk.[25] One cohort study found that a triplet pregnancy nearly triples the risk of pre-eclampsia compared with a twin pregnancy (relative risk 2.83, 95% confidence interval 1.25 to 6.40).[26] The likelihood of pre-eclampsia nearly quadruples if diabetes is present before pregnancy (relative risk 3.56, 95% confidence interval 2.54 to 4.99) (three cohort studies).[11,24,27] In a population based nested case-control study, Davies et al found that the prevalence of chronic hypertension was higher in women who developed pre-eclampsia than women who did not.[28] Sibai et al found that higher systolic and diastolic blood pressures at the

first visit were associated with an increased incidence of pre-eclampsia.[29] In another population based nested case-control study Odegard et al found that a systolic blood pressure e" 130 mm Hg compared with ≤110 mm Hg at the first visit before 18 weeks was significantly associated with the development of pre-eclampsia later in pregnancy (relative risk 3.6, 95% confidence interval 2.0 to 6.6).[15] The association with a diastolic pressure e" 80 mm Hg compared with ≤ 60 mm Hg was similar but not significant (relative risk 1.8, 95% confidence interval 0.7 to 4.6). In a case-control study Stamilio et al found that a mean arterial pressure ≥ 90 mmHg at the first prenatal visit was significantly associated with the development of severe pre-eclampsia (relative risk 3.7, 95% confidence interval 2.1 to 6.6).[16] The antipho-spholipid antibodies have more than nine fold risk of preeclampsia (relative risk 9.72, 95% confidence interval 4.34 to 21.75) (two cohort studies).[30,31] One cohort study showed that women with a body mass index > 35 before pregnancy had over four times the risk of pre-eclampsia compared with women with a pre-pregnancy body mass index of 19-27 (relative risk 4.39, 95% confidence interval 3.52 to 5.49).[32] The protein–calorie mal nutrition has been identified as an important risk factor in developing countries however a negative correlation between calcium intake and incidence of preeclampsia was found in Guatemala, Colombia and India. This finding is in support with the observation that calcium supplementation is beneficial to women at high risk of gestational hypertension and in communities with low dietary calcium intake.[33]

Preeclampsia and associated complications-Chesley, who is the father of modern preeclampsia research was of the opinion that once the condition was over, the mothers had no greater risk of adverse long – term out comes than women without preeclampsia from the general population.[34] In contrast, many studies have linked preeclampsia to increased risk of both renal disease and cardiovascular disease in mothers in later life.

- **Cardiovascular disease-**The data obtained from a cohort study of 626,272 live births in Norway between 1967 and 1992 states that the risk of death from cardiovascular causes had increased eight fold in preeclamptic women with a child of low birth weight than the control subjects.[35] Sattar and Greer focused on pregnancy complications and maternal cardiovascular risk, suggested that women with a history of adverse pregnancy outcome are at increased risk for cardiovascular disease later in their life.[36]
- **Ischemic heart disease-**Smith et al studied the pregnancy complications and the maternal risk of ischemic cardiac death in 129,290 births [37] and found that preeclamptic women, who delivered a small infant early, had a risk of ischemic heart disease or death seven times higher than the control women.
- **Hypertension and Stroke-**Wilson et al examined the relationship of preeclampsia and the subsequent risk of hypertension and stroke later in life and found that any hypertensive disorder of pregnancy increased the later risk of hypertension and stroke.[38] The relative risk of stroke was increased in women who had preeclampsia (Relative Risk: 3.59).
- **Renal disease-** Bar et al reported that microalbuminuria persisted in most of the preeclamptic women for three to five years after the child birth.[39] Davies et al also found that the prevalence of renal disease was higher in women who developed pre-eclampsia compared with those that did not[38] .A Norwegian study which investigated comprehensive data from the Medical Birth Registry of Norway and Norwegian Kidney Biopsy Registry found a strong correlation between preeclampsia during pregnancy and later incidence of kidney disease in mothers and especially when the babies had very low birth weight.
- **Microvascular complications-**Preeclampsia is associated with endothelial dysfunction, insulin resistance and elevated homocysteine levels and these conditions continue after delivery and represent a long term risk.

Conclusion-This review of 1000 controlled studies (from 1966 to 2002) brings up certain interesting conclusions. Firstly, a previous history of preeclampsia, multiple pregnancy, nulliparity, pre-existing diabetes, high BMI before

pregnancy, maternal age more than 40 years, renal disease, hypertension, ten years or more than ten years of difference between the pregnancies, presence of antiphospholipid antibodies, insulin resistance in concert with obesity and thrombophelia are the major risk factors of preeclampsia. Further, data on these risk factors of preeclampsia will have an immense value as it would help to assess risk at the first antenatal clinical visit. A suitable surveillance regimen could be initiated to detect pre-eclampsia and instituted for the rest of the pregnancy (Table-2). Also the studies on associated complications of preeclampsia necessitate the need to monitor women throughout life who are suffering from this condition. In addition, effective preventive steps, and or the use of early maternal serum markers to screen for the condition together with the development of a truly effective therapy would go a long way towards reducing the morbidity and mortality of both mothers and their babies, thereby increasing hope for safe motherhood in the world.

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Table-1, Studies on risk factors of preeclampsia

Risk factor	Study Design	Number of studies	Unadjusted relative risk (95% CI)	Reference
Time between pregnancies> 59 months	Cross sectional	1	1.83(1.72 to1.94)	Conde-Agudelo et al 2000
Age ≥40 primiparous	Cohort	1	1.68 (1.23 to 2.29)	Bianco et al 1996
Age ≥40 multiparous	Cohort	1	1.96 (1.34 to 2.87)	Bianco et al 1996
Nulliparity	Cohort	3	2.91 (1.28 to 6.61)	Coonrod et al 1995 Lawoyin et al 1996 Lee et al 2000
	Case control	6	2.35 (1.80 to 3.06)	Coonrod et al 1995 Eskenazi et al 1991 Stone et al 1994 Chen et al 2000 Odegard et al 2000 Stamilio et al 2000
Previous pre-eclampsia	Cohort	5	7.19 (5.85 to 8.83)	Lee et al 2000 Campbell et al 1985 Sibai et al 1986 Makkonen et al 2000 Dukler et al 2001
Family history 1990	Cohort	2	2.90 (1.70 to 4.93)	Arngrimsson et al Cincotta et al1998
Twin pregnancy	Cohort	5	2.93 (2.04 to 4.21)	Coonrod et al 1995 Lee et al 2000 Odegard et al 2000 Santema et al 1995 Ros et al 1998
Triplet *v* twin pregnancy	Cohort	1	2.83 (1.25 to 6.40)	Skupski et al 1996
Pre-existing diabetes	Cohort	3	3.56 (2.54 to 4.99)	Lee et al 2000 Ros et al 1998 Garner et al 1990
Systolic ≥130 mm Hg at booking	Cohort	1	3.6 (2.0 to 6.6)	Odegard et al 2000
Diastolic ≥80 mm Hg at booking	Cohort	1	1.8 (0.7 to 4.6)	Odegard et al 2000
Mean Arterial pressure ≥ 90	Case control	1	3.7 (2.1 to 6.6)	Stamilio et al 2000
Autoimmune disease	Case control	1	6.9 (1.1 to 42.3)	Stamilio et al 2000
Antiphospholipid antibodies	Cohort	2	9.72 (4.34 to 21.75)	Pattison et al 1993 Yasuda et al 1995
BMI>35	Cohort	1	4.39 (3.52 to 5.49)	Bianco et al 1998

Table-2, Risk factors that can be assessed at first antenatal visit

History	**Pre-existing medical conditions**	**Examination**
Age	Insulin dependent diabetes (IDDM)	Body mass index (BMI)
Parity	Chronic hypertension	Blood pressure
Previous pre-eclampsia	Renal disease	Proteinuria
Family history of pre-eclampsia	Autoimmune disease	
Multiple pregnancy	Antiphospholipid syndrome	
Time between pregnancies		

7

Review Article

Renal Tubular Acidosis(RTA) in Children

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Acidosis due to renal disease is considered in two categories, depending on whether the predominant site of renal involvement are the glomeruli or the renal tubules.Predominantly tubular damage – "normal anion gap acidosis"- Distal (or type 1) RTA; Proximal (or type 2) RTA; Type 4 RTA. Predominantly glomerular damage – "high anion gap acidosis"-Acidosis of acute renal failure; Uremic acidosis

Definition- It is a disease state secondary to reduced proximal tubular reabsorption of bicarbonate ions (HCO_3^-) or the distal secretion of protons (H^+ ions) or both, resulting in an impaired capacity for net acid excretion and persistent hyperchloremic metabolic acidosis. Three main clinical categories of renal tubular acidosis (RTA) are now recognized and classified on the basis of their pathophysiology as -

- Type 1 (DISTAL) RTA
- Type 2 (PROXIMAL) RTA
- Type 4 (secondary to true / apparent hypoaldosteronism).

The above conditions are either secondary to other causes, or primary with or without known genetic defects.[1]

Type 1 (Distal RTA)- It is also referred to as the classical RTA. The problem here is inability to maximally acidify urine.Metabolic acidosis secondary to decreased secretion of H^+ ions in the absence of a marked decrease in the glomerular filteration rate (GFR) is characteristic of distal RTA. Patients with distal RTA have inappropriately low NH_4^+ ion excretion when compared with the normal rate of acid production. The deficiency here is secondary to either a secretory (rate) defect or a gradient (permeability) defect. In the secretory defect, the rate of secretion of H^+ ions is low for the degree of acidosis. It is due to defective function of H^+ ATPase, H^+/K^+ ATPase or the Cl^-/HCO_3^- exchanger ("weak pump"). In the gradient (permeability) defect, there is normal secretion of H^+ ions but an increased back leak resulting in dissipation of the pH gradient ("leaky membrane") as seen in RTA due to amphotericin B. The low titrable acidity and NH_4^+ secretion in distal RTA leads to systemic acidosis. Hypokalemia is attributed due to increased potassium losses in the tubular lumen, urinary sodium losses and volume contraction leading to aldosterone stimulation which inturn causes increased tubular potassium secretion and decreased proximal potassium reabsorption.[2] Chronic acidosis also lowers the tubular reabsorption of calcium causing renal hypercalciuria and hyperparathyroidism. Acidosis and hypokalemia stimulate the proximal tubular reabsorption of citrate and decrease its urinary excretion. This hypercalciuria, hypocitraturia and alkaline urine leads to calcium phosphate stone formation in the kidneys (nephrocalcinosis and nephrolithiasis).

Etiology

Primary -Genetic(Autosomal dominant:- Mutation in the Cl^-/HCO_3^- exchanger of intercalated discs; Autosomal recessive:- Mutation in the H^+/ATPase as found in some families associated sensorineural hearing loss (SNHL) is common; Sporadic – medullary sponge kidney

Secondary- Autoimmune-Sjogren syndrome (most common), systemic lupus erythematosis (SLE); Disorders causing nephrocalcinosis-Primary hyperparathyroidism, Vitamin D intoxication; Toxins- Amphotericin B, lithium, toluene, cisplatin; Miscellaneous- obstructive uropathy, vesicoureteral reflux (VUR), pyelonephritis.

Clinical Profile

- Failure to thrive, growth retardation (most common).
- Polyuria, polydipsia
- Nephrocalcinosis, nephrolithiasis
- Rachitic manifestations (later in childhood)
- Weakness, transient paralysis (due to hypokalemia)

- Sporadic or autosomal recessive cases may have associated SNHL that may present at birth or later.

Type 2 (Proximal) RTA-It is called as proximal RTA because the primary defect here is the impaired reabsorption of bicarbonate ions in the proximal tubule resulting in bicarbonaturia. The primary defect in proximal RTA is the reduced renal threshold for HCO_3 resulting in bicarbonaturia. The proposed mechanisms include defective pump secretion or function of the H^+/ATPase, the Na^+/H^+ antiporter, the Na^+/K^+ ATPase or the deficiency of carbonic anhydrase in the brush border membrane. This results in increased urinary loss of HCO_3 causing systemic acidosis with inappropriately high urinary pH. The increased distal Na^+ delivery results in hyperaldosteronism with consequent renal K^+ wasting. As plasma HCO_3^- levels fall, the lowered filtered load of HCO_3^- can now be reabsorbed by proximal tubule resulting in a normal distal delivery of HCO_3^-. At this point, the distal nephrons can acidify urine normally resulting in a normal excretion of daily metabolic acid produced. Hypercalciuria is present but as urine citrate levels are normal, nephrocalcinosis or lithiasis is a rarity.

Etiology- It may present as an isolated or generalized proximal tubular dysfunction[3] (i.e. Fanconi syndrome with tubular proteinuria and aminoaciduria with variable degrees of bicarbonaturia, phosphaturia, Na^+, K^+ wasting and glucosuria).

Clinical Profile

- Failure to thrive, growth retardation (most common).
- Polyuria, polydipsia
- Dehydration (due to sodium, H_2O Losses)
- Rachitic Manifestations.
- (Common in fanconi syndrome because of hypophosphatemia)
- Irritability, listlesseness, anorexia or preference for savoury foods.

Type 4 RTA-The underlying defect here is the impaired cation exchange in the distal tubules with reduced secretion of H^+ and K^+. It occurs as a result of impaired aldosterone secretion (hypoaldosteronism) or an impaired renal response to aldosterone. Aldosterone increases Na^+ reabsorption (pseudohypoaldosteronism) and results in a negative intratubular potential. It also increases luminal membrane permeability to K^+ and stimulates basolateral Na^+/K^+ ATPase, causing increased K^+ losses in urine. Since, aldosterone directly stimulates proton pump, aldosterone deficiency or resistance should lead to hyperkalemia and acidosis. Other factor that causes a decreased H^+ excretion in type 4 RTA is the inhibition of ammoniagenesis due to hyperkalemia.[4]

Etiology-Type 4 RTA is most often seen in children with obstructive uropathy or as a transient phenomena during infancy.[5] Primary-(Sporadic; Hereditary); Secondary *(*Hypoaldosteronism, Pseudohypoladosteronism, Chronic kidney disease; Drugs (NSAIDS, b-blockers, ACE inhibitors, K^+ sparing diuretics, cyclosporine)

Clinical Profile

- Growth retardation (most common)
- Polyuria, polydipsia, dehydration.
- Signs and symptoms of obstructive uropathy and features of pyelonephritis.
- Bone diseases are generally *absent.*

Diagnosis-Metabolic acidosis can result from either renal (RTA, CKD) or extrarenal processes which result from an increased indigenous acid production (ketoacidosis) or enhanced HCO_3^- losses (diarrhea, pancreatic/ biliary fistula). RTA may be due to either HCO_3^- wasting (proximal) or inability to generate new HCO_3^- ions to buffer endogenous acid (distal RTA).Since all types of RTA are associated with a normal plasma anion gap, it is the initial step in evaluation of metabolic acidosis.

Plasma Anion Gap-It represents the difference of unmeasured anions and cations in the plasma and is measured as -Anion gap = $Na^+ - (Cl^- + HCO_3^-)$.The normal value of plasma anion gap is 12 + 2 meq/L.

Metabolic acidosis with normal anion gap- Diarrhea, RTA (Both distal and proximal). This normal plasma anion gap metabolic acidosis is also known as "Hyperchloremic metabolic acidosis."

