

National Board of Examinations

Considering the variations in the level of standards of post graduate and post doctoral examinations in our country and based on the recommendations of an Expert Group set up for maintaining uniform standards, the Ministry of Health & Family Welfare, Government of India, established the National Board of Examinations (NBE) in 1975, with its headquarters at New Delhi.

Objectives of NBE

Conduct postgraduate examinations in the disciplines of modern medicine at the national level.

Maintain a high standard of examination, so as to ensure that candidates have received adequate training and are competent in every way to practice as specialists, in their respective fields.

Constitute Speciality Boards in which the examinations are to be conducted.

Formulate basic training requirements for eligibility to appear for the respective examinations.

Prescribe course curricula for postgraduate studies.

Organize postgraduate courses, workshops, seminars, symposia and training programmes of specialised nature.

Institute professorships, other faculty positions, fellowships, research cadre positions and scholarships etc. for realising the objectives of the Board.

Constitute an Accreditation Committee to approve centers for DNB courses.

Co-ordinate with national and international bodies, agencies, universities for the furtherance of the objectives of the Board.

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In one of the interviews for selecting an orthopaedic surgeon for a hospital, the candidate was asked what is AO philosophy and principles. The candidate immediately replied. "Always Operate"!! In many centres where orthopaedic surgery is taught, the candidates are not taught in detail about the operative fracture management properly. A five member "Core group" consisting of Maurice E. Muller, Hans Willenegger, Martin Allgower, Robert Schneider and Walter Bandi established the AO (Arbeits gemeinschaft fur osteosynthesefragen) or the Association for the internal fixation (ASIF) in 1958 in Switzerland

AO'S AIM -Before 1960's all fractures were treated by prolonged immobilization in plaster or in traction. This resulted in atrophy of the soft tissue, osteoporosis, thinning of articular cartilage, severe joint stiffness, oedema of the limbs and causalgic pain called as "Fracture Disease". This early group of Swiss authorities established after extensive examination of treatment goals, the principles of complete functional restoration of the injured limb through perfect anatomical reduction and rigid internal fixation with use of atraumatic surgical techniques and early mobilization. During this early period, the AO developed

the compression plate and the lags screw to achieve rigid internal fixation of fractures¹.

This evolved the expression "Life is Movement, Movement is life". The operative treatment of fracture was a new concept and the demands for this type of treatment were great. The reduction of fractures had to be anatomic and fixation had to be sufficiently strong, stable and allow good functional movement without the risks of failure to the metal, delayed union, non union. Soft tissue handling was also of high importance since infection should not mar the outcome. Many techniques, implants and instruments were developed, courses how to use them were taught and they were popularized by the "AO Manual" which was published in 1970².

AO documentation-Internal fixation of most fractures especially open fracture, was revolutionary concept and many senior orthopaedic surgeons could not swallow this concept. Clearly, the AO founders, like all revolutionaries, had to prove that, their way was better if it was to be accepted. The documentation of more than 150,000 operatively treated fractures over twenty eighty years of AO principles and techniques of fracture care and also created the basis for the AO fracture classification system, which was first described in 1987 by Muller et al³. This AO

Classification system of fracture type and fixation techniques has been accepted world wide now.

Further AO research and development -AO based its success on its research. Wolff et al showed that implants coupled to bone always participate in load transmission and may cause stress shielding. The more the rigid, fixation of fractures the more the Stress-Shielding⁴. Since refractures following plate removal were thought to be due to stress-Shielding, plate stiffness attracted the attention. While many researchers continued to investigate the mechanical effects of plates on bone, the AO researchers in Davos investigated the biological effects of the plates on bone circulation. They showed that plates interfered substantially with the blood supply to the underlying bone and caused the underlying cortex to become necrotic⁵. Similar studies on intra-medullary nailing revealed that reaming and nailing destroyed the inner two thirds of the cortical blood supply⁶. AO research also showed a large diminution in the cortical blood supply during reaming⁶. These discoveries made the AO researchers to shift away from mechanics and toward preservation of the local biology. This shift resulted in a powerful stimulus to design new minimally invasive implants to match these changes in the principles and

techniques of fixation. The major break through was the advent of locked intra medullary nailing, which was based on the development of what Kuntscher⁷ called the “Detensor Nail” and was described by Klemm et al⁸ and Kempf et al⁹. Open nailing was replaced by closed nailing which preserved the fracture haematoma, soft tissue attachment of fracture fragments which in turn preserved their blood supply. The innovation of locked nailing greatly increased the indications for intra medullary nailing, since multi fragmentary fractures of long bones could be restored in length and securely with use of transfixing bolts or screws. Closed locked intramedullary nailing of diaphyseal fractures long bones produced rapid healing with abundant formation of callus. As long as the main fragments were locked to the nail, the gaps between the intervening fragments were seen to fill with callus which resulted in good union. The closed intra medullary nailing technique was superior to application of a plate for most diaphyseal fractures of femur and tibia. Plating of diaphyseal fractures produced delayed union due to periosteal and soft tissue stripping non union, infection and implant failure. Additional improvements in mechanical locking with the second generation of reconstruction nail is useful in managing subtrochanteric fractures and also for ipsilateral fracture of femoral neck and shaft fractures. Throughout the world closed intra medullary nailing is used extensively for all diaphyseal fractures of tibia and femur

without much complications. Despite the advances in the techniques of intramedullary nailing, application of a plate has continued to be a very important technique in achieving stable fixation of fractures. It was realized that contact of the plate with the underlying cortex lead to the damage of the cortical blood supply resulted in redesigning of the plate. Perren et al¹⁰ described the dynamic compression plate (DCP) which succeeded the round – hole plate in 1969. In the mid 1980’s this again was replaced by limited contact dynamic compression plate and then again “Point Contact Fixation” in 1987. A whole new family of fixation devices has developed from the concept of locked internal fixation. The Less Invasive Stabilization System (LISS) for the distal femoral and proximal tibial fractures are the whole family of locked compression plates. Classical open reduction and internal fixation called as the direct reduction, produces varying degrees of devitalisation of the fracture fragments. To avoid this devitalisation AO has developed various techniques of indirect reduction. Indirect reduction is obtained by distraction of the fragments with use of a distractor, an external fixator, a plate or by traction applied to the limb by an assistant. Reduction is achieved by so called ligamentotaxis, which avoids direct manual manipulation of the fragments. The techniques of indirect reduction and application of a bridge plate have resulted in the development of the concept of minimally invasive plate

osteosynthesis. In this method the fracture is first reduced by indirect means¹¹. The plate is then slid through a small skin incision, deep to the investing muscle layer but extraperiosteally. The position of the plate is checked under C arm and once it is found in the best position, it is fixed to the bone with screws inserted percutaneously. This technique of plate fixation minimise intra medullary nailing with the obvious difference that the fixation device i.e the plate lies in an extra medullary position – Fixator interne.

Metaphyseal fracture fixation

-Lot of advances have been made in the fixation of metaphyseal fractures. The problem with the use of conventional open plate fixation is the complication of stiffness of the joint, skin break down and infection. The less invasive stabilization system has therefore been developed with fractures that greatly facilitate percutaneous fixation of the plate to the underlying bone, especially in the metaphyseal regions. In this system, the plate is fixed to an insertion device, which acts to guide the insertion of the fixation screws. Further development of “locked internal fixation system”, the special fixation locking screws, which lock in to the plate, are self drilling and self tapping and incorporate radial pre load to increase their cortical fixation. Similarly the locking compression plate concept offers many advantages for all plate applications but especially for percutaneous techniques as the use of a “locked screws” in any hole provides stable fixation (bicortical or unicortical) without

the need for perfect plate , contouring or additional soft tissue dissection. The concept combines angular stable anchorage with traditional compression and is especially suited for fracture in osteoporotic bone.