Metabolic acidosis with increased anion gap-Diabetic ketoacidosis (DKA) ,Lactic acidosis due to shock, Ethylene glycol, aspirin

poisoning, Uremia, Some inborn errors of metabolism

Urinary Anion Gap (UAG)- The next step is to distinguish RTA from extrarenal causes. Urinary anion gap (net charge) provides an estimate of urinary $NH4^+$ ion excretion. According to Principle of electroneutrality- Sum of urinary cations = Sum of urinary anions. i.e. $Na^+ + K^+ + Ca^{2+} + Mg^{2+} + NH_4^+ = Cl^- + So_4^{2-} + Po_4^{3-}$ etc. On usual diets, excretion of Ca^{2+}, Mg^{2+}, So_4^{2-}, Po_4^{3-} and other organic ions is fairly constant. Also, urinary Na^+, K^+, Cl^- can be easily measured but NH_4^+ and other ions are usually unmeasured and since the contribution of HCO_3^- to urinary anion is negligible unless the urine is alkaline, therefore, Urinary $Na^+ + K^+ + NH_4^+ = Cl^-$ + other anions; Urinary $Na^+ + K^+ - Cl^- = -NH_4^+$ + other anions. Now, from a practical point of view:- *urinary anion gap i.e. ($Na^+ + K^+ - Cl^- = -NH_4^+$)* and this gives us a fair estimation of NH_4^+ ion excretion. *Normal value of urinary anion gap is 30-35 meq/L.*

Positive UAG-RTA (because of decreased NH_4^+ production, DKA, toluene poisoning, alcoholic ketoacidosis.)

Negative UAG-**Diarrhea**

URINE pH-It assesses the overall integrity of distal urinary acidification and provides an estimate of the number of free H^+ ions in the urine secreted in response. In the presence of systemic acidosis present spontaneously or induced by ammonium chloride (NH_4Cl) loading, the urinary pH is <5.5 normally. If the pH >5.5 during metabolic acidosis, it suggests defective distal secretion of H^+. Acidic Urine-Proximal RTA; Alkaline Urine- Distal RTA, Acute/chronic Diarrhea , Urinary tract infection (with urea splitting organisms).

Ammonium Chloride (Nh_4Cl) Loading Test-Administration of oral NH_4Cl (0.1mg/kg) challenge might be given followed by measurement of urine pH every hour for the next 8 hours to look for renal response to the induced metabolic acidosis. Normally, a fall in plasma total HCO_3 levels by 3-5meq/L induces urinary pH to be <5.5. If in the presence of metabolic acidosis Urinary pH <5.5(Normal response rules out distal RTA); Urinary pH >5.5(Distal RTA – likely cause). However, patients with chronic metabolic acidosis (e.g. after chronic diarrhea) show increased ammoniagenesis that consumes most distally secreted H^+ ions resulting in an enhanced urine NH_4^+ excretion, therefore, "urine pH in these cases may be high despite appropriate H^+ excretion."

Bicarbonate Loading Test-Sodium bicarbonate is administered as half strength intravenous infusion at 3 ml/ min, while measuring urine pH in timed samples every 30-60 minutes apart. A steady state is achieved after 3 to 4 hours of start of infusion, and the test terminated when three urinary samples with pH > 7.5 are collected. Interpretation of this test allows characterization of type of RTA as follows:

Urine to Blood CO_2 Gradient- In alkaline urine (i.e after a $NaHCO_3$ loading) urine PCO_2 increases due to distal H^+ secretion and is considered a sensitive indicator of distal acidification. After achieving a urine pH >7.5 and plasma HCO_3^- levels > 23-25 meq/L, difference between the urine and blood PCO_2 (i.e. U-B PCO_2) is measured as- U-B PCO_2 >20mmHg - Normal / Proximal RTA; U-B PCO_2 <10mmHg - Distal RTA

Fractional Excretion of Bicarbonate ($FeHCO_3$%)- It is an important marker of proximal tubular handling of bicarbonate. Normally, proximal tubules reabsorb most of the filtered bicarbonate (i.e. Fractional excretion is < 5%). The fractional excretion of bicarbonate is calculated following adequate alkalinization as shown -

$FeHCO_3$% = urine bicarbonate x plasma creatinine x 100 plasma bicarbonate x urine creatinine

$FeHCO_3$ < 5% - Normal / Distal RTA; $FeHCO_3$ > 5% - Proximal RTA; Hyperchloremic distal RTA - $FeHCO_3$ varies from 5-10%.

Tests for phosphate handling- Fractional excretion of PO_4 ($FePO4$ %) - Phosphate homeostasis is chiefly regulated at level of proximal tubules. $FePO_4$ (%) determined on timed (6hr, 12hr, 24hr) urine specimen is used as a measure for phosphate handling.

$FePO_4$ (%) = Urine phosphate x plasma creatinine x 100 Plasma phosphate x urine creatinine

Now, tubular reabsorption of PO_4 (%) = 100 - $FePO_4$ (%).Normal range is 85 - 95%. It is reduced in cases of proximal tubular defect and hyper-parathyroidism. Since, tubular reabsorption is markedly

influenced by changes in GFR and dietary changes, it has led to anincreasing use of the index: Tubular maximum of PO_4 corrected for GFR i.e TmP/GFR (Bijovet index).

Bijovet Index (TmP/GFR)- Tubular maximum of phosphate corrected for GFR (TmP/GFR) represents the concentration above which most phosphate is excreted and below which most is reabsorbed. It is an index of renal threshold for phosphate which can be calculated as follow- TmP/GFR (mg/dl) = Plasma PO_4 - urine phosphate x plasma creatinine. Normal value = 2.8 - 4.4 (mg/dl).

Transtubular potassium gradient (TTKG)-Renal tubular disorders are associated with both hypokalemia and hyperkalemia. TTKG provides an accurate estimate of aldosterone effect on sodium potassium exchange in the late distal and cortical collecting tubules. TTKG is an index of the gradient of potassium in distal tubular lumen and interstitial blood capillaries, independent of urine flow rates.[7] It is calculated as follows:

TTKG = urine K^+ × plasma osmolality plasma K^+ x urine osmolality

Normal value = 6-12;TTKG < 2 - hypokalemia (extrarenal causes); TTKG is higher - hypokalemia (renal losses) e.g hypoaldosteronism. In hyperkalemia - expected TTKG is >10; an inappropriately low TTKG (<8) in hyperkalemia suggests hyoaldosteronism or renal tubular resistance to aldosterone.

Frusemide Test- Response to frusemide helps determine the possible site and mechanism of defect in type 1 RTA. Frusemide increases the luminal electronegativity by increasing Na^+ delivery to and reabsorption in the cortical collecting tubule. The changes brought about by frusemide in H^+ and K^+ excretion in normal subjects and in those with various defects of distal RTA **(Table-1)**.[8]Once the diagnosis of RTA is established, it can then be categorized further as summarized by the results of investigations in different forms of RTA (**Table-2).** In addition to these, children with proximal (Type 2) RTA should undergo evaluation for other proximal tubule functions (phosphate, electrolytes, glucose, amino acid excretion) and screening for an underlying etiology (wilson disease, cystinosis). Children with distal RTA, on the other hand should be investigated for urinary calcium excretion, ultrasound for renal calcification, a work up for secondary causes (e.g. obstructive uropathy, reflux nephropathy, chronic tubulointerstitial nephritis) and hearing evaluation.

Management

Alkali supplements are the standard therapy in all types

Type I (Distal) RTA-Electrolyte abnormalities should always be corrected before treating acidosis. Acidosis is corrected by administration of alkali solutions. Initial dose is 2-3meq/kg/day and can be increased until the blood bicarbonate levels become normal. The amount of bicarbonate required to maintain acid base status may be as high as 5-10meq/kg/day and the duration of therapy is usually lifelong. Various alkali solutions used are-Sodium bicarbonate solution (7.5%);Citrate solutions (Polycitra solution (2 meq/ml),Shohl solution (1 meq/ml),Potassium alkali salts should be used if hypokalemia is a persistent problem). In case of associated rickets or osteopenia, Vitamin D should be supplemented. The relatives of patients with idiopathic distal RTA should be screened for this disorder as timely intervention can prevent growth retardation in children.

Type 2 (Proximal) RTA-

Alkali supplementation again remains the treatment of choice. Children with proximal RTA generally require greater amounts of alkali per day (approximately 5-20 meq/kg/day) as compared to distal RTA patients. A thiazide diuretic can be used in conjunction with low salt diet to reduce the amount of bicarbonates required. Thiazides act by causing extracellular fluid contraction and increasing proximal bicarbonate reabsorption. Potassium supplementation is done to compensate for the increased potassium excretion caused by thiazides.Phosphate supplements (e.g. joulie solution, neutral phosphate solution) and moderate doses of Vitamin D may be required. Joulie solution-1ml= 30mg inorganic phosphorous; Neutral phosphate solution-1ml=20mg inorganic

phosphorous. Specific therapy for an underlying disorder (cysteamine for cystinosis, D-penicillamine for wilson disease and lactose free diet in galactosemia) is indicated in few patients.

Type 4 (Hyperkalemic) RTA- The main goal of therapy here is to reduce serum potassium levels (as acidosis improves once the hyperkalemic block of ammonium production is removed). Children are put on a low potassium diet and any drug suppressing aldosterone production is discontinued. Mineralocorticoid supple-mentation with fludro-cortisone will improve hyperkalemia and acidosis. In children with hypertension or heart failure, mineralocorticoids are contraindicated, potassium exchange resins (e.g kayexelate), however, may be required.

Follow Up- A regular follow up must be done for Assessment of growth;Blood levels of electrolyes, pH and bicarbonate levels; Ultrasound screening for nephrocalcinosis in subjects with distal RTA.

Prognosis- Usually depends on the nature of underlying disease. Subjects with RTA usually demonstrate a dramatic improvement in growth provided serum bicarbonate levels are maintained within the normal range. Patients of fanconi syndrome and systemic illnesses may have difficulties with growth failure, rickets and various signs and symptoms pertaining to their disease.

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Table-1, Response of urine Ph and potassium (K^+) excretion following frusemide administration in normal subjects and various defects causing distal RTA.[8]

Defect	Site of Defect	Urine pH		K^+ Excretion	
		During Acidosis	After Frusemide	Baseline	After Frusemide
Normal	None	<5.5	Further Decline	Normal	Increased
H^+ ATPase defect	Diffuse, cortical collecting tubule	>5.5	>5.5	Normal	Increased
H^+ ATPase defect	Medullary collecting tubule alone	>5.5	<5.5	Normal	Increased
Voltage defect	Cortical collecting tubule	>5.5	>5.5	Decreased	Unchanged

Table-2, comparison of various types of RTA

	Proximal RTA	Distal RTA		Type 4 RTA
		Classic	Hyperkalemic	
Plasma K^+	Normal/Low	Normal/Low	High	High
Urine pH	<5.5	>5.5	>5.5	<5.5
Urine anion gap	Positive	Positive	Positive	Positive
Urine NH_4^+	Low	Low	Low	Low
Fractional HCO_3^- excretion	>10-15%	<5%	<5%	5-10%
U-B PCO_2 mmHg	>20	<20	L</>20	>20
Urine Ca^{2+}	Normal	High	High	Normal/low
Other tubular defects	Often present	Absent	Absent	Absent
Nephrocalcinosis	Absent	Present	Present	Absent

Hippocrates contribution to medicine

Tradition knows seven physicians named Hippocrates, of whom the second is regarded as the most famous. Of his life we know but little. He was born at Cos in 460 or 459 B.C., and died at Larissa about 379. How great his fame was during his lifetime is shown by the fact that Plato compares him with the artists Polycletus and Phidias. Later he was called "the Great" or "the Divine". The historical kernel is probably as follows: a famous physician of this name from Cos flourished in the days of Pericles, and subsequently many things, which his ancestors or his descendants or his school accomplished, were attributed to him as the hero of medical science. The same was true of his writings. What is now known under the title of "Hippocratis Opera" represents the work, not of an individual, but of several persons of different periods and of different schools. It has thus become customary to designate the writings ascribed to Hippocrates by the general title of the "Hippocratic Collection" (Corpus Hippocraticum), and to divide them according to their origin into the works of the schools of Cnidus and of Cos, and of the Sophists. How difficult it is, however, to determine their genuineness is shown that even in the third century before Christ the Alexandrian librarians, who for the first time collected the anonymous scrolls scattered through Hellas, could not reach a definite conclusion. For the development of medical science it is of little consequence who composed the works of the school of Cos for they are more or less permeated by the spirit of one great master. The secret of his immortality rests on the fact that he pointed out the means whereby medicine became a science. His first rule was the observation of individual patients, individualizing in contradistinction to the schematizing of the school of Cnidus. By the observation of all the principles were gradually derived from experience, and these, uniformly arranged, led by induction to a knowledge of the nature of the disease, its course, and its treatment. This is the origin of the famous "Aphorismi", short rules which contain at times principles derived from experience and at times conclusions drawn from the same source. They form the valuable part of the collection. The school of Cos and its adherents, the Hippocratics, looked upon medical science from a purely practical standpoint; they regarded it as the art of healing the sick, and therefore laid most stress on prognosis and treatment by aiding the powers of nature through dietetic means, while the whole school of Cnidus prided itself upon its scientific diagnosis and, in harmony with money with the East, adopted a varied medicinal treatment.

8

Review Article

Recurrent Pain abdomen in children

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Recurrent abdominal pain (RAP) in children is defined as continuous or near continuous abdominal pain on 3 or more occasions over a period of at least 3 months in a school going child or adolescent with evidence of limitation in daily activities[1, 2]. RAP is a description and not a diagnosis. It affects 15% of middle and high school children. Five to 10% percent have organic cause for pain [1, 3].

Causes of RAP- The causes of recurrent pain abdomen are extensive. It is useful to classify them as either organic or functional (non organic) causes.

Functional	Organic			
	Gastrointestinal	GB&Pancreas	Genitourinary	Miscellaneous
Functional abdominal pain syndrome Nonulcer dyspepsia Irritable bowel syndrome Aerophagia Abdominal migraine	Chronic constipation Lactose intolerance Parasitic infestation Fructose/sorbitol ingestion Crohn disease Peptic ulcer Esophagitis Meckel's diverticulitis Recurrent intussusception Inguinal/abdominal wall hernias Chronic appendicitis Appendiceal mucocoel	Cholelithiasis Choledochal cyst Recurrent pancreatitis	Urinary tract infections Hydronephrosis Urolithiasis	Abdominal epilepsy Gilbert syndrome Sickle cell crisis Lead poisoning Henoch -schonlein purpura Angioneurotic- edema Acute intermittent porphyria.

Functional Gastrointestinal disorders [4, 5]**-** Specific functional gastrointestinal disorders are diagnosed if the following criteria are met-Functional dyspepsia-(Persistent or recurrent pain centered over upper abdomen (above umbilicus);Not relieved by defaecation or associated with change in form or frequency of bowel action

Irritable bowel syndrome- Abdominal discomfort or pain associated for 25% of the time or more with 2 or more of the following-Improvement with defaecation ,Change in frequency of stool , Change in form or appearance of stool

Functional abdominal pain syndrome-It is diagnosed when there is abdominal pain with one or more of the following-Some loss of daily functioning, Additional somatic symptoms (headache, limb pain, sleep difficulty)

Abdominal migraine- Paroxysmal episodes of intense periumbilical pain lasting 1 or more hours (2 or more times in the preceding 12 months) ; Healthy in between for weeks or months; Pain interferes with normal activities; Pain associated with 2 or more of Anorexia,Nausea, Vomiting, Headache, Photophobia, Pallor

For all of the above subtypes, there should be no evidence of inflammatory, anatomical, metabolic or neoplastic processes to explain the pain and the criteria should be fulfilled for at least once a week for 2 months prior to diagnosis.

Pathophysiology of Functional pain abdomen-There are multiple factors which are thought to influence the perception of pain by the brain from stimuli emanating from visceral receptors in the gastrointestinal tract (G.I.T). Some of these factors are genetic and environmental whereas others are either physiologic or

psychosomatic in nature. Studies have found that children with recurrent pain abdomen have increased sensitivity to stress which impact the physiology of the G.I.T leading to pain as well as slow recovery of autonomic nervous system following stressful responses. They have abnormal perception of gastrointestinal sensation and also have a lower threshold to pain. Studies in patients with irritable bowel syndrome indicate that these patients have altered brain response to rectal stimuli and may be related to central noradrenergic modulation[6]. Children with RAP have also been found to have attentional biases and often associate their pain to certain environmental factors or normal gastrointestinal sensations and increase their anxiety and fear which in turn exacerbates the pain[7]. And finally parents and caregivers may reinforce the child's symptoms and encourage the child to adopt a sick role.

Clinical features-Non organic pain (Age is usually more than 6 years and the commonest site is periumbilical. Pain can sometimes be localized to epigastric or suprapubic region. It interrupts routine activity. Pain is not associated with vomiting or diarrhea and has no relation to meals. It does not wake up the child from sleep. In case of IBS, pain is associated with bloating sensation and incomplete evacuation and relieved by defecation). Organic Pain(More common in children less than 6 years. Site is usually away from the umbilicus, well localized and consistent. Tenderness and rigidity can be present on local examination. Systemic symptoms like fever, weight loss, rash, vomiting, diarrhea, hematochezia and joint pain may be present. Child may have jaundice. The pain disturbs sleep and may cause growth deceleration. In one large Indian series, parasitic infestation was found to be the most common cause of recurrent pain abdomen in children aged between 3 and 12 years [8]).

Red flag symptoms indicating organicity[5]- Involuntary weight loss;Growth faltering; Gastrointestinal bleeding; Pain abdomen in right upper or right lower quadrant; Significant vomiting or chronic diarrhea.

Evaluation-Extensive lab tests are not necessary for nonorganic pain. However following screening tests may be helpful - Complete blood count for evidence of infection or inflammation; ESR (increased in inflammatory bowel diseases, infections and neoplasm); Stool microscopy, reducing substance, occult blood, parasite ova and cyst; Urine analysis and culture sensitivity for cystitis, pyelonephritis or renal calculi. Other investigations depending upon history and clinical findings for organic pain (Liver function tests, serum amylase, ultrasonography of abdomen, radiograph of abdomen, barium series, fluoroscopy, Upper G.I.endoscopy. Breath hydrogen test, breath urea and rapid urease test to diagnose H.pylori particularly in patients with gastritis and peptic ulcer disease, EEG, urine for porphyrias, serum lead levels and Hb electrophoresis in selected cases).

H.pylori infection and recurrent pain abdomen- Community based case control studies from the west have shown that there is no association between H.pylori infection and recurrent pain abdomen and therefore investigating for H.pylori infection in these children are not recommended[9]. However the data was obtained from children from higher socioeconomic strata and hence extrapolating the same to the Indian context would not be applicable. Indian studies on recurrent pain abdomen have yielded mixed results with some studies not recommending evaluation for H.pylori[10] and other studies indicate the need for H.pylori eradication therapy[11].

Treatment-Treatment of underlying cause if organic (antibiotics for urinary tract infection & bacterial overgrowth syndrome, deworming for parasitic infestations, surgery for acute appendicitis, intussusception etc).

Non organic Pain-Reassurance of children and family members is important. Instructions to avoid reinforcing symptoms for secondary gain. Provide less attention to the symptoms and more attention to the child. Biofeedback and relaxation techniques for stress management are often helpful. Medications have a limited role particularly visceral muscle relaxants and antacids. Close follow up is necessary in doubtful and difficult cases.

Specific Treatment

- Irritable bowel syndrome (IBS): Dietary modification in

the form of avoiding or limiting fat, alcohol, caffeine, sorbitol, fructose and corn. Medical management includes anti cholinergics like dicyclomine or hyoscine daily initially and then as and when necessary. Low dose tricyclic antidepressants or 5HT3 receptor antagonists and 5HT4 receptor blockers like tegaserod may be useful.

- Functional Dyspepsia: A diet similar to that of IBS. Medical management essentially consists of H2 receptor blockers or prokinetics and low dose tricyclic antidepressants.
- Abdominal Migraine: Propranolol, cyproheptadine, pizotifen, tricyclic antidepressants or carbamazepine can be tried.
- Aerophagia: Reassurance and limitation of gum chewing and avoiding consumption of carbonated beverages.
- Functional constipation: Increase dietary fibres, fruits and green leafy vegetables. Laxatives and stool softeners to ease the pain associated with passing hard stools. Polyethylene glycol or lactulose solution is often used with dose titration to achieve the required stool frequency. Chronically distended rectum and fecal impaction are managed by administration of rectal enema.
- Cyclical vomiting: Adequate hydration and antiemetics like ondansetron are helpful.

Cognitive behavioral therapy- Contingency management training for parents and self regulation training for the affected child has shown to be effective in the management of recurrent pain abdomen. When compared to standard pediatric care, children receiving cognitive behavioral therapy have shown significant improvements in the domains of pain intensity and pain behavior with complete resolution of symptoms and a very low relapse rate[12].

Prognosis[13]- One third of Children with recurrent pain abdomen can go on to develop chronic abdominal pain in adulthood. Children with chronic abdominal pain are more likely to have emotional and psychological problems later in life. Irritable bowel syndrome is likely to persist well into adulthood often needing longer duration of treatment especially cognitive and behavioral therapy.

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Hirschowitz fiberoptic Endoscope, 1960

Fiberoptic endoscopy entered the realm of practicality in February 1957 when Basil Hirschowitz passed the first prototype instrument down his own throat and, a few days later, down that of a patient. Hirschowitz began work on the "fiberscope" in 1954 when he was on a fellowship with Marvin Pollard at the University of Michigan. After reading an article by Hopkins and Kapany describing recent advances in fiberoptics, Hirschowitz visited the authors in Britain and discussed the application of fiberoptics to endoscopy. Over the next three years, Hirschowitz and his associates in Ann Arbor, physicist C. Wilbur Peters and his student, Larry Curtiss, devised a makeshift, but effective method of drawing out their own glass fibers. In late 1956 Curtiss succeeded in producing the glass-coated fiber with the optical qualities required for the fiber bundle of a gastroscope. Following the demonstration of the new fiberscope incorporating this advance in 1957, Hirschowitz collaborated with ACMI (American Cystoscope Manufacturing Inc.) to produce a practical instrument. Finally, in October, 1960, Hirschowitz received the first production model, and presented it in *Lancet*, confidently asserted that "the conventional gastroscope has become obsolete on all counts."

This instrument diminished patient discomfort by enhancing flexibility and by reducing bulk. Notable endoscope refinements of the late 1960s and early 1970s included re-positioning of lenses

Basil Hirschowitz examining a patient with the fiberscope, 1961.

for wider field of vision, addition of channels for biopsy forceps, suction, air, or water, and four-way controlled tip deflection.

Fiberoptic technology transformed gastrointestinal endoscopy in ways even more profound than its most ardent advocates might have imagined. Endoscopic procedures become safer and hence more commonplace, and virtually no region of the gastrointestinal tract remained unexplored. William Haubrich, editor of *Gastrointestinal Endoscopy*, recalled that "improvements in endoscopic design were so numerous and rapid during the early 1970s that one could hardly purchase a new instrument and become acquainted with its use before that instrument was rendered obsolete by a new model." The expanding diagnostic capabilities of endoscopy were soon complemented by new therapeutic applications, including colon polypectomy with a wire loop snare (1971), cannulation of the pancreatic duct (1972), removal of biliary stone (1975), and placement of feeding tubes by gastrostomy (1979). The range of technical developments in gastrointestinal endoscopy was so extensive across a broad front that John F. Morrissey was prompted to claim that "I think we are approaching a plateau in instrument development." This conclusion proved premature, but nonetheless conveys the amazement that Morrissey and his fellow gastrintestinal endoscopists felt when surveying the recent instrumental development of their field. Indeed, fiberoptic technology spread rapidly from gastroscopy to colonoscopy, bronchoscopy, and other endoscopic domains.

9

Review Article

Neonatal Necrotizing Enterocolitis

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Necrotizing enterocolitis (NEC) is primarily a disease process of the gastrointestinal (GI) tract of premature neonates that results in inflammation and bacterial invasion of the bowel wall. It occurs in 1%to 5% of all NICU admissions and 5% to10% of very low birth weight infants. More than 75% of cases occur in infants born at less than 36 weeks of gestation and weighing under 2000 g. The postnatal age of onset is a function of the gestational age, with the peak incidence occurring approximately 3 weeks after birth in infants born at <32 weeks, whereas disease develops approximately 2 weeks after birth in infants born between 32 and 36 weeks and under 1 week of postnatal age in infants born at >36 weeks of gestation. Although NEC occurs primarily in infants born prematurely, approximately 10 % 0f NEC occurs in full term infants.Necrotizing enterocolitis is predominantly a disease of preterm. NEC in term infants is often assosciated with risk factors like maternal toxemia, birth asphyxia, cyanotic heart disease, polycythemia, acidosis ,shock, exposure to cocaine etc.

Pathophysiology- Epidemiologic studies have identified multiple factors that increase an infant's risk for the development of NEC, although premature birth, bacterial colonization and intestinal ischaemia are thought to play central role in disease pathogenesis. The sequence of events leading to the development of NEC is complex and still incompletely defined. Although the pathophysiology of NEC has not been completely elucidated, progress has been made in the characterization of the molecular events which may take place during an episode of ischemia. This possible initiating event is followed by a complex cascade of inflammatory mediators active in NEC; epidermal growth factor, platelet activating factor and nitric oxide. Platelet-activating factor has been considered as one of the most important mediator in the pathophysiology of NEC. PAF has a short half-life, and is regulated by PAF-degrading enzyme acetyl hydrolase (PAF-AH) activity of which degrades PAF into the inert lyso-PAF. There is considerable evidence that PAF-AH may play a role in the occurrence of NEC. PAF-AH activity is decreased in sick infants with NEC, and the administration of PAF-AH in animal models of NEC reduces the incidence of NEC. PAF-AH activity has also been demonstrated in breast milk, suggesting it might be one of the factors which makes breast milk protective against NEC[1]. EGF also plays an important role in intestinal barrier function. In response to injury, EGF enhances the migration and proliferation of intestinal epithelial cells, leading to a reduction in the severity of intestinal injury. In animal models, EGF administration increased intestinal barrier strength and reduced the severity of experimental NEC. Furthermore, decreased levels of EGF have been shown in the saliva and serum of premature infants with NEC, decreased heparin-binding EGF-like growth factor have been found in NEC-affected areas of the intestine and a recent study suggests that salivary EGF levels in the first and second week of preterm life may have predictive value for NEC. Nitric oxide plays a paradoxical role in intestinal physiology, low levels enhance the mucusal blood flow and are key to maintaining mucusal intergrity , whereas sustained high levels cause cytopathic effects on gut epithelium. Upregulation of nitric oxide plays an integral role in the development of epithelial injury in NEC. Nitric oxide (NO), an important second messenger and inflammatory mediator and its reactive nitrogen derivative, peroxynitrite, may affect gut barrier permeability by inducing enterocyte apoptosis (programmed cell death) and necrosis, or by altering tight junctions or gap junctions that normally play a key role in maintaining epithelial monolayer integrity[2]. As a result, some treatment strategies have been aimed at abrogating the toxic effects of nitric oxide.

Prematurity- In the preterm infant, mucosal cellular immaturity and the absence of mature antioxidative mechanisms may render the mucosal barrier more susceptible to injury. Intestinal regulatory T-cell aggregates are a first-line defense to luminal pathogens and may be induced by collections of small lymphoid aggregates, which are absent or deficient in the premature infant[3]

Fig-1, Pathogenesis of NEC

Bacterial colonization- Whether bacteria are primary in the initiation of NEC, or whether bacterial invasion occurs secondarily following the breakdown of the epithelial barrier is not known. So far, however, a single bacterial species or virus has not been consistently isolated in cases of NEC . *Enterobacteriaceae* sp. are the most commonly described bacteria to be found in association with NEC . *Clostridia* sp. and *Staphylococcus* sp. have also been isolated from infants with NEC . Although bacteria are clearly the most commonly associated microbe with this disease, isolation of viruses and fungus have been described .

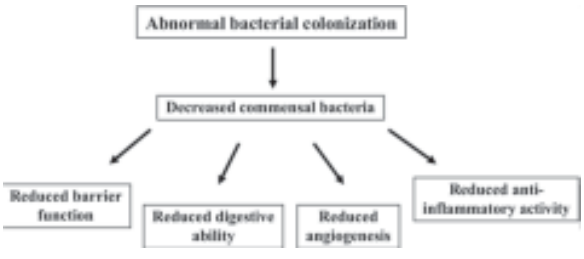


Fig-2, Bacterial colonization and NEC

Intestinal ishaemia-NEC in term infants is due to risk factors which implicate an insult to the intestinal blood supply. The diving seal reflex is a mechanism by which intestines suffer most following a hypoxic injury. The ileocaecal region is most frequently involved which is watershed area in the intestine, also suggesting the hypoxic ishaemic event in the pathophysiology of NEC. Despite convincing that evidence that hypoxic ishaemic stress is involved in term NEC, preterm NEC appear to involve a different disease altogether , althogh it still plays a secondary role due to immature circulatory regulation in response to ishaemia.

Clinical Features-Initial symptoms may be subtle and can include one or more of the following:Feeding intolerance, delayed gastric emptying ,abdominal distention, abdominal tenderness decreased bowel sounds ,abdominal wall erythema, bloody stools, persistent localized abdominal mass, ascites. Systemic signs are nonspecific and can include any combination of the following: Respiratory distress, apnea ,lethargy, decreased peripheral perfusion, temperature instability,poor feeding, irritability, acidosis , shock, cardiovascular collapse, bleeding diathesis.The physical findings in patients who develop NEC can be primarily gastrointestinal, systemic, indolent, fulminant, or any combination of these. A high index of clinical suspicion is essential to minimize potentially significant morbidity or mortality.

Laboratory Studies- Abdominal X-ray should be obtained if any sign suggestive of NEC is present Laboratory studies are helpful if the baby is having systemic signs-CBC count with manual differential to evaluate the WBC, hematocrit and platelet count; WBC count: marked elevation may be present, but leukopenia is more concerning; RBC count: Premature infants are prone to anemia due to iatrogenic blood draws,as well as anemia of prematurity; however, blood loss from hematochezia and /or a developing consumptive coagulopathy can manifest as an acute decrease in hematocrit; Platelet count: NEC is commonly associated with thrombocytopenia (<100,000/ì L). Thrombocytopenia may become more profound in severe cases that become complicated with consumption coagulopathy. Consumption coagulopathy is characterized by prolonged PT, prolonged aPTT, and decreasing fibrinogen and increasing fibrin degradation product concentrations; Blood culture: Obtaining a blood culture is recommended before beginning antibiotics in any patient presenting with any signs or symptoms of sepsis or NEC. Although blood cultures do not grow any organisms in most cases of NEC, sepsis is one of the major conditions that mimics NEC and should be considered in the differential diagnosis. Therefore, identification of a specific organism can aid and guide further therapy; Serum sodium: Hyponatremia is due to capillary leak and "third spacing" of fluid within the bowel and peritoneal space. Depending on the baby's age and feeding regimen, baseline sodium levels may be low-normal or subnormal, but an acute decrease (<130 mEq/dL) is more significant; Metabolic acidosis: Low serum bicarbonate (<20) is seen in conjunction with poor tissue perfusion, sepsis, and bowel necrosis. Thrombocytopenia, persistent metabolic acidosis and severe refractory hyponatremia constitute the most common triad of laboratory signs; Stool analysis- presence of blood and carbohydrate is a frequent and early indicator of NEC when associated with the signs of NEC; Serial CRP may help in monitering the progress of the disease. Although all of these initial laboratory studies taken together may aid in the diagnosis of NEC, they do not substitute for an appropriate appreciation of clinical presentation and appearance of the infant. The laboratory values can give insight into the severity of the disease and can aid in the provision of appropriate therapy.