AO international - AO International was founded in 1972 with the intention that operative fixation of the fractures should become a safe method of treatment with a low prevalence of complications, Operative treatment of fractures was never advocated as being the only method of treatment . From its inception of AO , it was stressed that the indications for surgery were dependent on the surgical environment, the skills of the surgeon and operating team (Nurses, Theatre Assistants etc) , the personality of the patient and the personality of the fracture . Once the surgeon has decided to operate on a fracture , it was necessary for the surgeon to have requisite and complete instrumentation and to use excellent surgical technique according to the established AO principles to maximize the quality of the treatment . In 1960, the first course was taught in Davos, Switzerland. Education was and has remained one of the cornerstones of AO.AO International, is doing a Yeomon service to the Orthopaedic Community World Wide by teaching them by conducting AO courses with experienced fracture trauma surgeons who spend their time and expertise as faculty to maximise the learning experience for course participants. In our Country catastrophic results following surgery of fractures

due to lack of exposure to the knowledge of AO Principles , lack of operation theater facilities nurses and O.T. Technician. Any orthopaedic surgeon must be capable of doing fracture surgery with full competency only, otherwise he should not do it. They must question themselves whether I am doing do the right type of surgery in the right type of patient ? and also regarding implants choosing .Each surgeon may have his own way of doing it but at the end, the result must be excellent following the AO Principles.

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Commentary

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Training of personnel consists in providing them with the necessary facilities & opportunities to acquire knowledge, develop skills and cultivate attitudes, behaviour & habits for the efficient and effective discharge of their duties and responsibilities. Administrative skills can be grouped into technical skills, human skills and conceptual skills. Training should enable people to perform their present duties effectively and at the same time prepare them to shoulder greater responsibilities in the future. The ultimate objective of training for personnel is improvement in the performance thereby facilitating achievement of organizational goals. The training can be grouped into pre-service training, induction training, placement training, in-service training, on-the-job training and promotional training etc. This article provides an overview of different types of training methods that needs to be considered depending upon the specific situation, background of trainees, job responsibilities, objectives, scope and task involved, attributes to be developed etc.

Competency Based Training- Competency based training [CBT] is distinctly different from traditional education process. CBT is learning by doing. It is based on social learning theory

which states that when conditions are ideal, a person learns more rapidly and effectively from watching someone [model] perform a skill or activity. Unlike traditional teaching, which emphasizes evaluation of what information the participant has learned, CBT emphasizes evaluation of how the participants perform i.e. combination of knowledge, attitude and most important skills.

Terms used to describe levels of clinical skill performance are:

- **Skill Acquisition:** The trainee knows the steps and their sequence 'to perform' the required skill or activity but 'needs assistance';
- **Skill Competency:** The trainee know the steps and their sequence and "can perform" the required skill or activity;
- **Skill Proficiency:** The trainee knows the steps and their sequence and "efficiently perform" the required skill or activity.

The criteria for efficiently performing the skill are standardized and are judged by using a checklist when the trainee performs. The coaching process ensures that the trainee receives feedback regarding performance at each level i.e. before, during and after practice.

Brainstorming - A technique for finding solutions by means of stimulating ideas. A small group of people with or without conscious knowledge of the subject meet and contribute any suggestion or idea that comes into their mind, no matter how fantastic or impossible it may sound. All suggestions are encouraged and criticism is not allowed at this stage, although contributors are later invited to explain their ideas. Subsequently, all the ideas are submitted at the meeting and are assessed. *Main Uses:* Problem solving; consolidating previous learning. *Advantages:* Uses participant experiences and ideas; very active participation. *Disadvantages:* Time consuming; requires high trainer skill; and some learners may not participates.

Coaching - Systematically increasing the ability and experience of the trainee by giving him/her planning tasks coupled with continuous appraisal, advice, counseling by the trainees supervisor. *Main Uses:* Development of knowledge and skill. *Advantages:* The learner may have undivided attention from the trainer in the one-to-one to situation; level of pace of coaching can be quickly adapted; trainer and learner are likely to have more immediate feedback of results compared with some other methods. *Disadvantages:* Can

be expensive on trainers time; very small numbers of trainee can be dealt at one time; success depends very much on the qualities of the trainer.

Demonstration- The trainer by actual performance shows the learner what to do and how to do it and with his associated explanations indicates why, when and where it is done. This method is invariably clubbed with other training methods. *Main Uses:* It gives learner a yardstick to aim at by visualizing the correct/incorrect procedures of an action. *Advantages:* Stimulates interest and large group can be handled simultaneously. *Disadvantages:* Takes a lot of time and efforts to produce; little or no contact between direct trainer and learners whilst it is actually taking place; can be too fast for the learners to absorb or understand what is going on when several action or skills are being demonstrated simultaneously.

Lecture method- A straight talk or exposition, possibly using visual or other aids but without group participation other than at the conclusion. *Main Uses:* For transmission of facts and information, which may be classified as of interest value only and which the learners would not be expected to remember in full. *Advantage:* A large amount of material can be covered in a relatively short time. One lecturer can handle large number of trainees. Content and sequence under the lecturer's complete control. *Disadvantages:* lack of learner involvement- they are

passive players with little or no opportunity for participation; knowledge/information imparted by talking is not easily memorable; lecturer has little or no immediate feedback from the learners; saturation point is reached relatively early; learner attention can be easily distracted.

Project- A form of exercise leading to the accomplishment often within a fixed time of a definite task e.g. a report containing recommendation on a stated problem or the design and manufacture of equipment at a given specifications. *Main Uses:* Development of skill. Transfer of off-job learning to real situation. *Advantages:* Onus of learning is put on the learner shoulders; stimulates interest and creativity; can involve application of a range of skills self pacing; can be worked by the learner at convenient times; end product may have a practical use. *Disadvantages:* Needs very careful control by the trainer; learner must accept responsibility for the project; motivation wanes if inadequate guidance is given; confidence of learner may be undermined by negative feedback.

Case study method- A learning technique in which a real or fictional situation or series of events is presented to trainees for their analysis and consideration of possible solutions of problems identified. Their finding in real situation can be compared subsequently with what actually occurred. Case studies are often used in interpersonal industrial relations

situations such as disciplinary cases and grievance handling. *Main Uses:* Problem solving; developing analytical skills; gaining confidence in decision making; changing/modifying attitudes; introducing and consolidating other sessions; team work. *Advantages:* provides concrete subjects for discussion; participant's experience can be brought into use and shared with others; provides opportunity for active participation. *Disadvantages:* consumes lot of time in drafting cases; difficulty in validating when there is no quantifiable solution; close relationship to 'real-life' may be difficult to achieve; difference between training situation and real world may not be recognized.

Computer based learning-It involves use of computer as a teaching medium and/or learning resource in an educational or training system. Used as a teaching medium, the computer programme controls the presentation of instructional material to a learner on the basis of his/her responses to previous questions. The computer thus adapts teaching to the individual. Computer acts as a tool for learning resources providing calculation, stimulation, modeling, problem-solving and information facilities. In this case computer does not necessarily teach in any direct sense e.g. a flight stimulator in aircrew training. *Main uses:* knowledge learning; Descriptions, procedure, facts and principles. *Advantages:* learner proceeds at its own pace; level of material can

be matched to learner; individual receives immediate feedback; record of individual learner performance is possible, highly interactive can be motivating. *Disadvantages:* limited range of commercial programme; expensive and time consuming to produce; computer hardware necessary for each individual; learner may feel manipulated by the computer.