Imaging Studies- The mainstay of diagnostic imaging is abdominal radiography. An anteroposterior (AP) abdominal radiograph and a left lateral decubitus radiograph (left-side down) are essential for initially evaluating any baby with abdominal signs. Abdominal radiograph should be taken serially at 6-hour or greater intervals, depending on presentation and clinical course. Characteristic findings on an AP abdominal radiograph include an abnormal

gas pattern, dilated loops, and thickened bowel walls (suggesting edema/inflammation). Serial radiographs helps in assessing disease progression. A fixed and dilated loop that persists over several examinations is especially important. The finding of a fixed loop that remains unchanged for 24 to 48 h is often associated with transmural necrosis. Radiographs can sometimes reveal scarce or absent intestinal gas, which is more significant than diffuse distention that changes over time. Pneumatosis intestinalis is a radiologic sign pathognomonic of NEC. It appears as a characteristic train-track lucency configuration within the bowel wall. Intramural air bubbles result from bacterial invasion, fermentation and hydrogen production in the intestinal wall. Pneumatosis intestinalis is thought to be the hallmark of NEC disease but may also be present in advanced cases of Hirschsprung's enterocolitis or severe gastroenteritis.

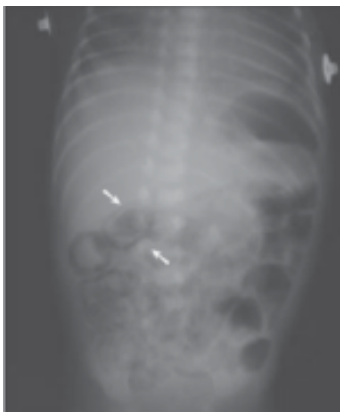


Fig-3, Pneumatosis intestinalis

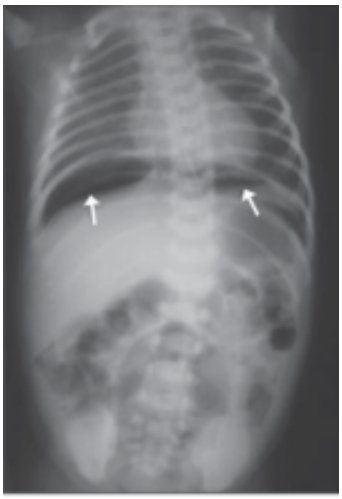
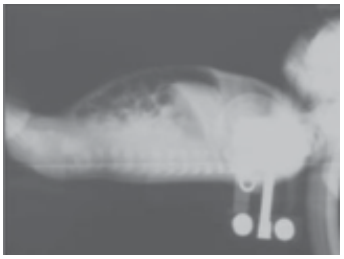


Fig-4, Pneumoperitonium



Abdominal free air is ominous sign. The presence of abdominal free air can be seen as oblong lucency over the liver and abdominal contents. It represents the air bubble that has risen to the most anterior aspect of the abdomen in a baby lying in a supine position.Left lateral view allows the detection of intraperitoneal air which rises above the liver shadow and can be visualized easier than on other views. Free air in the abdomen can be seen as a central collection of air on the anteroposterior film of the abdomen, or can highlight the falciform ligament. Portal gas is thought to be ominous when detected. Portal gas appears as linear branching areas of decreased density over the liver shadow and represents air present in the portal venous system and occurs when intramural air is absorbed into the mesenteric venous circulation Ascites is a late finding that usually develops when peritonitis is present or after bowel perforation. Ascites is observed on an AP radiograph as centralized bowel loops that appear to be floating on a background of density.

Ultrasonography- It can be used to identify areas of loculation and abscess consistent with a walled-off perforation when patients with indolent NEC have scarce gas or a fixed area of radiographic density. Ultrasonography is excellent for quantifying ascites. Serial examinations can be used to monitor the progression of ascites as a marker for the disease course. Portal air can be easily observed as bubbles present in the venous system. Ultrasonographic assessment of major splanchnic vasculature can help in the differential diagnosis of NEC from other more benign disorders. Doppler study of the splanchnic arteries early in the course of NEC shows increased peak flow velocity and it can help distinguish developing NEC from benign feeding intolerance in a mildly symptomatic baby. Imaging techniques, such as contrast radiography, portal vein ultrasonography, MRI, and radionuclide scanning, may play a role in diagnosis. These techniques are not currently in common use. GI tonometry is an infrequently used technique that may be helpful in distinguishing benign feeding intolerance from early NEC.

Modified Bells Staging

Stage	Systemic signs	Intestinal signs	Radiological signs	Treatment
Stage 1A (suspected disease)	Lethargy, apnea, bradycardia, temperature instability	Increased gastric residuals, emesis, mild abdominal distention, gauic positive stool	Normal or mild nonspecific dilatation	NPO -3days & IV antibiotics IVF, TPN
Stage 1B	Same as above	Gross bloody stool	Same as above	Same as above
Stage IIA (definite disease) (mildly ill)	Same as above	Same as above plus abdominal tenderness absent bowel sounds	Illeus, intestinal dilatation, pneumatosis intestinalis	Supportive treatment, NPO, iv antibiotics for 14 days, TPN
Stage IIB (moderaty ill)	Same as above plus mild metabolic acidosis and mild thrombocytopenia	Same as above plus definite tenderness, erythema or other discolouration, right lower quadrant mass	Same as above plus portal vein gas, +/- ascitis	NPO, antibiotics for 14 days, Surgical consultation as needed
Stage IIIA (advanced NEC) severly ill, bowel intact	Hypotension, bradycardia, respiratory failure, severe metabolic acidosis, coagulopathy, neutropenia	Marked distension with signs of generalized peritonitis	Definite ascitis	NPO for 14 days, fluid resuscitation, ventilator support, surgery consultation, TPN
Stage IIIB severly ill, bowel perforated	Same as above	Same as above	Intestinal perforation	Same as above and surgery

Treatment

Medical Care-Diagnosis of necrotizing enterocolitis (NEC) is based on clinical suspicion supported by findings on radiologic and laboratory studies. Treatment of NEC depends on the degree of bowel involvement and severity of its presentation. Objective staging criteria developed by Bell have been widely adopted or modified to help tailor therapy according to disease severity.

Antibiotics-Although no single infectious etiology is known to cause NEC, clinical consensus finds that antibiotic treatment is appropriate. Broad-spectrum parenteral therapy is initiated at the onset of symptoms after obtaining blood, spinal fluid, and urine for culture. Antibiotic coverage for staphylococcus should be considered in neonatal ICUs (NICUs) that have a high colonization rate. Antifungal therapy should be considered for premature infants with a history of recent or prolonged antibacterial therapy or for babies who continue to deteriorate clinically or hematologically despite adequate antibacterial coverage. Various antibiotic regimens can be used; one frequently used regimen includes ampicillin, amino glycoside (eg, gentamicin) or third-generation cephalosporin (cefotaxime), and clindamycin or metronidazole. Vancomycin should be included if staphylococcus coverage is deemed appropriate. This combination provides broad gram-positive coverage (including staphylococcal species), excellent gram-negative coverage (with the exception of pseudomonas), and anaerobic coverage.

Diet-When NEC is suspected, enteral feedings are withheld and parenteral nutrition is initiated. Centrally delivered formulations with appropriate nutritional

components are infused for optimal IV nutrition. Enteral feedings can be restarted 10-14 days after findings on abdominal radiographs normalize in the case of nonsurgical NEC. Reinitiating enteral feeds in postsurgical babies may take longer and may also depend on issues such as the extent of surgical resection, return of bowel motility, timing of reanastomosis, and preference of the consulting surgical team. Because of the high incidence of postsurgical strictures, intestinal patency can be evaluated by contrast studies prior to initiating enteral feeds. When feeds are restarted, formulas containing casein hydrolysates, medium-chain triglycerides, and safflower/ sunflower oils may be better tolerated and absorbed than standard infant formulas.

Surgical treatment-Despite appropriate and timely medical management, approximately 30% of patients with NEC require surgical intervention.Clinical deterioration or the development of worsening signs on the abdominal x rays may indicate a need to proceed with surgical management. Paracentesis can be performed at the bedside in the event of deterioration at the bedside when there is no clearcut radiographic evidence of perforation. However, there are no standard guidelines for when this tool should be used. With a reported specificity of 100%, a positive tap, evidence by an aspirate containing bile or stool or one which shows organisms on gram stain, is an absolute indication for abdominal exploration. As the sensitivity is somewhat lower, a negative tap does not exclude perforation and should not be considered evidence against exploration if clinical signs suggestive of necrosis or perforation. Free air visible on abdominal radiograph is an indication for surgery. Surgical treatment includes resecting the affected portion of the bowel, which may be extensive. Initially, an ileostomy with a mucous fistula is typically performed, with reanastomosis performed later. Strictures may occur, with or without a history of surgical intervention, which may require surgical treatment. Patients who are extremely small and ill may not have the stability to tolerate laparotomy. If free air develops in such a patient, one may consider inserting a peritoneal drain under local anesthesia in the nursery which will allow stabilization of the infants before laparotomy.

Complications-The management of NEC is not without complications. The most serious complications of acute NEC include intestinal necrosis and perforation, which may occur in up to one-third of patients. However, some patients who initially appear to respond well to medical management develop signs of intestinal obstruction upon resuming enteral feedings due to the development of ischemic strictures in the small or large intestine. Intestinal strictures develop in up to one-third of patients with a history of NEC. The most commonly affected areas include the terminal ileum, splenic flexure and the junction of the descending and sigmoid colon. Radiographic imaging may confirm bowel obstruction, with a transition zone and air–fluid levels. If a stricture is suspected a contrast enema (or an upper gastrointestinal study) should be performed to assess intestinal patency. If a stricture is demonstrated, surgical resection is indicated at this time. In addition to intestinal strictures, almost 10% of patients with a history of NEC and surgical intervention develop short gut syndrome. The neonatal gut grows and adapts over time, but long-term studies suggest that this growth may take as long as 2 years to occur. During that time, maintenance of an anabolic and complete nutritional state is essential for the growth and development of the baby. This is achieved by parenteral provision of adequate vitamins, minerals, and calories; appropriate management of gastric acid hypersecretion; and monitoring for bacterial overgrowth. The addition of appropriate enteral feedings during this time is important for gut nourishment and remodeling. Many of these infants eventually require small bowel transplantation and occasionally, combined liver and small bowel transplantation

Prognosis-Currently the mortality remains estimated at 20% to 50%. Very low birthweight infants and those with low gestational age continue to have the highest mortality. In several studies, extent of bowel involvement has been found to be predictive of mortality. Infants requiring surgical intervention also tend to be lower gestational age and have a smaller birth

weight. Necrotizing enterocolitis was an independent risk factor for an abnormal neurologic examination .

Prevention

Feeding practices- Human milk feeding reduces the incidence of NEC. Human milk contains secretory immunoglobulinA (IgA), which binds to the intestinal luminal cells and prohibits bacterial transmural translocation. Other constituents of human milk, such as interleukin (IL)-10, EGF, TGF-â1, and erythropoietin may also play a major role in mediating the inflammatory response. Oligofructose encourages replication of bifidobacteria and inhibits colonization with lactose-fermenting organisms. However, breast milk alone does not prevent the development of NEC. Whereas conservative feeding practices can reduce NEC, prolonged NPO treatment may worsen gut function by causing gut atrophy and worsened inflammatory responses, which can predispose to NEC. Diet plays an important role in intestinal development and defense. Nonnutritive dietary substances, such as epidermal growth factor and polyamines, stimulate intestinal epithelial growth. Furthermore, certain nutrients (glutamine, arginine, omega-3 fatty acids) have been shown to counteract proinflammatory activation and promote intestinal barrier function, proliferation, and healing. Therefore, initiation of trophic feeds should be considered in all VLBW infants. Trophic feeds have been shown to improve activity of digestive enzymes, enhance digestive hormone release, intestinal blood flow, and motility in premature infants. In addition, infants provided early trophic feeds appear to have improved feeding tolerance, improved growth, reduced sepsis, and reduced hospital stay compared with infants who do not receive trophic feeds. Furthermore, early trophic feeds do not increase the incidence of NEC.

Probiotics-A proposed strategy for the prevention of NEC is the administration of oral probiotics. Probiotics are food supplements containing live bacteria that benefit the recipient by improving the microflora balance within the intestine. Several studies suggest that the administration of probiotics may have a prophylactic effect for NEC and may reduce morbidity and mortality rates for low birth weight infants. The most frequently used probiotics are lactobacillus and Bifidobacterium. Potential mechanisms by which probiotics may protect high risk infants from developing NEC and/or sepsis include increased barrier to migration of bacteria and their products across the mucosa , competitive exclusion of potential pathogens , modification of host response to microbial products , augmentation of IGA mucosal responses, enhancement of enteral nutrition that inhibit the growth of pathogens, and up-regulation of immune responses [4,5]. However, the data are insufficient to comment on their short- and long-term safety. Type of probiotics used, as well as the timing and dosage, are still to be optimized. Further understanding of the pathogenesis of NEC and the mechanisms by which probiotics prevent it may lead to evidence-based treatment strategies.

Epidermal growth factor- Heparin-binding epidermal growth factor-like growth factor (HB-EGF) is a potent intestinal cytoprotective agent. HB-EGF reduces the incidence and severity of NEC in a neonatal rat model, with simultaneous preservation of gut barrier integrity. These results support that HB-EGF administration may represent a useful therapeutic and prophylactic therapy for the treatment of NEC. In addition, several investigators have reported the cytoprotective effect of epidermal growth factor, which is found in high levels in breast milk, on the intestinal epithelium. Thus, fortification of infant formula with specific growth factors could soon become a preferred strategy to accelerate intestinal maturation in the premature neonate to prevent the development of NEC[6,7]

Oral antiobiotics- There have been reports published suggesting that the use of enteral antibiotics may be effective as prophylaxis[8]. However concerns about adverse outcomes persist, particularly related to the development of resistant bacteria.

Pentoxiyflline- Agents that modulate inflammation may improve outcome in NEC. Pentoxifylline, a phospho-diesterase inhibitor when used as an adjunct to antibiotics reduces mortality without any adverse effects[9]

Arginine- Metabolic abnormalities are also associated with NEC, one of which is reduced plasma arginine concentrations. Decreased arginine availability causes diminished NO production via the NOS pathway, and that this may be involved in the pathophysiology of NEC. Both oral and intravenous arginine supplementation suggests a beneficial role against NEC in premature infants[10].

Immunoglobulins- Immunoglobulins are one of many possible factors in human milk responsible for it is protective effects on NEC. Neonates have decreased immunoglobulin levels, particularly secretory IgA. However, oral immunoglobulin administration has largely been ineffective in preventing NEC, although studies of enteral IgA are lacking. Intravenous immunoglobulin(IVIG) has also failed to demonstrate significant reductions in NEC, sepsis, or mortality[11].

Glucocorticoids-Clinical studies have shown that the antenatal administration of glucocorticoids decreases the incidence of NEC. However, postnatal steroids do not appear to be as promising[12].

Erythropoitien-Erythropoeitin (Epo) is another breast milk component that may play a role in intestinal development,cell migration, and intestinal restitution. Receptors for Epo are also present in the intestine. Contact with Epo occurs both pre- and postnatally, through exposure to amniotic fluid and breast milk, respectively. These findings suggest that Epo plays a role in intestinal development. Further, Epo has been shown to increase cell migration and to have protective effects when cells are exposed to injury. These encouraging findings provide rationale to further investigate the possible role of Epo as a preventive strategy for NEC[13].

Carbon monoxide- Carbon monoxide (CO), a byproduct of the catabolism of heme, is known to have anti-inflammatory and antiapoptotic properties. Animal studies have shown that carbon monoxide decreases enterocyte production of inducible nitric oxide synthatse(iNOS) and nitric oxide ,inflamatory cytokines and nitrites[14].

Resveratrol- Resveratrol, a polyphenol compound from phytoalexins has antioxidant and scavenger properties and also play a critical role in modulating key enzymes in cell cycle including iNOS. Animal studies with newborn rats have shown that enteral resveratrol has beneficial effect on NEC by attenuating the realese of iNOS and preservation of mucosal integrity[15].

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Arabian medical science

Arabian medical science forms an important chapter in the history of the development of medicine, not because it was especially productive but because it preserved Greek medical science with that of its most important representative Galen. It was, however, strongly influenced by oriental elements of later times. The adherents of the heretic Nestorius, who in 431 settled in Edessa, were the teachers of the Arabs. After the expulsion these Nestorians settled in Dschondisapor in 489, and there founded a medical school. After the conquest of Persia by the Arabs in 650, Greek culture was held in great esteem, and learned Nestorian, Jewish, and even Indian physicians worked diligently as translators of the Greek writings. In Arabian Spain conditions similarly developed from the seventh century. Among important physicians in the first period of Greek-Arabic medicine — the period of dependence and of translations — come first the Nestorian family Bachtischua of Syria, which flourished until the eleventh century; Abu Zakerijja Jahja ben Maseweih (d. 875), known as Joannes Damascenus, Mesue the Elder, a Christian who was a director of the hospital at Bagdad, did independent work, and supervised the translation of Greek authors, Abu Jusuf Jacub ben Ishak ben el-Subbah el-Kindi (Alkindus, 813-73), who wrote a work about compound drugs, and the Nestorian Abu Zeid Honein ben Ishak ben Soliman ben Ejjub el 'Ibadi (Joannitius, 809-about 873), a teacher in Baghdad who translated Hippocrates and Dioscurides, and whose work "Isagoge in artem parvam Galeni", early translated into Latin, was much read in the Middle Ages. Wide activity and independent observation — based, however, wholly upon the doctrine of Galen — were shown by Abu Bekr Muhammed ben Zakarijia er-Razi (Rhazes, about 850-923), whose chief work, however, "El-Hawi fi'l Tib" (Continens) is a rather unsystematic compilation. In the Middle Ages his "Ketaab altib Almansuri" (Liber medicinalis Almansoris) was well known and had many commentators. The most valuable of the thirty-six productions of Rhazes which have come down to us is "De variolis et morbillis", a book based upon personal experience. We ought also to mention the dietetic writer Abu Jakub Ishak ben Soleiman el-Israili (Isaac Judaeus, 830-about 932), an Egyptian Jew; the Persian, Ali ben el Abbas Ala ed-Din el-Madschhusi (Ali Abbas, d. 994) author of "El-Maliki" (Regalis dispositio, Pantegnum). Abu Dshafer Ahmed ben Ibrahim ben Abu Chalid Ihn el-Dshezzar (d. 1009) wrote about the causes of the plague in Egypt. A work on pharmaceutics was written by the physician in ordinary to the Spanish Caliph Hisham II (976-1013), Abu Daut Soleiman ben Hassan Ibn Dsholdschholl.

10

Original Article

Assessment of Bronchial Liability on Exposure to Isometric Exercise during Different Phases of Menstrual Cycle

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The effect of sex hormones on airway function has not been well studied inspite of much evidence to suggest that they are important. Epidimiologic studies have demonstrated greater airway obstruction in men than women even when corrected for smoking habits [1]. The menstrual rhythm has been well documented for exacerbations of asthma [2,3] and a third of female asthmatics reportedly suffer from 'premenstrual asthma' [4]. These findings suggest possible role of gonadal steroids in cyclical variation of bronchial tone. The respiratory stimulating effect of progesterone is well known. It is also known that the level of progesterone varies during the menstrual cycle in adult women [5]. The reported effects of exogenous progesterone administration include hyperventilation, partially compensated respiratory alkalosis etc [6]. Inspiratory muscle endurance was found to be higher in the mid luteal phase than in the mid follicular phase when the subjects had high plasma progesterone levels in the luteal phase, whereas no difference in the inspiratory muscle endurance was seen in subjects whose plasma progestrone level was not high enough in the mid luteal phase [7] .Some studies have concluded that physiologic changes in hormone levels during the menstrual phases are not in themselves associated with changes in airway or skin responsiveness to histamine [8]. Chen and Tang (1989) documented no obvious difference in pulmonary functions in different phases of menstrual cycle. Cortisol is known to increase under stressful conditions. Also there is cyclic variation in the basal levels of ACTH during the menstrual cycle [9,10]. It seemed worthwhile to study the interplay of these hormones during the menstrual cycle after exposing the subject to isometric stress of short duration. Also estradiol increases the relaxant effect of catecholamines , a falling estrogen level may reduce sensitivity to catecholamines which in turn affect airway response. [10] Although the effect of corticosteroid hormones on bronchial smooth muscle is well established, the effect of female sex steroids has not been well studied. Hence, the present study was planned to assess the role of gonadal steroids (estrogen and progesterone) on bronchial lability under resting conditions and when exposed to simple isometric exercises (hand grip) in different phases of menstrual cycle.

Material and methods-The study was conducted in the Department of Physiology, Maulana Azad Medical College, New Delhi, India.It extended over a period of one year between March 2004 and March 2005.

Selection of subjects-30 healthy female volunteers (25-40 yrs) with regular and normal menstrual cycle were selected from amongst the students and staff of the college. They were studied in different phases of the menstrual cycle viz menstrual phase (MP), proliferative phase (PP) and luteal phase (LP)

Excusion criteria-Subjects with irregular cycles;Subjects on OCPs; Subjects with history of bronchial asthma; History of cardiovascular disease; History of restrictive lung disorders; Subjects with musculo – skeletal deformities.

Menstrual phase was based on subjects' statement. They were further confirmed by measuring the plasma level of estrogen and progesterone. The basal oral temperature was also recorded during each phase.

Recording of pulmonary functions-Spirometric measurements were done on the 2nd day of the menstrual cycle . 8th – 12th day was taken as proliferative and 18th -24th day of menstrual cycle

was taken as the luteal phase.[11]The pulmonary functions were tested under basal conditions and then following hand – grip exercise in the three phases of menstrual cycle. The spirometric lung functions were recorded in the sitting posture using precalibrated spirometer '*spirolab – II*' with nose clip on. All spirograms were recorded by one investigator to minimize inter – observer variation. The ambient laboratory temperature was maintained between 20-25^{0}C. In order to allay anxiety and apprehension associated with testing , they were explained the purpose of the study and also the technical procedures to be performed. Before the actual testing, each subject was familiarized with various test procedures viz breathing through mouth piece and valve. The forced expiratory maneuvers were performed atleast 3 times for each subject and best of three attempts were selected for data computation.A hand – grip sustained isometric contraction (SIC) was performed in the supine position using a hand mechanical dynamometer . Initially each subject was familiarized with the experimental device and systematically trained. The subjects were asked to grip maximally with their dominant hand.The highest value of three contractions was taken as the maximum voluntary contraction (MVC). Hand grip was maintained steadily at 30 % of MCV till the subject got fatigued.[12] Spirometric measurements were done within five minutes of cessation of hand grip exercises.Statistical analysis was done with the statistical package PRISM. The data before and after had grip test was compared using student's 't' test with 'P' < 0.05 considered to be significant.

Results - The general characteristics of subjects are given in Table-1. Sex hormones level fluctuated as expected with highest level of progesterone during luteal phase and that of estradiol during proliferative phase as shown in Table-2. The pre- exercise and post- exercise values of different parameters of pulmonary functions in the three phases of menstrual cycle can be seen in Table -3**.**All values are expressed as mean ± S.E . Fall in FVC, PEFR, FEV_1 (%) and $FEF_{25-75\%}$ was seen following exercise in all three phases of menstrual cycle . However only the fall in PEFR was found to be significant (P< 0.05) (Fig-2) ,whereas FVC **(**Fig-1), FEV_1 (%) (Fig-3) and $FEF_{25-75\%}$ (Fig-4) decreased non – significantly (p>0.05) after isometric exercise.

Discussion-There is compelling evidence for hormonal influence on airways and changes in airway responsiveness might occur during menstrual cycle. Our results showed a generalized fall in pulmonary function after sustained isometric contraction during all three phases of menstrual cycle. No difference was observed in pulmonary function test under resting conditions in the menstrual,proliferative and luteal phases of the menstrual cycle. This is in accordance to the findings of Chen and Tang (1988) who showed that inspiratory muscle endurance in the mid luteal phase of the menstrual cycle when the plasma progesterone level was relatively high was greater than in the mid follicular phase. The muscle strength and resting pulmonary function , on the contrary , were similar in these two phases of the menstrual cycle.[7] It is possible that the effect of sex hormones relate not to peak serum levels but rather to falling levels.[8]The general fall seen in all respiratory parameters in our study could be due to psychic factors or fatigue.It could also be attributed to isometric exercise mediated bronchoconstriction due to á adrenergic discharge.[13-15] In our study, significant decrease in PEFR was seen in all the phases of menstrual cycle when exposed to hand grip test. This is in contrary to the findings of Pauli and co-workers (1989)[16] who stated that an increase in asthma symptoms and a slight decline in PEFR only in luteal phase was seen in asthmatics. Therefore it seemed worthwhile to study the relationship between the menstrual cycle and the measures of airway function and airway reactivity in normal subjects also.It is well known that there is isotonic exercise induced broncho-constriction after completion of exercise rather than during it. This has been attributed to increased nor – adrenaline levels in the early post-exercise period which interacts with histamine , a probable mediator of broncho – constriction after exercise. [17-18]It has been seen in our study that there is significant fall in PEFR

values after hand grip exercise. Decrease in PEFR generally correlates with FEV_1 which is a measure of airway obstruction. [19] The absence of such correlation in our study may be due to menstrually related variation in effort. Also the importance of PEFR is more for longitudional studies ,it is also not sufficiently sensitive to detect changes in airway function on its own .[20] We conclude that changes in healthy normal women of reproductive age group with normal menstrual cycle show no deterioration (change) in airway responsiveness after isometric exercise. Our negative findings do not exclude the possibility of other sex hormones (testosterone) and of the fluctuating levels of female sex hormones to affect bronchial lability under different conditions. Thus it may be an interaction of many factors rather than hormone levels during menstrual cycle before and after exercise which may lead to change in airway responsiveness.

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Table-1,Baseline characteristics of the subjects (values are expressed as mean ± SD)

Age (years)	29.2 ± 0.98
Height (cms)	159.4 ± 1.98
Weight (kg)	56.3 ±1.67

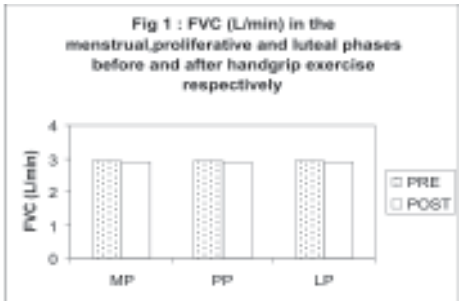
Table-2, Serum sex hormone levels (values are expressed as mean ± SD)

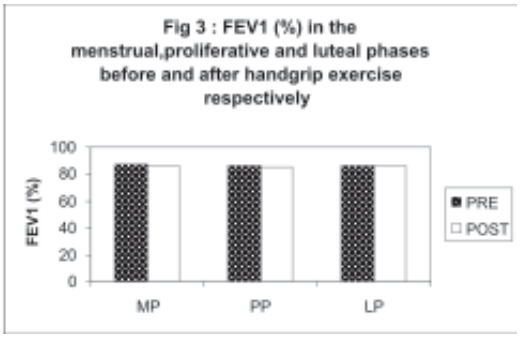
	Proliferative phase	Luteal phase
Estradiol (pg/ml)	156 ± 12.6	123 ± 10.6
Progesterone (ng/ml)	1.06 ± 0.22	10 ± 0.98

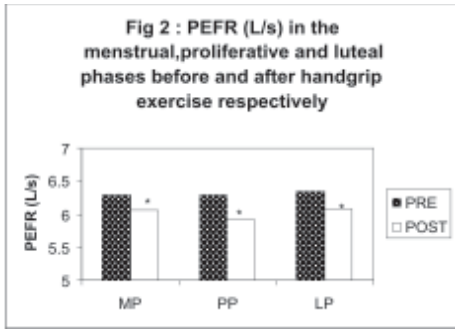
Table-3, Pre exercise and post exercise values of pulmonary function parameters in the menstrual, proliferative and luteal phases (values are expressed as mean ± SE)

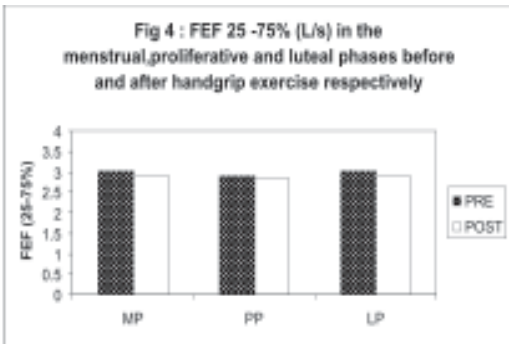
Parameter	Mentrual phase		Proliferative phase		Luteal phase	
	Pre-exercise	Post-exercise	Pre-exercise	Post-exercise	Pre-exercise	Post-exercise
FVC (L)	2.94±0.12	2.89±0.11	2.93±0.09	2.90±0.11	2.93±0.09	2.90±0.09
PEFR(L/s)	6.29±0.3	6.07±0.3*	6.30±0.2	5.92±0.2*	6.35±0.3	6.08±0.2*
FEV_1(%)	86.8±1.1	85.9±1.05	85.8±1.1	85±1.1	86.5±1.1	86.4±1.0
$FEF_{25-75\%}$(L/s)	3.02±0.18	2.92±0.16	2.9±0.16	2.84±0.15	3.01±0.17	2.9±0.14

* - p value < 0.05









11

Original Article

Availability and Consumption Pattern of Iodised Salt in the Villages of Ballabgarh District, Haryana

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Iodine deficiency is the world's most prevalent, yet easily preventable, cause of brain damage. It is the cause of an Ancient Scourge of mankind. This scourge includes goitre and brain damage at all ages beginning with the foetus during pregnancy. Elimination of iodine deficiency is an important health and social development goal for most governments. Its elimination is within reach and would constitute an unprecedented public health success in field of non communicable disease. In 1990, seventy heads of state gathered at the World Summit for children and pledged to make the elimination of iodine deficiency disorder (IDD) one of the health and social development goals to achieve by year 2000. Salt iodisation was identified as the main intervention to deliver iodine on a continuous and self sustaining basis to population around the world. Considerable progress has been made in improving the availability and accessibility of quality iodised salt. UNICEF estimates that less than 20 % of households in the developing world were using iodised salt in the early 1990s (UNICEF 2001). By 2000, the average had jumped to some 70 %. This is a remarkable achievement, especially considering that as late as 1994, 48 countries with established IDD problems had no salt iodisation programme at all. The most recent UNICEF global database indicates that the proportion of households in the developing world consuming adequately iodised salt officially remains at about 70 %. While this lack of change since 2000 reveals the challenges that some countries face, it also reflects maturation of the IDD elimination programme, which is significant but less visible. The studies done in South Asia region has shown that, the second lowest regional rate of household coverage, with just 51 % of households consuming adequately iodised salt in India.

Iodine-Iodine is an essential component of the thyroid hormones that are involved in the regulation of various enzymes and metabolic processes. Table-1 shows recommended daily intake of iodine.

Table-1, Recommended daily intake of iodine

Age group	Requirement (mcg/d)
Preschool children (0-59 months)	90
School children (6-12 years)	120
Above 12 years	150
Pregnant women	200
Lactating women	200
Source: www.iccidd.org	

Causes of iodine deficiency- Iodine is only present in soil, hence iodine deficiency results from geological rather than socio-economic conditions. The problem of IDD is aggravated by environmental factors, such as accelerated deforestation and soil erosion. Iodine is present in top crust of the soil, frequent floods cause washing of iodine from soil crust and same happens when glaciers slide down mountains.