Group exercises - Group exercises require a small group of learners to undertake an activity together. The content of the activity is not important. What is important is how the group undertook the activity and the result achieved. Experiential learning occurs when a person engages in some activity, looks back at the activity critically, abstracts some useful insight from the analysis and puts the results to work. This is an inductive process, proceeding from observation rather than from given truth. A structured experience provides a framework in which the Inductive process can be facilitated. The experience centres on a topic-related activity where the trainees participate in, for example, making products transactions, problem solving, non-verbal communication, planning competing etc. the experience so created provide the basis for learning. *Main uses:* develop interactive/interpersonal skills; team building activities. *Advantages:* highly participative; learner are usually highly motivated. *Disadvantages:* process skills learning can be obscured by the output of the activity. High

trainer skills are required to review and help transfer of learning.

Guided practices - a method in which the learner has to perform the operation or procedure being learned under controlled conditions. Main uses: all types of skill learning; increasing knowledge and modifying attitudes. *Advantages:* learners are actively engaged; creates interest; there is exchange of ideas, experiences etc. *Disadvantages:* can be time consuming and expensive; there may be conflict of personalities; may be easy for individual to 'opt out'.

Interactive video-Interactive video bring together video and computer systems to provide the learning event. The video provides colour moving and still images with stereo sound and the computer provides the text and manages the interaction with the learner. The interaction can include explanation, demonstration, questioning, exploring situations and alternatives and responding to questions with video and text. *Main uses:* develop interpersonal skills; knowledge based learning; introducing computer based system; exploring attitude to people and situations. *Advantages:* individually tailored learning experience exactly matching to the needs; stimulating and motivating use of multimedia; pace controlled by learner; individual learner feedback; records of individual performance can be maintained. *Disadvantages:* high initial cost of setting up a system; limited range of commercial software.

Expensive and time consuming to produce or amend software; may quickly be replaced by new technology.

In-tray exercises- A form of training which attempt to stimulate the working situation by setting the trainee realistic tasks. The trainees are presented with papers such as letters and memos, placed in the 'in' basket or 'in' tray to which they respond individually. The results of the exercise are then analyzed, discussed and assessed on the basis of decision made. *Main uses:* problem solving; development of analytical skills; for gaining confidence in decision-making; transfer of theory learned to practical applications. *Advantages:* provides concrete subjects for practical work and discussion opportunities for active participation. *Disadvantages:* time consuming to produce; sometimes difficult to achieve 'real life' situations; if handled insensitively it may undermine the confidence of some learners.

Programmed learning- A form of instruction in which the following elements are present [1] There is a clear statement of exactly what the trainee is expected to be able to do at the end of the programme; [2] the material to be learned which has been itemised and tested is presented serially in identifiable steps or frames; [3] trainees follow a sequence of frames which may be determined according to their individual needs; [4] frequent and unambiguous responses are usually required from each

trainee through out the whole sequence;[5] feedback of information about the correctness or otherwise of responses is usually given to the trainee before the next frame is presented. *Main uses:* for all types of knowledge learning; teaching Descriptions and procedure. *Advantages:* learner can work at their own pace; learning material is carefully structured into learning steps; learners get immediate knowledge of results; learners are usually highly motivated. *Disadvantages:* time consuming and costly to produce; can be administratively difficult to run. **Role play-** a learning technique in which students are presented with a situation which they are required to explore by acting out the roles of those represented in this situation. *Main uses:* for changing/modifying attitudes; developing interactive knowledge and skills. *Advantages:* can create a great deal of interest; active participation by role player; provides a 'living' example; only exercise where emotions become the predominant features. *Disadvantages:* role players may learn more than observers; observers may be passive until the exercise is discussed. Success depends on the imagination of the player; Attitude change may be short lived. **Algorithm/flowchart-** A mathematical term, meaning an exact prescription defining a computational process leading from various initial data to the desired result. In logical tree analysis, its meaning has been extended to reducing the process of decision making to a sequence

of "Yes/No" [either/or] responses to specific questions, stemming from previous decision made and or prior statement of action. Provided there are no ambiguities of instructions, a successful outcome is guaranteed. It may be used as a performance aid to supplement the job holders knowledge and skills.

Assertion training-Training designed to help people to increase their own self-esteem and self-respect and to recognize and respect these qualities in others. It involves helping people to understand the difference between assertion and aggression, between non-assertion and politeness, and when each is appropriate to use.

Behaviour therapy-A form of behaviour modification technique, which is based on a particular learning theory and involves the abandonment of inappropriate or undesirable behaviour, through the use of reward and punishment but does not necessarily involve the learning of new skills to replace the old behaviour.

Counseling-Where learners are given an opportunity to talk through their problems and concerns with a counselor who will not direct them but use their knowledge and experience to help them identify what is right for them.

Critical incident training-The process of establishing through the experience of supervision and peers, the priorities of those activities deemed critical to performing the job. It focuses on

actual examples of job behaviour and on judgements as to what behaviour makes for success or where the lack of success is attributable to human errors.

Distance learning-A form of learning in which the trainers and learners are not at the same place and covers Correspondence education and Open University type teaching by TV and Radio.

Encounter groups - An approach to improving self analysis, self understanding and individual growth and development through exchanging personal experiences and exploring and externalizing feelings in a group situation.

Field trips-Learners go out to study where the object of their study is located. This may involve visit to a situation/entity, supplier, or customer to allow on the spot collection of information and observation.

Forum-A group of experts are brought together and learners are invited to ask them questions related to the area of study. The members of the forum answer the question and debate the issue, which emerge.

Group dynamics-The study of the interaction of the behaviour of individual as members of a group and of the behaviour of groups generally. A demanding process for learners and trainees as each person's behaviour is analyzed and reviewed in detail.

Heuristic method - An educational method, the principle of which is to arrange the work so that the pupil discovers laws and principles for himself rather

than learning them directly from the teacher.

Job rotation-This system is based upon the idea that people can become most effective by having an opportunity to perform a wide variety of different jobs as part of their training or development.

Mentoring-An approach where in mentor provides support and advice to learner. The mentor does not have to possess expertise in the area of learning but acts as a father figure and can provide influence and help to gain resources and opportunities to learn. The mentor is usually a senior faculty/manager in the employing organization with an interest in the development of junior staff.

Micro teaching-An approach that 'breaks' a skilled performance into its component elements and individual practices each element separately. Feedback is offered on the performance of each element to allow areas for improvement to be identified. After practice of each element they are all practiced together to allow the achievement of skilled performance.

On-the-job training-Training given at the usual work situation. It may constitute the whole of the training to be combined with off the job training and/or further education.

Self development-The concept that individuals have a responsibility for their own development. This includes what is to be learned, how it is to be learned, how the learning is to be organized, implemented and assessed. Help should be available from the employing

organization to encourage, counsel and assist the individual.

Simulated training-The training provides in a specially created environment which reproduces the important conditions of the working situation, in which formal instruction can be followed and opportunity given for practicing and applying the skills learned in workshop or classroom. It may include work on equipment withdrawn from the working situation for training purpose and/or specially designed simulators. The representation of physical phenomena by computers or by models to facilitate the study of these phenomenon or in other words, representation of the essential characteristics of a system by means of a simpler one.

Syndicate-A small group of students formed to consider and to report on a question, problem or exercise set as part of a training course. The object of the exercise is to promote learning by means of intra and inter group analysis and discussion.

Cancer Update from Johns Hopkins

Every person has cancer cells in the body. These cancer cells do not show up in the standard tests until they have multiplied to a few billion. When doctors tell cancer patients that there are no more cancer cells in their bodies after treatment, it just means the tests are unable to detect the cancer cells because they have not reached the detectable size. Cancer cells occur between 6 to more than

10 times in a person's lifetime. When the person's immune system is strong the cancer cells will be destroyed and prevented from multiplying and forming tumours. When a person has cancer it indicates the person has multiple nutritional deficiencies. These could be due to genetic, environmental, food and lifestyle factors. To overcome the multiple nutritional deficiencies, changing diet and including supplements will strengthen the immune system. Chemotherapy involves poisoning the rapidly-growing cancer cells and also destroys rapidly-growing healthy cells in the bone marrow, gastro-intestinal tract etc, and can cause organ damage, like liver, kidneys, heart, lungs etc. Radiation while destroying cancer cells also burns, scars and damages healthy cells, tissues and organs. Initial treatment with chemotherapy and radiation will often reduce tumor size. However prolonged use of chemotherapy and radiation do not result in more tumor destruction. When the body has too much toxic burden from chemotherapy and radiation the immune system is either compromised or destroyed, hence the person can succumb to various kinds of infections and complications. Chemotherapy and radiation can cause cancer cells to mutate and become resistant and difficult to destroy. Surgery can also cause cancer cells to spread to other sites. An effective way to battle cancer is to starve the cancer cells by not feeding it with the foods it needs to multiply.

Effectively

Vasumathi Sriganesh

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Commentary

PubMed is an index to articles published in biomedical journals. This index is a product of the National Library of Medicine, USA. It covers about 4800 journals mostly English, but many other foreign languages too. Many journals are indexed back to the 1950s. The newer issues are added as they are published; in some instances, they are included in PubMed, even before the print version is released. Searching PubMed is easy, if you learn some theories about PubMed and also a few steps about structured searching of databases. If you neglect going through these processes, you will spend lots more time retrieving a lot of irrelevant or not-so-useful articles. In other words, you will pick up some good articles, but not the best on the topic

Need to search PubMed-Two very obvious reasons – one is its coverage of a significant number of peer-reviewed medical journals and the other is that searching PubMed is free and a large number of journals it indexes are available free online. You will search PubMed for journal references in one or more of the following situations

- For your thesis topic
- When you treat patients who have conditions that you may not have encountered earlier
- When you believe you have done something unique in

your medical practice and wish to report it in a journal

- When you have an incomplete or incorrect journal reference and wish to verify it

What happens when you search PubMed? -Most often as a beginner, you would search PubMed in the same way as you would search Google. You may type in one or more words or a phrase in the Search box and click “Go”. Then you would go through the first 30 to 40 references and choose a handful of references and go ahead. You may feel happy with your references (if you have been lucky) or you may be grumbling about your luck, or in worst cases curse computers or even PubMed!

Searching Pubmed -The problem is not with computers or PubMed. If you learn some search techniques, you will save yourself a lot of time (and negative feelings too). First let us understand the problem – of getting irrelevant references – as we have just described. If you understand why it happens, you have already learnt half the theory. It is simple. When you simply enter a word or two, or a phrase for searching PubMed, you would actually be asking PubMed for every article that contains the same. Which means – you would retrieve articles “about” your search term/s and also articles where the terms are just

present. For instance, if you search for “acute otitis media” you would get articles on it, but also maybe a case report on pregnancy complications, where the patient “also happened to have otitis media”. This article is *not about otitis media*. If there are 50 good articles on acute otitis media, you would obviously not want to choose this one, which is about pregnancy complications and simply mentions otitis media.

So – how do we get articles that are only “about a specific topic”? -The National Library of Medicine that produces PubMed “has indexers” who work on the articles. Every article from journals that are included in PubMed gets what is called “MeSH terms” assigned to it. MeSH stands for Medical Subject Headings. *These terms describe the article.* For instance, an article on “Nocardia infection following phacoemulsification” will be assigned some MeSH terms like “Phacoemulsification/adverse effects” and “Nocardia Infections/etiology”. These are the two “Major” terms and are obvious going by the title of the article. In addition, it may be assigned terms like “Aged”, “Male”, “Retreatment”, Nocardia Infections/drug therapy – and these terms describe the coverage of the article.

Step 1: Opening PUBMED and Locating MESH-Going by this explanation, you obviously would like to know how you

would search using MeSH. Let us first understand MeSH

Go to PubMed www.pubmed.gov You will find a Drop-down option after the word “Search” and before the Search box. Choose “MeSH” from the drop down. Once you do this, you can find MeSH terms used for searching PubMed. MeSH terms are standardized by the National Library of Medicine. (Figure- 1).

Step 2: Using MESH-Let us take an example. If we wanted to find articles on “Pregnancy induced diabetes”. Let us find the MeSH term for this concept. Choose MeSH as described above, and in the Search box, type in the phrase Pregnancy induced diabetes, and click Go. (Figure- 2) In the resulting page you will find that PubMed has “mapped your term” to “Diabetes, Gestational”. The “Scope note” below the term, is a note that explains the meaning of the term. It also means, that if an article is assigned this MeSH term, we can understand from the scope note – what the article covers and what it does not. For example, if an article is assigned this term - “diabetes, gestational”, it will be about the disease condition where there is “Diabetes mellitus induced by pregnancy but resolved at the end of pregnancy”. The article will not cover the condition or patients who “previously diagnosed diabetics who become pregnant”. Below the Scope note – after the Subheadings etc (which will be explained later), there are a set of “Entry terms”. These are the possible terms you may have used

while searching, and PubMed has mapped to a single standard term. In our case, we tried searching with the entry term “Pregnancy induced Diabetes”.

Step 3: Using “Send to Search box with And”-If you now wish to search for articles on Gestational Diabetes, Select the check box next to 1:Diabetes, Gestational. Then choose “Send to Search box with And” from the drop-down menu. (Figure- 3)

Step 4 : The role of temporary search box-The page will refresh automatically. Your search term (The MeSH term you chose) will be placed in a temporary search box (just for you to check). Once you are sure, click PubMed Search. (Figure- 4) . The screen will again refresh, PubMed will run a search for you on articles “About” Diabetes, Gestational. In other words, it will search for articles for which indexers in the NLM, have assigned this term, because they cover the concepts in this term.

Step 5 : The initial retrieval -Clicking Search PubMed, will retrieve over 3000 references. (Figure- 5)

Step 6: Fine tuning the search for certain Specific options-If you wish to search for certain Specific options – so that you do not have to go through 3000 plus references, you can restrict your search. Go back by clicking your browser’s back button. In the MeSH page, below the scope note for your Search term, please select the aspects of the topic which you wish to search for. For example, choose Diet therapy and Drug therapy, if you wish to find articles on treating the

condition. You can also check “Restrict to Major Topic” and “Do not explode this term”. (Figure- 6)

Step 7: Fine tuning the search and limiting the article -The first choice will restrict your search by retrieving articles where the major focus is Diabetes, Gestational – and the treatment of the condition by diet modification, or drugs or both. The second choice will ensure that you do not search for articles on Fetal Macrosomia, which is a specialized subtopic and which falls below Diabetes, Gestational, in the MeSH tree. Repeat the steps “Send to Search box with AND”, and then PubMed Search. Your search results come down to less than 200. If you further wish to Limit your search, you can use the Limits page options to restrict your search results to manageable numbers.