Health consequences of iodine deficiency-Lack of iodine in the environment has serious consequences for both humans and animals as follows:

- **Fetus-**abortions, Still births, Congenital Anomalies Increased Perinatal Mortality, Increased Infant Mortality ;
- **Neurological Cretinism** (Mental deficiency, Deafmutism., Spastic diplegia, Squint); Myxoedematous cretinism; Psychomotor defects
- **Neonate** -Neonatal Goitre, Neonatal hypothyroidism

- **Child and Adolescents-** Goitre, Juvenile hypothyroidism, Impaired mental function, Retarded physical development
- **Adult** - Goitre with its complications, Hypothyroidism, Impaired mental function

Source: www.iccidd.org

A less obvious but more serious condition affecting millions of iodine deficient children includes impaired mental function, poor intellectual performance, lowered IQ, muscular disorders and impaired coordination and sluggishness. In pregnancy, iodine deficiency causes spontaneous abortions, still birth and infant deaths.

Magnitude of IDD in India- India is the second most populous country in the world, and there is a high prevalence of goitre and cretinism in the Himalayan and sub-Himalayan region, from Jammu and Kashmir in the West to Arunachal Pradesh in the east. In addition to the well known Himalayan endemic belt, iodine deficiency and endemic goitre has been reported from many other states in the country as well.

National Iodine Deficiency Disorders Control Programme (NIDDCP)-Ministry of Health and Family Welfare is the nodal Ministry for policy decisions on NIDDCP. Other ministries such as HRD, Railways, and Information & Broadcasting are also involved in several ways with the NIDDCP.

Objectives of NIDDCP-The goal of NIDDCP is to reduce the prevalence of IDD below 10 % by 2010.

The important objectives and components of NIDDCP are as follows:

- Surveys to assess the magnitude of IDD, universal salt iodisation and supply of iodated salt all over the country.
- Resurvey after every 5 years to assess the extent of IDD and impact of iodated salt.
- Laboratory monitoring of iodated salt and urinary iodine excretion.
- Health education.

Iodisation of salt-Salt is universally consumed by all households. Hence this has been used as carrier of iodine to mitigate the problem of iodine deficiency. On an average10g of salt is consumed per day per person. To meet daily requirement of 150 mcg of iodine from 10 g of salt so we need to ensure 15 ppm or 15 mg of iodine kg of salt, at consumer level. To ensure 15 ppm at consumer level it is necessary to ensure 30 ppm of iodine at production level so that when salt reaches at household level it retains at least 15 ppm of iodine.

Present status of the programme according to National Family Health Survey - 3 (NFHS- 3)-There was virtually no change in consumption of iodised salt at the household level since the time of NFHS-2(1998-99), when 50 % of households were using adequately iodised salt. According to NFHS-3 (2005-06), 25 % of households were using salt that was inadequately iodised (< 15 ppm), and the remaining 25 % were using salt that was not iodised at all. The use of adequately iodised salt was much higher in urban areas (72 %) than in rural areas (41 %).The use of iodised salt varies dramatically from one state to another. The variations are due to a number of factors, including the scale of salt production, transportation requirements, enforcement efforts, differences in state regulations, the pricing structure, and storage patterns. The use of adequately iodised salt is uniformly high (72 % or higher) throughout the Northeast Region, in most states in the North Region, and in Kerala, reaching a high of 94 % in Manipur. The use of adequately iodised salt is lowest (< 40 %) in Andhra Pradesh, Madhya Pradesh, Uttar Pradesh, and Orissa. Despite the fact that the overall use of adequately iodised salt has not changed since NFHS-2, several states have made substantial improvements over time but the situation has deteriorated in other states. The largest gains have been made in Kerala (from 39 % in NFHS-2 to 74 % in NFHS-3), Goa (42 % to 65 %), Jammu and Kashmir (53 % to 76 %), Tamil Nadu (21 % to 41 %), Meghalaya (63 % to 82 %), and Nagaland (67 % to 83 %). The states in which the use of adequately iodised salt has deteriorated substantially are Haryana (71 % to 55 %), Himachal Pradesh (91 % to 83 %), and Assam (80 % to 72 %)

The study was conducted in twenty one villages of Ballabgarh, district Haryana with an aim to determine the availability and consumption pattern of iodised salt. The specific objectives were as follows

- To determine availability of iodised salt.
- To find out the awareness of the community about different types, and brands of salt and cost.
- To study the cooking and storage practices of salt at household.
- To assess the knowledge among people regarding the advantages and disadvantages of iodised salt and health impact of iodine deficiency.

Methodology

Study Design-The study was a cross-sectional community based field survey. The probability proportionate to size (PPS) 30 cluster methodology was used for sample selection.

Study Area-The study was done in villages under the Comprehensive Rural Health Services Project, Ballbagarh, district Faridabad, Haryana. The study area was selected because it has been adopted by the Centre for Community Medicine, All India Institute of Medical Sciences, New Delhi.

Study population-The study population comprised of the shop keepers selling salt and the adult female house-hold member involved in cooking and who could give information on its storing and addition of salt during cooking in the selected houses.

Sampling-Twenty one villages of Ballabgarh were selected to be the part of the study. Thirty clusters from these villages were determined by the method of simple random sampling, using random number tables.For household section, 7 households were selected from each cluster. Nearly all retail shops selling salt in the cluster were included. Hence, the sample size comprised of 210 households and retail shop owners (a maximum of 6 in each cluster)

Survey Instrument(s) / Tools and Techniques- The standardized ICCIDD interview schedules were used to assess, knowledge, attitude, practices and beliefs about IDD and Iodised salt amongst household and shopkeepers. The interview schedule had both closed and open ended questions. The interview was conducted in the Hindi and the answers were translated into English and were marked on the interview schedule. Salt testing kit (STK) by ICCIDD lab, was used to determine the presence of iodine in salt samples. This is a qualitative and rapid test at field level and at consumer level.

Data collection-The interview schedule was administered by the students involved in the project with the help of local coordinators (health workers). The household questions were asked from the women of the selected households. If there were more than one woman in the house, the senior-most one who looks after the family kitchen was interviewed. The data collection was started on 30th May 2008 and was completed by 13th June 2008.All participants were explained the purpose of the study and a verbal consent was taken.

Laboratory Analysis-Iodine in the salt samples from retail outlets were analysed by iodometric titration at ICCIDD lab, Shahapurjat, New Delhi.

Data Processing and Analysis- The responses to the questions were entered into Epi info and analysis was done in Statistical Package for the Social Sciences (SPSS).

Results

A total of 211 households and 135 retailers were interviewed. The iodisation status of salt samples taken from house holds (211) and retailers (234) was tested with Salt Testing Kit (STK). A total of 13 salt samples, collected from the retailers were analysed for iodine content by iodometric analysis.

Responses of retailers on sales of salt- According to retailers interviewed (Table-2), the type of salt that was being sold most in the villages, was iodised salt (88.9 %). The reason given by the retailers for maximum sale of a given brand of salt, irrespective of it being iodised or non-iodised was that the customers asked for it (77 %). Only 10.4 % of the respondents mentioned that the iodised salt is good for health reasons.

Responses of household on consumption of salt-In the household survey data was collected from 211 respondents (Table-3). Majority of the respondents (53.6 %), procured 1 kg of salt at a time, and 43.6 % mentioned that they procured more than 1 kgs of salt at a time. 90.6 % of these respondents procured company packed salt, 7.6 % loose salt and the rest had

no fixed choice.Besides the human consumption of salt, 84.1 % of these households were also using the same salt for feeding the cattle and 15.9 % used the salt for agricultural purposes. Most of the respondents (48.8 %) were not aware how to differentiate iodised salt from non-iodised salt. Some gave reasons that iodised salt was cleaner (2.8%) or that it was finer (1.4 %), and only 1.4 % said that they identified iodised salt by looking at the smiling sun logo. The households were also questioned on the cooking and storage practices regarding salt, as the iodine in salt is a volatile substance, 88.2 % respondents said that they stored salt in a separate container with a lid, while 4.2 % stored in containers without lid. Most of the households (65.4 %) added salt while cooking right in the beginning. Only 3.3 % responded that they add salt in the end.

Awareness of retailers and household on consumption of salt-The awareness level about iodised salt of retailers and households were computed (Table-4), 34.6 % women perceived that consumption of iodised salt was important, while 54.1 % of the retailers thought that consumption of iodised salt was important. Of the small percentage (33.4 %) of households, who had heard about iodised salt, 17.8 % did not know the reason as to why consumption of iodised salt was important (Figure-1). Amongst the reasons given for the use of iodised salt, "*good for health"* was the most common response given by the 75.3 % respondents from the households and 52.1 % from retailers. Another reason given was that iodised salt was important to prevent goiter. From the results obtained, it was seen that most of the respondents were ignorant regarding the importance of iodised salt in the diet. Prevention of cretinism as a reason for use of iodised salt was given by very few households and retailers.The major source of information (Figure-2) regarding the use and advantages of iodised salt at the rural level were television (households, 83.9 % and retailers, 64.2 %). As most of the respondents were illiterate only 4.9 % households said teachers as the source of information,. Among retailers, 13.8% reported that they got information regarding iodised salt from their school teachers. Health workers as a source of information scored very low responses.

Salt Analysis-The iodisation status of salt, on testing with Salt Testing Kit (STK), revealed that most households were consuming iodised salt (Table-5). Also, of the various salt samples kept with the retailers, 90.5 % were iodised.Of the various salt brands available, most were within the price range of Rs.3-10/- per kilogram. The iodised salt samples available were available in the range of Rs. 3-10/-per kilogram, while the company packed non-iodised salt brands were available for Rs.3/- or Rs.4/ - per kg. The loose or the crystal salt was within the price range of Rs.1-4/-per kg. The availability of iodised salt at the retail level was adequate as all shopkeepers store iodised salt. A total of 13 salt samples, collected from the retailers were analysed for iodine content by iodometric analysis (Table-6). A number of brands of salt were available at the rural level, of which very few brands had salt that was adequately iodised (>15 ppm).

Table-2, Responses of retailers on the type of salt sold in the villages of Ballabgarh

Aspect covered	No of Response (n=135)
➢ **Type of salt sold maximum***	
Iodised	121 (88.9)
Non-iodised	12 (9.3)
➢ **Reason for maximum sales**	
Customers ask for it	104 (77)
Easy to store	5 (3.7)
Health reasons	14 (10.4)
Others	12 (8.9)

The figure in parentheses denotes percentage,* n=133

Table-3, Responses of household on consumption of salt

Aspect covered	No of Response (n=211)
Procurement	
➢ **Quantity of salt bought at a time**	
< 1 Kg	6 (2.8)
1 Kg	113 (53.6)
>1 Kg	92 (43.6)
➢ **Type of salt bought**	
Company packed	191 (90.6)
Loose	16 (7.6)
No fixed pattern	5 (1.8)
Consumption	
➢ **Use of salt besides human consumption***	
Agriculture	7 (15.9)
Cattle	37 (84.1)
Storage and cooking practices	
➢ **Storage of salt**	
Same packet	16 (7.5)
Container with a lid	186 (88.2)
Container without lid	9 (4.2)
➢ **Addition of salt while cooking**	
In the end	7 (3.3)
Beginning	138 (65.4)
In between	61 (28.9)
Others	5 (2.4)
Awareness	
➢ **Identification of iodised salt**	
Cleaner	6 (2.8)
Finer	3 (1.4)
Smiling logo	3 (1.4)
Don't know	103 (48.8)
Others	15 (7.1)
No answer	81 (38.5)

The figure in parentheses denotes percentage;* n=44

Table-4, Retailers and household perception on consumption of salt

Type of salt	Retailers (n=135)	Household (n=211)
Iodised	73 (54.1)	73 (34.6)
Non-iodised	17 (12.6)	19 (9)
Don't know	44 (32.6)	101 (47.9)
No answer	1(0.7)	18 (8.5)

The figure in parentheses denotes percentage

Table-5, Iodisation of salt on testing with salt testing kit

Type of salt	Retailers (n=234) Company packed	Loose	Household (n=211)
Iodised	212 (90.5)	0 (0)	189 (90.5)
Non-iodised	4 (2.1)	18 (7.4)	22 (9.5)

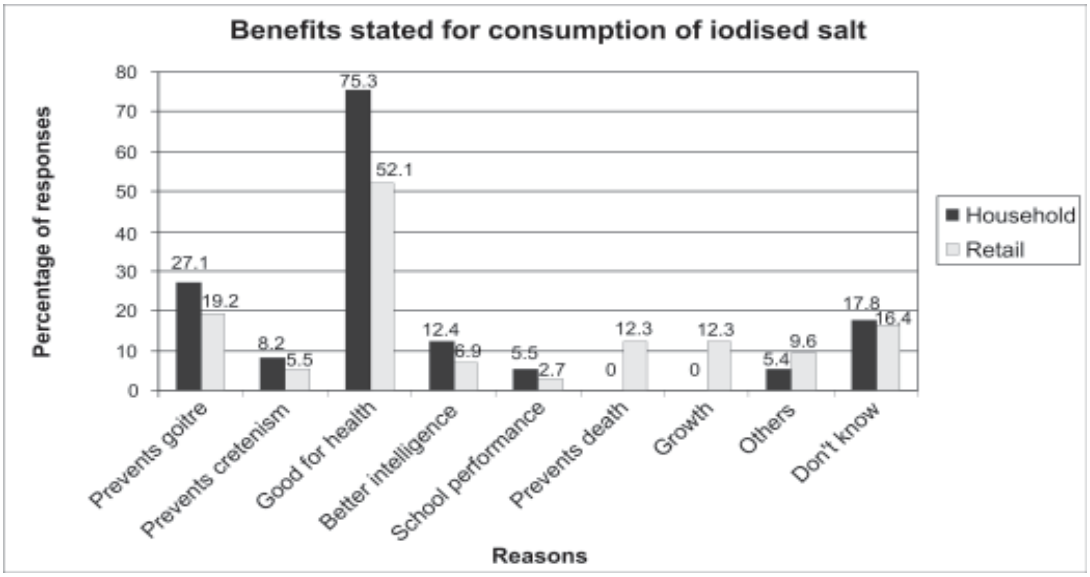
The figure in parentheses denotes percentage

Table-6, Iodisation status according to brands of the salt

Brand	No. of Shopkeepers keeping each salt (n=135)	Iodisation status on testing with spot test kit	Iodine content of the salt (ppm)
Crystal	18 (13.3)	Non-iodised	0
International	1 (0.7)	Iodised	5.3
i-shakti	7 (5.2)	Iodised	31.7
Tata	76 (53.3)	Iodised	43.4
Prince	1 (0.7)	Non-iodised	0
Sri Ram	1 (0.7)	Iodised	9.5
Captain cook	42 (31.3)	Iodised	34.9
Shudh	58 (42.9)	Iodised	6.3
Reliance	22 (16.2)	Iodised	14.8
Taja	1 (0.7)	Iodised	8.5
Amber	3 (2.2)	Iodised	5.8
Sharma	2 (1.4)	Iodised	5.3
Hindustan shudh	2 (1.4)	Non-iodised	0

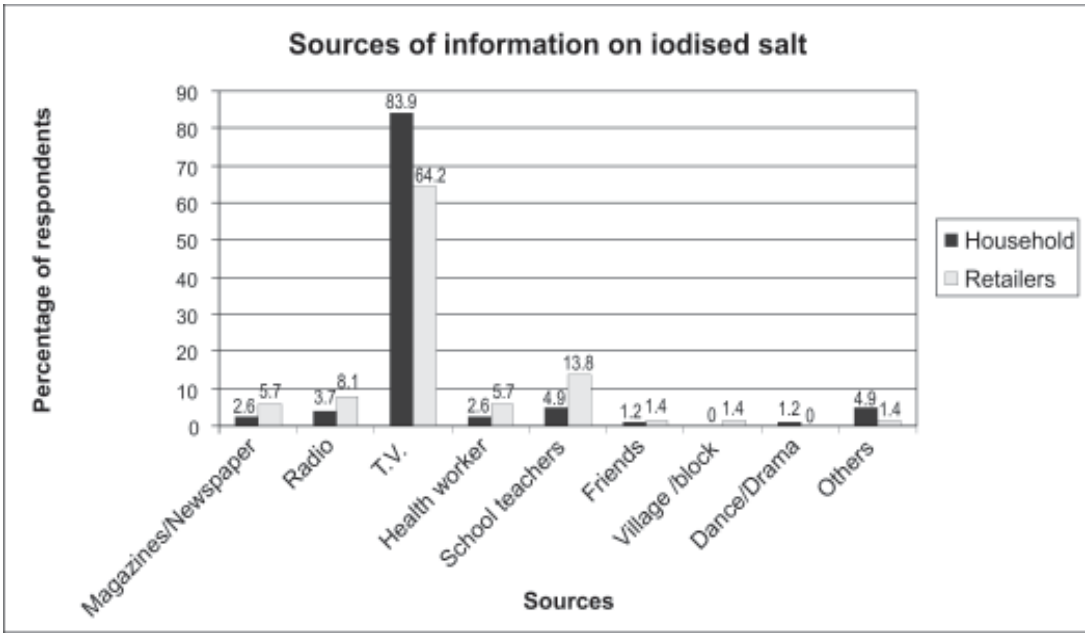
The figure in parentheses denotes percentage