The Limits that can be applied are:

Searching for articles on the topic,

- Written by one or more authors
- Published in one or more specific journals
- Limited to Full text, free full text, or articles with abstracts
- Limited by date ranges
- And other very explanatory options.

Once you choose your options, Click Go at the bottom of the page. Your search results will be reduced to numbers, depending on the number of options that you choose. Playing around with these options, will help you arrive at some manageable numbers.

The “Limits” options are in most cases options of convenience. The only options that really meaningful are the ones that you choose under “Type of article”, and if you are a specialist in Paediatrics or Geriatrics, if you choose to limit to the respective age groups. Under type of article, choosing Meta-analysis on any topic, will give you articles, where authors have studied several papers and summarized the results. Only ensure that such meta-analyses are not very old; if they are, you will have to read newer articles on the topic that have appeared after such meta-analyses. Review articles give you an overview of the topic. Practice guidelines are articles that give you the guideline to follow for treatment or management. Randomized controlled trial is the publication type limit to choose, if you wish to find the best articles on treatment of a condition.

In our present topic – ie Diet therapy or Drug therapy of Diabetes, Gestational, if we only apply the limit of RCT as a publication type, our results come down to 25. (Figure- 7)

Fine-tuning the search for certain Specific options-Do note that if there is a green icon on the left of the reference, it means the article is available free online. Simply click the authors name, you will see in the next page, a link to the free article. (Figure- 8)

Fine tuning the search for certain Specific options-If there is a blank icon – it means the article does not even have an abstract. If the icon has three

lines marked across – then it means it has an abstract. So now you have 25 references and wish to save them. First display all references on one page, by changing the number against “Show”. Next, choose “Send to Email”. Choose your options for formats and sorting, and enter your email address. All references and abstracts (as available) will come to you by email. This is the cleanest way to save references. In case you do not wish to save all 25, then choose the ones you like by ticking the check boxes. Then choose Send to Email

What if the term you wish to search, is not a MeSH term?- For example, if you wish to search for articles on “molecular basis of tuberculosis” – If you go to the MeSH database and search for Tuberculosis, you will find that it is a MeSH Term. But there is nothing for Molecular Basis. (Figure -8). Go to the Main PubMed page. In the Search box, type in tuberculosis[ti] AND molecular basis[ti] And then click “Go”. When you do this, you are asking PubMed to search for articles where the word Tuberculosis is in the title, the phrase Molecular basis is in the title and that you want both search terms to be present in the title (since you have used AND). By doing so, you will get a handful of very relevant references. In the result page, change the display to “Citation format” Except for the unindexed articles that maybe there at the top, all others will have MeSH terms assigned to them. Go through this lot and it appears that all indexed

references have one term in common - Mycobacterium tuberculosis/genetics*

Click this term, and once it shows options, choose “Add to Search” (Please ensure that you clear your search box before you do this step. You would now be searching for “Mycobacterium tuberculosis/genetics”[MAJR] and retrieve many more articles. You can apply limits once again as taught earlier

Combining more than one term-Sometimes you have to cover more than one search term. You need to use Boolean operators.

- AND – is a Boolean operator you use, when you want two or more concepts to be searched together. The articles you retrieve *must have* both concepts.
- OR – is an operator, where you need all articles of two or more concepts.
- NOT – is an operator, where you specifically ask to leave out one or more concepts

Here are few examples of combining more than one term.

- AND – If you search using Pregnancy AND Lactation, then will get references where both these terms are definitely present. You will not get articles about pregnancy where there is NO mention of lactation, and vice versa
- OR – if you search using Pregnancy OR lactation, then you will get articles on pregnancy alone, lactation alone as well as articles

covering both concepts. If this sounds confusing – here is a simple tip. Remember – Boolean AND is opposite of the English word “and”. And Boolean OR is the opposite of the English word “or”

- NOT – If you search using Pregnancy NOT lactation – then you will receive all articles on Pregnancy, but if the word/concept of lactation is absent, such articles will not be retrieved.

Conclusion

- Understand the difference between searching for the presence of a Search term, and searching for references “about” the search term. When you simply type in a word and search, you are searching for the presence of the term

- In order to search for articles “about” a term, go to the MeSH database. Search for your term. Understand the scope for the term, by reading the scope note carefully. Choose subheadings if you wish and also restrict your search to Major, if you wish. Using the Send to search box feature, search for articles
- In the resulting page of references, if there are too many, go to the Limits page and choose limits you wish to apply
- Once you have narrowed down your results, if you wish to save the references you have retrieved, use the Send to email feature. If you wish to be selective, then choose specific references by selecting the check boxes and then use the Send to email

feature. You will receive your references by email

- In case the term you are searching for is not a MeSH Term, then go to the main PubMed Screen and do a title search using [ti] against each of your search terms. In the results page, change the format to Display Citations. Clear the search box. Choose the term most appropriate to your search, from the list of MeSH terms below each reference. Add this to the search box, and search
- Use Boolean operators AND, OR, NOT to combine concepts. Remember that Boolean AND is opposite of English “and”. Boolean OR is opposite of English “or”

With regular practice you will learn how to do better searches. Reading more articles as well as the Help section of PubMed will help you discover more tips.



Figure -1, Opening PUBMED and Locating MESH



Figure-2, Using MESH

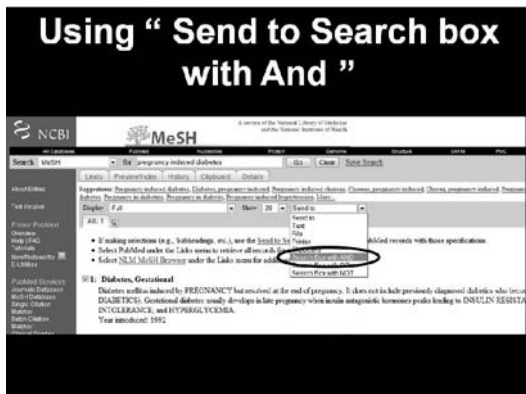


Figure- 3, Using “Send to Search box with And”



Figure- 4, The role of temporary search box

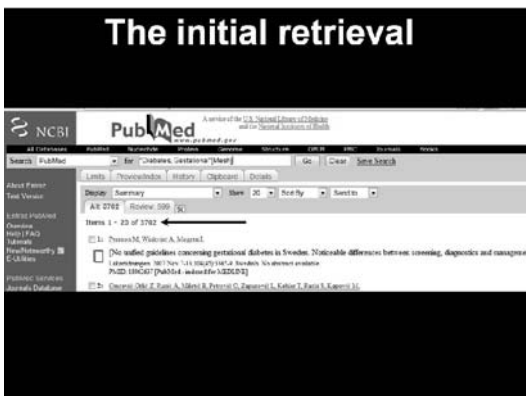


Figure- 5, The initial retrieval

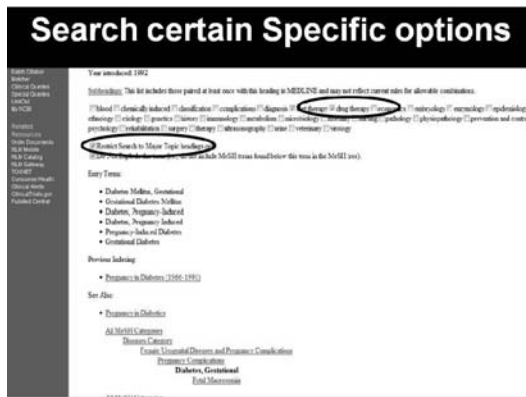


Figure- 6, Fine tuning the search for certain Specific options

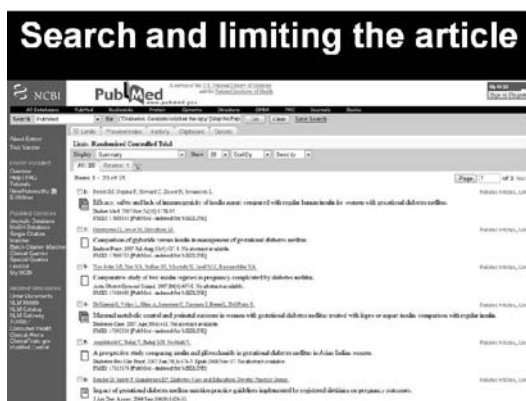


Figure- 7, Fine tuning the search and limiting the article

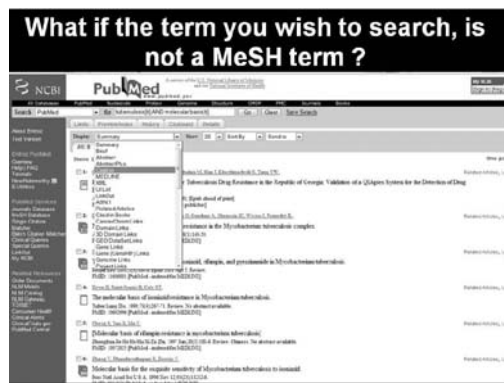


Figure- 8, What if the term you wish to search, is not a MeSH term?

Commentary

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The suffering and anguish blindness brings has been documented throughout the history however curing blindness is a more a recent phenomenon brought about by medical and surgical advances that have occurred primarily in the 20th century. The concept of Avoidable blindness is even more recent idea that has been defined as blindness that could reasonable be prevented or cured within the limits of resources that are likely to be made available. It further encompasses two terminologies i.e. Curable blindness and Preventable blindness. Curable blindness is that stage of blindness where the damage is reversible by prompt management [It is mostly related to lack of access to effective health service delivery network e.g. cataract services]. Preventable blindness could have been completely prevented by institution of effective preventive or prophylactic measures e.g. xerophthalmia, trachoma etc. Approximately, 75% to 80% of all blindness is considered avoidable.¹ Traditionally, the diseases responsible for an increase in the prevalence of corneal blindness in a population have included trachoma, onchocerciasis, leprosy, ophthalmia neonatorum, and xerophthalmia. These diseases still remain important causes of blindness, but the recent success of public health programme in controlling

onchocerciasis and leprosy, as well as the gradual worldwide decline in the number of cases of trachoma, has generated new interest in other causes of corneal blindness including ocular trauma, corneal ulceration, and complications from the use of traditional eye medicines.² As per available information, there are an estimated 12 million blind person in India with visual acuity [VA] < 6/60 in the better eye. The 2001-04 survey in 25 districts of the country indicated that blindness due to corneal lesion was approximately 0.90% of the total blindness.

Need for eye banking - Relatively greater attention has been given to cataract surgeries considering the fact cataract blindness is the major cause of blindness in India. Though, corneal blindness is much less in frequency, the gravity of the problem is serious considering the fact, firstly, over 50% of corneal blindness occur in children in contrast to cataract blindness which is the disease of old age. Secondly, the economic loss due to corneal blindness is much more than cataract blindness. This again is due to two factors. The corneal grafting being a super-specialized branch requires trained corneal surgeons, dependent on donor cornea, more tedious surgery and demands meticulous, close and longer follow up. Also being the childhood disease, man-year loss

is 5 times more than cataract patients which leads to less production and in turn indirectly adds economical burden on the society. According to estimate, there is a need of 1,00,000 corneas in the country however we are able to procure 38,000 only on annual basis. We are striving to fill this gap by having good eye banking services including proper tissue procurement, processing, and improved storage media with enhanced publicity for eye donation,

Corneal Transplantation-A high percentage of visually disabled individuals can be visually rehabilitated by corneal transplantation, a procedure that has a very high rate of success among organ transplants. Quality of donor cornea, the nature of recipient pathology and the availability of appropriate postoperative care are the factors that determine the final outcome of this procedure.³ The cornea is unique organ as it has no blood vessels and derives nourishment from other sources in the eye. It is this inherent property of the cornea, which makes it excellent graft material with minimal chances of rejection. Corneal transplant or keratoplasty is an operation in which an abnormal or a diseased cornea is replaced by a donor corneal tissue and sutured. The other parts of the eye cannot be transplanted. The graft may be partial thickness

[lamellar] or full thickness [penetrating].

History- Ever since the first “successful” human to human corneal transplant was done in 1903 at Czechoslovakia by Zirm to visually rehabilitate a patient with alkali burn, the technique of corneal transplantation underwent various changes and transformed into a clinically acceptable procedure for the corneal blind. However, no corneal grafting was performed till Filatov, a Russian Ophthalmologist, considered to be father of keratoplasty, performed the surgery in 1935 by utilizing human donor cornea from the eyeball stored in moist chamber at 4°C. In response to demand of human corneal tissue by increasing number of ophthalmologist, first Eye Bank for sight restoration was started in the state of New York in 1944 by Palton. Since then eye banking movement has spread worldwide. In India, the first eye bank was established in 1945 at Madras [Chennai] and the first successful corneal transplantation was carried by Dr. Dhanda of Indore in 1960.⁴

Concept- Eye Bank is an organization which deals with the collection, storage and distribution of the donor cornea for the purpose of corneal grafting, research and supply of eye tissue to other eye banks for ophthalmic purpose. Comprehensive and detail standards of eye banking have been formulated to assure consistency, quality, proficiency, and ethics in dealing with eye tissue for harvesting, transportation, transplantation and

research. It also deals with activities related to community awareness and motivation for eye donation. According to available information, there are more than 500 eye banks in the country however only 238 are functional in nature (Table- 1).

Organization and setup of an ideal Eye Bank⁵- An eye bank should be registered with competent authority under “Transplantation of Human Organs, Act 1994” and strictly adhere to related guidelines on health institutions issued by regulatory and civic agencies. It should ideally be located within or near a hospital complex and for long term sustainability should be attached to 4-5 eye donation centres. The Transplantation of Human Organ Act [1994] currently stipulates that only a registered medical practitioner shall remove organs from a human body including eye/cornea however a suggestion has been mooted that services of a trained eye technician could be utilized for the removal of cornea that would in turn have a positive impact on the number of corneas collected in the country.

Manpower- Health personnel are critical workforce for running any institution effectively and efficiently and same is true with eye bank. They should be trained in all measures related to quality control activities. Eye bank should be manned by an executive director/administrator- 1 who could be a trained ophthalmologist, eye bank manager -1, technician 2, counselors atleast- 2, secretary/

data entry operator/and telephone operator, sweeper, driver etc.

Infrastructure and equipments- Each eye bank should have space for office reception, waiting area, preparation area, processing area with laminar flow hood, sterile area, evaluation zone, store room, toilets etc. Basic units comprise of Refrigerator, slit lamp biomicroscope, specular microscope, hot air oven, autoclave, vehicle, and telephone connection. Each eye bank laboratory must possess a minimum of six sets of cornea rim excision and enucleation sets, four thermocol boxes and 20 collection bottles with eye ball stands. Instruments are mainly used either for donor eye ball enucleation procedure or corneoscleral tissue removal/preparation for donor tissue preservation.