Figure-1, Benefit stated by retailers and households for consumption of iodised salt



(n=73, household and retailers)

Figure-2, Benefit stated by retailers and households for consumption of iodised salt



(n=81, household and n=87, ratailers)

Discussions-The study was done in twenty one villages of Ballabhgarh. The study was a cross-sectional community based field survey. The probability proportionate to size (PPS) 30 cluster methodology was used for sample selection. The study population comprised of 211 households and 135 retailers.In the study it was observed, that 90.5 % of the respondents were consuming iodised salt but most of them were not aware of it. They used company packed salt as it was easy to store and use as compared to crystal salt. A study done by ICCIDD and UNICEF in the state of Orissa in 2003 showed that most people believe that only refined and packet salt is iodised, which is expensive. The same belief was observed among subjects of the villages of Ballabgarh. While studying, the awareness of iodised salt amongst retailers (64.2 %) and households (83.9 %), television was found to be the major source of information. The present study shows that, 65.4 % respondents added salt in the beginning during cooking, which was known to be a wrong practice, as salt should be added at the end so that iodine content is retained. As observed only 3.3 % of the households were adding the salt at the end.Two brands of salt were found to be non-iodised on iodometric analysis, but they gave wrong information on the label of being iodised. The present study reports that 53.4 % of salt available at the retailer level in the villages was adequately iodised (i.e. >15ppm), which was found to be consistent with the recent studies, NFHS-3. Bhat *et al. (*2008) reported that nearly 98.17 % of powdered salt samples in Jammu region had an adequate iodine content of 15 ppm, which was found to be very high when compared with the present study. Kapil *et al.* (1996) reported from Delhi that 41 % of the families consume salt with adequate iodine. According to NFHS-3 data, 41.2 % of the rural households in India are consuming adequately iodised salt. The data also shows that, in the state of Haryana the use of adequately iodised salt has deteriorated substantially from 71 % (NFHS-2) to 55 % (NFHS-3). The consumption of adequately iodised salt in Haryana state is 55.3 %, while 28.2 % of the households are not consuming iodised salt at all. Northeast India

is perceived to have poor access and availability to adequately iodised salt, but the results show that the entire Northeast region has access to adequately iodised salt. 93.8 % households in the state of Manipur are consuming adequately iodised salt. While the salt producing state of Gujrat has only 55.7 % households that are using adequately iodised salt.

Conclusion-The study has shown that iodised salt is available in the villages of Ballabgarh but people are not aware that they are consuming iodised salt. The health workers and the Anganwadi workers need to be trained to dissipate the knowledge on the benefits of consumption of adequately iodised salt and its cooking and storage practices.

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Quality Control program for HIV Diagnostic laboratories – an Indian experience

India is large country with second largest number of HIV /AIDS cases. No quality assurance program or government regulations were in place for HIV diagnostic laboratories. Discrepancy in results has grave consequences. Hence National AIDS Control Organization initiated the quality assurance program in year 2001 with the following objectives:

- To improve reporting of HIV tests
- To improve competency of laboratory staff
- To identify and document problems related to quality
- To monitor reliability of tests
- To inspect and analyze the cost effectiveness and feasibility

Methods-National policy makers initiated the External Quality Assurance Programme (EQAS) after many rounds of brain storming with experts in field of laboratories, epidemiology and programme managers along with administrative officers from Center and states.It was decided to introduce the programme in phased manner throughout the country. A three tier system was established i.e. Apex, National and State Reference labs were identified.

First Phase-A written EQAS scheme was prepared and one Apex and 12 National Reference Laboratories were identified and were provided with essential logistic and man power support. Standard Operative Procedures (SOP) for each laboratory were made and adhered to. Apex and National level laboratories were trained by Australian trainers in 5 days hands on training. At the end of training each participant was given coded panel sera containing true positives, true negatives and week positive samples. They were instructed to test them and send results within 4 weeks. Each lab complied with the instruction and they in turn were informed about their performance within one week.

Second Phase-National Reference Labs (NRL) trained their respective State Reference Laboratories (SRL) in a phased manner. Coded panel sera were prepared by National Reference Laboratories and was given to each participating lab at the end of the training for proficiency testing. Week performers were provided with re training. A time bound feed back was provided to each participating laboratory. Each State Reference Laboratory was supervised, monitored and given regular feed back on their performance by Apex lab.

Third Phase-State Reference Laboratories trained and supervised District level laboratories and also regularly participated in EQAS run by NRLs. In this way a net work of trained laboratories developed throughout the country and performance of laboratories improved over a period of time.Number of participating laboratories has now reached to 180, out of which 92 (approx 50%) were found to be proficient and regular.

Results-In first year only 12 laboratories were following quality assurance practices. These 12 National reference laboratories in turn trained 64 state reference laboratories in phased manner, over a period of one year. And now we have 180 trained laboratories with regular EQAS going on. Frequency of EQAS has also increased from once a year to twice a year. Number of poor performers is decreasing every year. Even private laboratories have requested to be included in the programme. Regular EQAS provides uniform results which gives credibility to our HIV testing laboratories.

Conclusion-Quality assurance has been followed by all the government laboratories. Process of Accreditation has also been introduced in the country; however cost and the large number of unregulated laboratories are the bottlenecks.

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Intra Abdominal Desmoid Tumor Presenting With Bleeding

A desmoid tumor is a rare type of tumor that develops in the fibrous tissue that covers muscles and other organs. It is also sometimes called desmoid type fibromatosis or aggressive fibromatosis as a group of locally aggressive fibro connective tissue neoplasia that share the capacity for infiltrative, destructive and commonly recurrent growth but have no capacity to metastasize. Their biological behaviour is intermediate between fibrous neoplasm and sarcomas. The intra abdominal lesion as usually divided into pelvic fibromatosis, mesenteric fibromatosis and Gardner's syndrome. Gardner's syndrome is inherited as an autosomal dominant trait and includes Polyposis, osteomata and cutaneous eysts in addition to fibromatosis.Mesentric fibromatosis occurs in the mesentry of retroperitoneum and occasionally in the gastrocolic ligament or omentum. In this report we present a rare type of gastric fibromatosis with presented as a intra gastric tumor with melena and anemia.

Case Report-9 years old female child was admitted with history of passing black stools for the last 15-20 days. She had generalized weakness and complaint of vomiting on and off for the last 4-5 days. She had been having chronic pain in epigastrium on and off for the last 2 years. She already had an upper GI Endoscopy which revealed chronic gastritis. She also had a Tc 99 Scan which showed ectopic gastric mucosa lateral to the stomach. For further elucidation of the lesion, a CT Scan was done which revealed the lesion to be a duplication cyst of the stomach. Her Hb was 6.2 gm %. Other hematological and biochemical investigation were with in normal limits. Peripheral Smear showed microcytic hypochronic anemia. Patient was given blood transfusions. 4 units of blood were transfused and Hb was brought upto 10 gm and then she was taken for the surgery. On laparotomy we found a tumor in the part wall of the stomach which was adherent to body of pancreas, from which it was dissected clear. There was no involvement of any other viscera. The tumor was only in the posterior wall of stomach. Hence, this tumor along with 1 cm margin of stomach was removed. The stomach edges were anastomosed with catgut and vicryle in 3 layers and ryles tube was left in. In post operative period patient was given IV fluids, antibiotics, analgesics and H2 blockers. Ater 96 hours clear fluids were started and on 5th day she was given all fluids orally and or 6th day she was given semisolids. She had uneventful Post op recovery and sutures were removed on 9th Post op day. Pathient's hemoglobin was maintained post op and did not fall down. There were no more episodes of melena. It is one year post operative now and she is maintaining normal Hb and no pain in stomach.

Specimen -Contained piece of stomach wall 5 x 3 x 3 cm with a polypoid mass of 1.5 cm diameter. On gross examination the mass showed white cut surface and the mucosa on the polyp was haemorrhagic.

Histopathology-Section from the polypoid mass. The gastric mucosa was essentially unremarkable except for focal congestion and erosion. There is extensive proliferation of spindle shaped fibroblasts and myofibroblasts in the serosa and omentum. These are extending focally into the submucosa which is other places appears oedematous, few histo cysts and no specific inflammation is also seen.

Immunostaining- On immunostaining there is positivity for SMA and the cells are negative for S 100 and CD 117. Focal CD 68 positivtiy is seen. There is no evidence of malignancy.

Diagnosis-Compatible with fibromatasis stomach or desmoid tumor of stomach.

Discussion - The cause of most desmoid tumor is unknown but inherited genes are sometimes involved as they can run in families. Hormones can be a factor in some desmoid tumors. For some people physical factors such as an earlier injury or trauma may be a trigger. In children desmoid tumors affect boys and girls equally. However in adults, they are more common in women. Pregnant women or women who have had a baby with in the past 2 years are affected more than average. So it is thought that female hormones such as oestrogen may sometimes have a role in triggering the growth of a desmoid tumor. Trauma to a

particular area of the body may occasionally trigger the growth of a desmoid tumor there. The trauma could be a injury, an operation or radiotherapy. Desmoid tumors, that occur in people with Familial adenomators Polyposis (FAP) often develop in an area, that has been previously operated on. Although desmoid tumors are rare sometimes more than one person in a family is affected. In particular, people with an inherited condition called familial Adenomatous Polyposis (FAP) have a much higher risk than average of developing them. FAP is mainly linked to an increased risk of Bowel Cancer. But about one in ten people with FAP develop desmoid tumors. It is universally agreed that desmoid tumors are not cancers because they cannot spread to other parts of the body, although they can grow into surrounding tissue. They are usually slow growing and the first sign is often painless or slightly painful lump. Many desmoid tumors occur in the tummy area (Abdomen) or in the Pelvis. Other parts of the body that can be affected include the chest, shoulders, thighs and the head and neck area. They can affect people of any age but are rarely found in children. The most common first sign of a desmoid tumor is a painless lump growing deep under the skin. But symptoms vary depending on where the lump and its size. If the mass is pressing on nearby nerve, organs or muscles this might cause pain. Rarely a tumor growing in the abdomen or pelvis may cause blockage or bleeding for the GIT. A number of tests may be done to diagnosis the tumor and help the doctors to plan the best treatment. These may include X-ray. Ultrasound, CT or MRI Scans and finally taking a Biopsy from the tumor and examining it under a microscope.

Treatment – Depends on the location of the tumor, its size, how quickly it is growing and whether it is causing symptoms and what are the symptoms.Treatment may include -Surgery ; Radiotherapy ; Chemotherapy; Hormonal therapy; Anti Inflammatory drugs. The most commonly used treatment is surgery to remove all the tumor. Unfortunately sometimes, these recur. Treatment maybe given after surgery to try to reduce chances of recurrence. (Tamoxifen or nonsteriod anti inflammatory drugs).Sulindac is an example of an NSAID that is commonly used. It induces cell cycle arrest and apoptosis in cancer cells lines by decreasing prostaglandin synthesis through the inhibition of cyclooxygenase – I enzyme (COX – 1). The anti-angiogenic property of Sulindac and the more recently used interferon alfa – 2b have been employed successfully to achieve tumor regression and sustained remission. Anti-oestrogens such as tamoxifen and other selectie oestrogen receptor modulators (SERMs) e. g. raloxifene, have been shown to be effective in regression of the tumor. Tumors may respond to second-line hormonal therapy as gosereline acetate (Zoladex) and medroxyprogesterone acetate. Cytotoxic chemotherapy has been used in cases of symptomatic desmoid tumor unresponsive to onventional medical therapy with various degrees of success. When an operation is not possible, radiotherapy, may be used to shrink the growth or to stop it from increasing in size. Because the tumors are often slow growing, it may take months before the effects of radiotherapy can be seen so it may be several month before a Scan can show whether the tumor has shrunk or stopped growing as a result of treatment. Occasionally a desmoid tumor completely disappears without any treatment. This is called spontaneous regression or sometime a desmoid tumor grows quickly and then stops growing. Because of this, in some situations, doctors may keep the tumor under observation rather than treat at once.

Conclusion-Desmoid tumours are slow growing deep fibromatosis with progressive infiltration of adjacent tissue but without any metastatic potential. Although rare, fibromatosis should enter into the differential diagnosis of masses developing in irradiated areas in patients treats for Hodgkin's disease. Complete excision is often impossible and therefore adjuvant treatments have been employed with various degrees of success.

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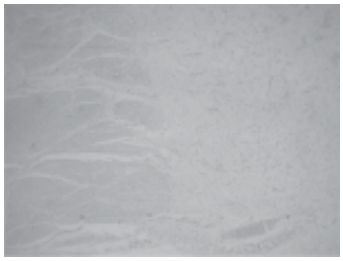

Fig 1 : Scanner picture showing muscle coat and a mass made up of fibrous connective tissue in submucosa.

Fig-2, Scanner picture showing disruption in muscle coat due to proliferation of fibrous connective tissue which is extending from submucosa to serosa

Fig-3, Low power picture showing the fibroblastic tissue creeping through the muscle coat.

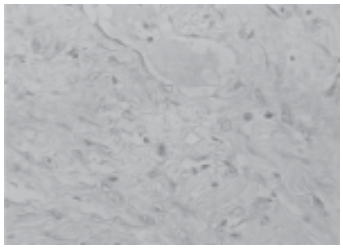

Fig-4, High mag showing the fibroblasts with plump nuclei and fibrillary cytoplasm

Fig-5, Low power picture of the centre of the polyp showing the fibrous connective tissue.

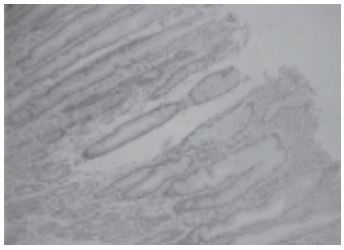

Fig-6, Scanner picture of mucosa showing haemorrhagic necrosis at the tip of polyp.

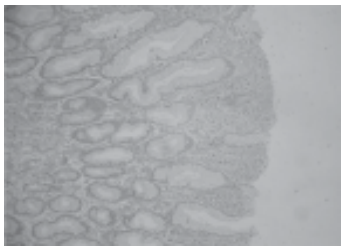

Fig-7, Another picture showing haemorhage in lamina propria and shedding off of the surface epithelium.

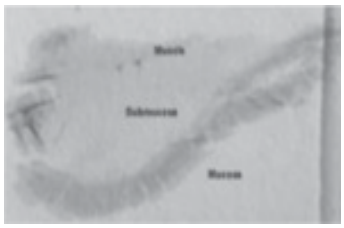

Fig-8, Naked eye-Gross picture of microsection showing the polyp sitting over the muscle and lined by mucosa.