Documentation- Clinical and administrative documents are very important for smooth functioning of eye banks and have to be preserved for atleast five years. Various recording and reporting are donor information; consent forms; death certificates form; harvested donor eye data; cornea evaluation format; eye donor medical particulars; tissue utility data/discarded data; distribution information; outcome forms; accounting/financial reports; waste disposal; accreditation, quality control measures forms and general correspondence

General code of ethics- Eye bank shall not compete with one another; eye tissue should be distributed without any

discrimination based on race, religion, creed or nationality; eye tissue shall be provided only to qualified ophthalmologist; the name of donor and recipient shall not be disclosed to each other kinship; eyes pledged shall be solicited in a dignified manner; fund raising shall be ethically conducted; all public information shall be medically approved; all eye bank personnel must operate under the universal precautions for health care workers and all waste disposed off as laid down in Biomedical Waste Management [BMW] rules; after the use of cornea or where the cornea is not usable the eye shall be disposed in any of the following manner-study of histopathology of various parts of the eye ball, eye research, preservation of tissues like sclera/cornea etc.

Contraindication for eye removal- For successful corneal transplantation proper selection of donor material is a prerequisite. Absolute contraindications for eye removal include unknown cause of death, rabies, hepatitis B and C, HIV, septicemia, leukemia, creutzfeld-jakob diseases, retinoblastoma, lymphoma etc.⁶

Challenges, Issues and Concerns- There are various challenges, issues and concerns that impede harvesting requisite number of cornea in the country. Some of these are lack of awareness amongst general public regarding eye donation; myth, misconception and religious taboo's associated with eye donation; inadequate infrastructure, facilities and services for removal of eyeballs/cornea; shortage of trained

manpower, time and place of death; lack of transport and poor means of communication.

National Programme for Control of Blindness [NPCB], Government of India initiatives in up scaling Eye Banking in India

- Support for setting/strengthening Eye Banks in Government/voluntary sectors as per the XIth five year plan approval- Non-recurring assistance upto Rs 15 [fifteen] lakh for medicine, equipments and furnishing & fixtures; Recurring assistance of Rs 1500 [one thousand and five hundred] per pair of eyes towards honorarium of eye bank staff, consumables including preservative material and media, transportation, POL [petrol-oil-lubrication], contingencies; Recurring assistance of Rs 10,000 [ten thousand] only per month towards salary of eye donation counselor on contract basis.
- Support to Eye Donation Centres-Non recurring assistance upto Rs 1 [one] lakh for strengthening/developing Eye donation centres; Recurring assistance of Rs 1,000 [one thousand] per pair of eyes collected
- Training of health personnel in corneal surgeries and enucleation
- NPCB has been working with various stakeholders including voluntary organizations like Eye Bank Association of India [EBAI], an umbrella body of all eye banks/eye

donation centres in the country to strengthen eye donation movement in the country.

- ORBIS International, an NGO assisted government in Eye Banking and Eye donation activities by appointing 'Grief Counselors' on contract basis in few hospitals.
- NPCB has organized various workshops and consultative processes to formulate road map for eye banking in India including adoption of international standards to optimize resources.
- NPCB has been organizing various community awareness generation activities with regard to consumption of vitamin A food/supplements, injury prevention, personal hygiene & sanitation and eye donation in the country. NPCB observes eye donation awareness fortnight from 25th Aug to 8th Sep, every year through out the country.
- NPCB has launched Hospital Cornea Retrieval Programme [HCRP] a strategy for increasing eye donation by informing, counseling and motivating relatives of terminally ill patients, accident victims and patients suffering from other grave diseases admitted in the hospitals
- NPCB is carrying out surveillance activities, planning, monitoring and evaluation with respect to amelioration of corneal/blindness throughout the country in consultation with various stakeholders.

Facts about eye donation

- Almost anyone of any age and sex can pledge to donate eyes after death. This can be done even if donor wears glasses, has cataract or has undergone eye surgery successfully or suffering from diabetes, hypertension etc. All that is needed is a clear, healthy cornea.
- The eyes of the deceased can be donated whether he/she has pledged the eye during life or not. At the same time, eyes cannot be removed without the consent of the next of kin, even if the deceased has already pledged his/her eyes.
- The eyes have to be removed within 6 [six] hours of death. So the nearest eye bank or eye collection centre must be informed immediately irrespective of the initial pledging centre/eye bank.
- Eye lids of the dead should be closed immediately after death. Head end should be elevated, fans should be switched off and a wet piece of cloth could be placed over the covered eyes. Antibiotic drops, if available may be applied to keep the eyes sterile.
- In case of death being reported from other than hospital, eye bank team with a doctor/technician will reach the donor site including home. No fee is charged to the family for eye donation.
- Eye removal takes only 15-20 [fifteen to twenty] minutes and leaves no scar or disfigurement of the face.
- Eye donation gives sight to two blind persons. One blind person is given one eye.

- On reaching eye bank, eyes are examined, processed and used for corneal transplant operation as early as possible.
- The recipient of cornea will always remain anonymous but the family should be satisfied knowing that the eyes have been used to restore vision of blind person[s].
- The donated eyes are never bought or sold. Eye donation is never refused.

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Table 1: Number of functional Eye Banks in India

States/UTs	Functional eye banks
1. Andhra Pradesh	24
2. Karnataka	14
3. Kerala	15
4. Puducherry	03
5. Tamilnadu	24
6. Chandigarh	06
7. Delhi	09
8. Haryana	07
9. Punjab	10
10. Rajasthan	10
11. Assam	02
12. Bihar	06
13. Orissa	02
14. W.B.	16
15. M.P.	10
16. U.P.	13
17. Gujarat	15
18. Maharashtra	52
Total	238

Source: Eye Bank Association of India [EBAI], 2008

Review Article

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The introduction of highly active antiretroviral therapy (HAART) has dramatically improved the long-term prognosis of human immunodeficiency virus (HIV)-infected patients, but several abnormalities of lipid and glucose metabolism have recently been reported with increasing frequency in patients receiving potent new antiretroviral combinations. In a clinical trial the incidence of DM in HIV-infected men with HAART exposure was greater than 4 times that of HIV-seronegative men, representing a risk that is higher than previous estimates.⁽¹⁾ Although a rare occurrence before the HAART era, insulin resistance has now been described as an important component of the lipodystrophy syndrome, including body fat redistribution, hypertriglyceridemia, hypercholesterolemia, hyperinsulinemia, and hyperglycemia. The etiology of such abnormalities remains unclear, but protease inhibitors and, to a lesser extent, nucleoside reverse transcriptase inhibitors are believed to contribute to the pathogenetic mechanism. The potential clinico-pathological consequences of glucose metabolism dysregulation, such as atherosclerosis and coronary heart disease, all make the

management of insulin resistance and diabetes mellitus a challenge in the management of HIV-infected patients.⁽²⁾

Incidence of diabetes mellitus in HIV patients-The prevalence of diabetes mellitus in HIV patients is about 8–10%; most cases are identified after oral glucose loading. Few cases seem to have symptoms such as polyuria, blurred vision, or weight loss, and ketoacidosis is rare. A further 15% of patients have impaired glucose tolerance.⁽³⁾ New-onset diabetes mellitus, clinically similar to type 2 diabetes, affects a small proportion (1% to 6%) of HIV-infected patients treated with Protease Inhibitors (PI)-based antiretroviral regimens. Many more patients receiving PI therapy have evidence of insulin resistance without frank diabetes.⁽⁴⁾ In a multi center AIDS cohort study trial the incidence of DM in HIV-infected men with HAART exposure was found to be greater than 4 times that of HIV sero negative men.⁽¹⁾ **Pathophysiology**-Insulin resistance and beta cell dysfunction-HIV-1 Protease inhibitors, such as indinavir, ritonavir, nelfinavir and saquinavir, not only induce peripheral insulin resistance, but also impair glucose-stimulated insulin secretion from beta cells.⁽⁵⁾