49th annual conference of the College of Surgeons of West Africa

My trip to the 49th annual conference of the College of Surgeons of West Africa has been a great eye opener for me.There are 25 medical colleges in Nigeria. Each country has at least one (or more) medical colleges and a sprinkling of doctors practicing surgery in rural settings. The symposium in rural surgery was the main symposium of the conference and had five speakers. Myself from India, one from South Africa, one from Gabon and two from Nigeria including Dr.Awojobi. I described the whole rural surgery movement and the training programme of the CRS/DNB course in India. It had a great impact and now many are keen to attend our conference. There were 1200 delegates from not only general surgery but other specialties as well. It seemd that Nigeria will start a postgraduate course in rural surgery soon. They are very polite, God fearing and warm in character. All of them had their independence after us and are now trying to emerge out of foreign (economic)domination against many odds. Both I and Shipra was overwhelmed with warmth and hospitality. Albeit they are poorer than us, and, I feel, would eagerly accept our support in the field of health development. This time we traveled by Emirates. Dubai airport is very "user friendly". And the airline service is definitely better than any other that I have traveled in before. My friend Dr.Awojobi was in Lagos airport to receive us. That night we spent in a hotel in Lagos. The next morning he drove us to his "rural" hospital in Eruwa 150kilometres from lagos to the north.On the way we visited a district hospital recently upgraded to a medical college, another rural surgeon and one of his teachers who had started the first community healthcare project in Nigeria. This gentleman, now 86yrs.young and an FRCP, had photographs with Dr. Radhakrishnan and Dr. A.L. Mudaliar of India and seemed a man with radical ideas. Dr.Awojobi runs a fifty bedded hospital. He has no papers of ownership either of the land or the building. His employees handles the money and pays him a "salary" every month. He has set up a stills distillation plant and makes his own IV fluids, his autoclave runs on fuel from discarded wood. He generates his own electricity when the govt. supply goes off which is sometime for days together. He does all types of surgery and maternity and child care. He has done rain water harvesting, and fish culture. We ate that fish which was excellent. The local villagers have great respect for him. The next day we came to Lagos and flew to Konakry, capital of the republic of Guimea (please take a look in the atlas in the map of west Africa.) Flight time 2hr.&40mts. This is a small country, smaller than Nigeria and poorer as well. The people are very nice. Konakry, the capital is part on an island and part on the mainland, earlier connected by a causeway. Now the causeway has been broadened.The parliament house is located on it, and also the hall where our conference was held. From the porch of the hall we could see the sea on either side. It was beautiful. There were more than 1200 delegates, all blacks except just one white a Dr.William Thomson, a rural surgeon from Gabon (American) and director of "Pan African Association of Christian Surgeons(PAACS)". Most of the blacks were either Christians or Muslims. My friend Awojobi was a Christian. But they gave more importance to the philosophy of their respective religions and little to the outward expressions. We were housed in a five star hotel next to the conference venue, where we could have western food, except lunch at the venue which comprised of a salad, and a large quantity of rice or cassava "pudding" and beef curry. I thought I could eat it. But after the first day, I just couldn't while the Africans devoured! No alcohol, even during banquet Half the people (including short papers)were French speaking. The inaugural address was also in French, by the new coup leader, a captain Camara. Our reception was very warm. I did not have a

reentry visa for Nigeria. So I had to visit the Nigerian embassy there. The chief of the conference accompanied me. The ambassador had already heard of my presentation! She entertained us to tea and not only gave the visa but also paid for it herself ! I have not had this treatment in Europe. Two days after return by dint of luck, I listened to an interview of Desmond Tutu, Emeritus bishop of Cape town in BBC world, and whose name and works we all know. I saw this picture exactly during my visit. Both Guinea and Nigeria grows a lot of cocoa. I tried to buy some cocoa powder locally. It was just not available. All of this is purchased by foreign buyers and chocolate made in those countries. The local people do not get any to eat. The owners get paid in foreign currency. The workers get paid precious little. Same with oil. All the oil from Nigeria goes to outside refineries where shares are owned by the chieftains of their country. The local people started small refineries in their backyards like home industry....many of them with excellent results! Guinea has the highest Bauxite deposit in the world plus a lot of minerals. All the ores are exported.

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Klippel Trenaunay Weber Syndrome : A Case Report

Introduction-The cause and processes surrounding Klippel Trenaunay Syndrome (KTS) are poorly understood.The birth defect is diagnosed by the presence of a combination of Capillary malformations, soft tissue and bone hypertrophy, an atypical varicosity (often on approximately ¼th of the body, though some cases may present more of less affected tissue)(1).This particular case is studied by various imaging modalities and their features described and presented. Few of the typical findings, not found in each case, is also presented in this case report.

Case History-A 8 year old boy presented with the complaints of swelling of the right lower limb, which was progressively increasing since birth to the present state [Figure-1].There was also presence of pinkish stain seen in the right groin region.The entire right lower limb showed features of stasis dermatitis. Anteroposterior radiograph demonstrated marked soft-tissue enlargement of the right lower extremity [Figure-2]. Ultrasound revealed extensive subcutaneous and soft tissue edema with few superficially dilated venous channels and presence of Trenaunay vein which is a large, lateral, superficial vein seen in the leg [Figure 3].CT scan of the lower extremities revealed hypertrophy of the right lower limb in respect of the increased length and diameter of femur and tibia [Figure-4].Triple Phase CT angiography showed prominent venous system in the right lower limb and also dilated and prominent varicose veins [Figure -5].Trenaunay vein seen on ultrasound was also nicely appreciated on CT[Figure-6]. MRI revealed extensive hypertrophy of the subcutaneous tissue and muscles of the right lower limb[Figure-7]. Contrast enhanced CT scan of abdomen revealed retroperitoneal lymphangiectasia [Figure- 8].

Discussion-*Klippel* Trénaunay Weber *syndrome* is defined as a combination of capillary malformations, soft-tissue or bone hypertrophy, and varicose veins or venous malformations. The diagnosis of *Klippel* Trénaunay Weber *syndrome* can be made when any two of the three features are present[1-4]. Most cases are sporadic; the syndrome affects males and females equally, has no racial predilection, and manifests at birth or during childhood.Klippel-Trénaunay Weber syndrome must be distinguished from Parkes-Weber syndrome, in which an enlarged extremity occurs which is related to an underlying arterio-venous malformation [5]. Hypertrophy is the most variable of the three classic features of *Klippel* Trénaunay Weber *syndrome*. Enlargement of the extremity consists of bone elongation, circumferential soft-tissue hypertrophy, or both. At clinical examination, hypertrophy often manifests as leg-length discrepancy, although any limb may be affected. Capillary malformations are the most common cutaneous manifestation of *Klippel*-Trénaunay Weber

syndrome[6]. Typically, capillary malformations involve the enlarged limb, although skin changes may be seen on any part of the body. The lower limb is the site of malformations in approximately 95% of patients. When found on the trunk, the malformations rarely cross the midline. If large enough, the cutaneous lesions may sequestrate platelets, possibly leading to Kasabach-Merritt syndrome, a type of consumptive coagulopathy[7]. Varicose veins are present in a majority of patients with *Klippel*-Trénaunay Weber *syndrome.* Venous malformations can occur in both the superficial and deep venous systems[2]. Superficial venous abnormalities range from ectasia of small veins to persistent embryologic veins and large venous malformations. Deep venous abnormalities include aneurysmal dilatation, aplasia, hypoplasia, duplications, and venous incompetence. The Klippel-Trenaunay vein is a large, lateral, superficial vein sometimes seen at birth[8]. This vein begins in the foot or the lower leg and travels proximally until it enters the thigh or the gluteal area.In our patient, the triad of marked enlargement of the right lower extremity, a cutaneous vascular lesion, and findings of extensive combined venous and lymphatic malformations suggested the diagnosis of Klippel-Trénaunay Weber syndrome.Other features of this syndrome includes lymphatic obstruction, spina bifida, hypospadias, polydactyly, syndactyly, oligodactyly, hyperhidrosis, hypertrichosis, paresthesia, decalcification of involved bones, chronic venous insufficiency, stasis dermatitis, poor wound healing and ulceration.Complications are most often related to the underlying vascular pathologic condition. These include thrombophlebitis; cellulitis; and more serious sequelae such as thrombosis, coagulopathy, pulmonary embolism, congestive heart failure (in patients with arterio-venous malformations), and bleeding from abnormal vessels in the gut, kidney, and genitalia[6,8].At radiography, bone elongation contributing to leg length discrepancy, soft-tissue thickening, or calcified phleboliths may be seen. At lymphangiography, hypoplasia of the lymphatic system has been reported. Sonography may be used to identify the abnormal veins and varicosities. CT of the abdomen and pelvis provides a simple, noninvasive means of assessing visceral vascular malformations. Spin-echo MR images demonstrate a lack of enlarged high-flow arterial structures, and T2-weighted images show malformed venous and lymphatic lesions as areas of high signal intensity. MR imaging depicts deep extension of low-flow vascular malformations into muscular compartments and the pelvis and their relationship to adjacent organs as well as bone or soft-tissue hypertrophy[9]. More recently, MR venography has been reported to display the significant findings in extremity venous malformations with a capability equal to that of conventional venography[10].Treatment in a majority of patients with Klippel-Trénaunay Weber syndrome is conservative and includes application of graded compressive stockings or pneumatic compression devices to the enlarged extremity. Percutaneous sclerosis of localized venous malformations or superficial venous varicosities may be indicated in some patients. Surgical treatment may include epiphysiodesis to control leg length discrepancy, excision of soft-tissue hypertrophy, stripping of superficial varicose veins, or, less commonly, reconstructive surgery at sites of deep venous obstruction.

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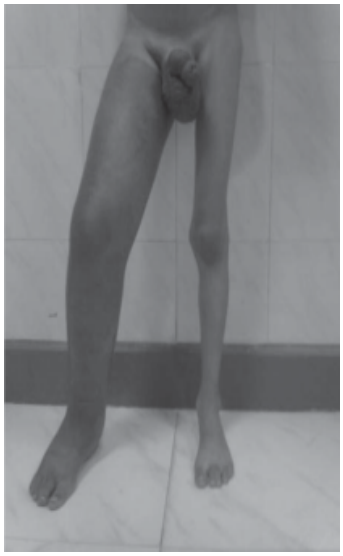

Fig-1, Clinical photograph of the patient reveals marked enlargement and swelling of right lower limb in contrast to the other limb with features of dermatitis.

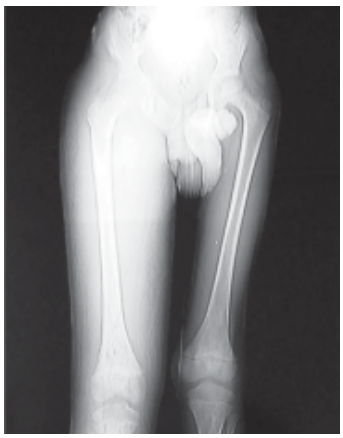

Fig- 2, Plain Radiograph of bilateral thighs show hypertrophy of the soft tissue with relative enlargement of the femur on right side.

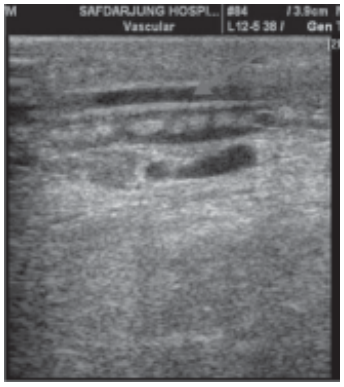

Fig- 3, Ultrasound reveals subcutaneous edema and a linear venous channel (Trenaunay vein) on the lateral aspect of right leg and thigh.

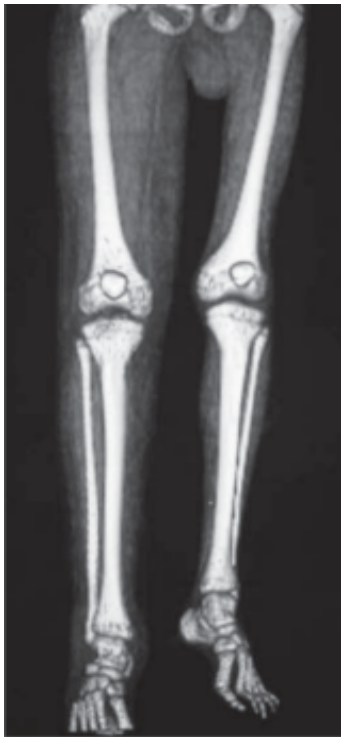

Fig-4, Volume Rendered(SSD) coronal CT image of bilateral lower extremities shows hypertrophy of femur and tibia on right side.

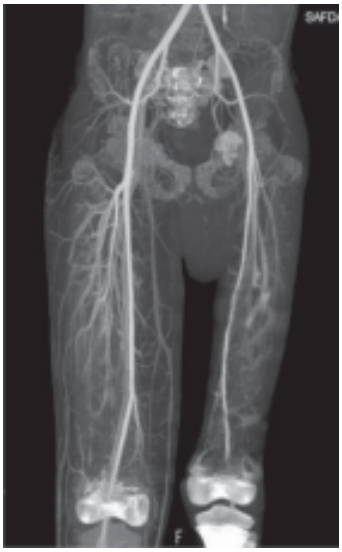

Fig-5, Volume Rendered(MIP) coronal CT angiography(venous phase)image of bilateral thighs show multiple prominent venous channels on the right side.

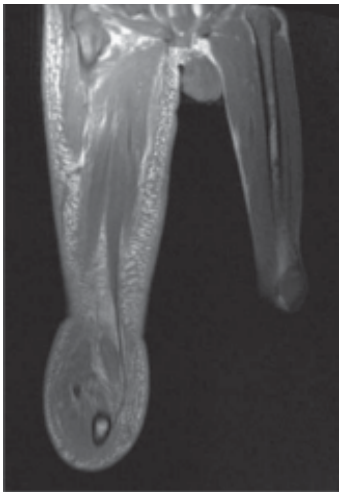

Fig-6, T1 weighted spin echo coronal MR image shows hypertrophic muscles and subcutaneous tissues of the right thigh.

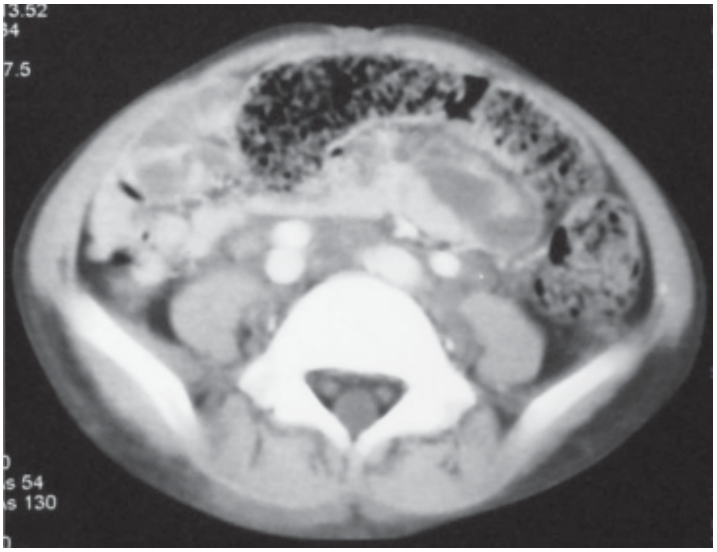

Fig-7, CECT image reveals nonenhancing hypodense foci in the retroperitoneum encasing the common iliac vessels consistent with lymphangiectasia

Anatomical Manikins

The anatomical manikin pictured here is a rarity among the cased sets of surgical instruments, amputation kits, and other medical items that make up the artifact collection of the University Archives. Often these manikins are confused with Chinese diagnostic dolls or "doctor's ladies". In Chinese culture, modesty forbade a woman from undergoing a physical examination or even mentioning parts of her body to a male physician. To circumvent this situation, during a house call the doctor brought along the diagnostic doll. By marking the section giving her discomfort, the woman could communicate her problems to the physician. While both anatomical and diagnostic manikins were somewhat similar in appearance, the craftsmen fashioned anatomical manikins with much more detail. Sometimes produced in male and female pairs, it was far more common to create only the female figure and always in an advanced state of pregnancy. Medical history contains little information on the origin or intended use of the manikins.

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