Various PIs have been shown to cause insulin resistance and DM. Administration of indinavir to healthy HIV-uninfected volunteers has caused reduced insulin sensitivity with as little as a single dose. PIs directly inhibit the Glut4 isoform, which mediates the transport of glucose, thus decreasing glucose disposal. This reduces uptake of glucose in muscle and adipocytes and increases intracellular lipolysis, subsequently increasing the release of unesterified fatty acids. This, in turn, stimulates hepatic glucose production and insulin secretion, thereby worsening hyperinsulinemia.⁽⁶⁾ Nucleoside reverse transcriptase inhibitors (NRTIs), specifically stavudine, are known to alter mitochondrial function in human immunodeficiency virus (HIV)-infected individuals. Stavudine administration has potent effects on insulin sensitivity among healthy subjects.⁽⁷⁾ In a clinical trial treatment for 3 months with a NRTI-containing, but not a NRTI-sparing, regimen resulted in a 25% decrease in insulin-mediated glucose disposal and a 22% increase in fasting lipolysis and thus contributing to insulin resistance.⁽¹⁾

Pancreatic damage - Acute pancreatitis is a potentially life-threatening condition that is

characterized clinically by abdominal pain, nausea, and vomiting and biochemically by elevations of lipase and/or amylase. Although the annual incidence in the general non-HIV-infected population is relatively low, estimated to be 17 to 30 cases per 100,000 population, the annual incidence of acute pancreatitis in the US HIV population is considerably higher. In the pre-highly active antiretroviral therapy (HAART) era, Dutta et al reported an acute pancreatitis rate of 14 cases per 100 HIV patients over a one year period. This rate may have been exceedingly high because of the co morbid conditions prevalent in their urban HIV clinic population (eg, ethanol use and biliary disease), the use of medications associated with pancreatitis (eg, pentamidine, high-dose didanosine [ddI], corticosteroids, ketoconazole, sulfonamides, metronidazole, isoniazid), HIV itself, and opportunistic infections (eg, cytomegalovirus, cryptosporidiosis, mycobacterial disease). Moore et al suggest that significant risk factors for pancreatitis include use of HU, CD4 count <200 cells/mm³, female gender, and history of pancreatitis.⁽⁸⁾ Of the various combinations of dual NRTIs that were studied, ddI/d4T seems to be associated with the highest rates of pancreatitis. The combination of IDV/ddI/d4T seems to be associated with particularly high rates of pancreatitis, reminiscent of high-

dose ddI monotherapy trials. The frequency of ddI-induced pancreatitis seems to be dose related. The Alpha trial found no difference in efficacy between doses of 200 and 750mg per day, but 5% of people taking the higher dose developed pancreatitis, compared with only 1% of the lower dose group. The observation that high ddI plasma levels may be associated with higher rates of pancreatitis was recently seen once again when clinicians began using 400 mg of ddI daily in combination with 300 mg of tenofovir daily. One ARV combination that demonstrated surprisingly high rates of pancreatitis was NVP/ZDV/ddI. This regimen should probably be used with caution in patients at increased risk of pancreatitis.⁽⁸⁾

Lipodystrophy syndrome- Lipodystrophy is part of a metabolic syndrome that includes dyslipidemias, insulin resistance and accelerated bone loss. Lipodystrophy affecting HIV-positive patients was first described in 1998. The main clinical features are peripheral fat loss (lipoatrophy) in the face, limbs and buttocks, accompanied by central fat accumulation in the abdomen and breasts and over the dorsocervical spine (the "buffalo hump") and lipomas. PI therapy has been most strongly linked to the lipodystrophy syndrome, although NRTIs, especially d4T, have also been associated with lipodystrophy. The overall prevalence of at least one physical abnormality related

to lipodystrophy has been estimated at about 50% after more than a year of antiretroviral therapy.⁽³⁾ Metabolic features significantly associated with lipodystrophy and protease-inhibitor therapy include hypertriglyceridaemia, hypercholesterolaemia, insulin resistance (raised C-peptide and insulin concentrations) and type 2 (generally non-ketotic) diabetes mellitus. Dyslipidaemia at concentrations associated with increased cardiovascular disease occurs in about 70% of patients. These metabolic abnormalities are more profound in those receiving protease inhibitors, and also in those with lipodystrophy.⁽⁹⁾

Management of patients on HAART- Routine laboratory monitoring should be done approximately every 3 months to determine whether the patient has asymptomatic abnormalities. High risk groups should be specifically identified and paid special attention. Monitoring laboratory tests include complete and differential blood counts and measurement of electrolyte, creatinine, liver transaminase, bilirubin and amylase levels. Patients should also be monitored at regular intervals (approximately every 3 months) for dyslipidemia, diabetes, and lipoaccumulation or lipoatrophy. This laboratory work should include determination of total cholesterol, LDL cholesterol, HDL cholesterol, triglyceride and fasting blood glucose levels. Patients should be asked about and examined for changes in fat

distribution. Imaging tests, such as abdominal CT to detect visceral fat, are not recommended for routine monitoring.⁽⁴⁾ One theoretical treatment option is withdrawal or substitution of HAART. Again, uncontrolled data suggest that protease-inhibitor substitution with nevirapine, and stavudine withdrawal might improve fat accumulation and lipodystrophy, respectively.⁽³⁾ Patients switching from PI-based therapy to NNRTI or triple-nucleoside regimens have shown improvements in lipodystrophy, dyslipidemia and insulin resistance. However, not all switch studies have shown beneficial effects. As well, some patients have no alternatives to PI-based regimens because their infection is resistant to other classes of antiretrovirals. In this situation, treatment for dyslipidemia should be the same as for dyslipidemia in the general population, including lifestyle modifications and pharmacotherapy. Diabetes and insulin resistance should also be treated like type 2 DM. Lipodystrophy has no easy and proven treatment.⁽⁴⁾

What happens if a patient is already a diabetic-It is likely that a patient who has diabetes and then takes HAART may have greater difficulties in controlling their diabetes and dyslipidemia. This could lead to an increase in the risk of heart disease and other diabetic related complications. It

is thought that patients who have both HIV and diabetes can continue to do well for many years, as long as they have access to good care and keep the diabetes under control by following a healthy diet, exercising regularly and taking anti diabetic medications regularly.⁽⁴⁾ Some statins (lipid-lowering agents) and glitazones (insulin sensitisers and possible peripheral adipocyte growth factors) are metabolised by cytochrome P450 3A (which is inhibited by protease inhibitors), so their use with protease inhibitors could increase the risks for myositis and hepatitis, respectively. The statin least likely to interact adversely with protease inhibitors is probably pravastatin. Uncontrolled data suggest that gemfibrozil and atorvastatin might be safe and have some efficacy in lowering lipids.⁽³⁾

Recommendation for hiv patient with dysglycemia⁽⁹⁾

- Maintain HbA1c < 7%.
- Measure urine microalbumin.
- Maintain low density lipoprotein cholesterol < 100 mg/dl.
- Maintain Triglycerides levels < 150 mg/dl (1.7 mmol/l) and HDL cholesterol levels > 40 mg/dl (1.0 mmol/l) in men and > 50 mg/dl (1.3 mmol/l) in women.

- Maintain blood pressure < 130/85 mmHg.
- Annual retinal examination by an experienced ophthalmologist.
- Lifestyle modification (smoking and alcohol cessation, increased exercise, weight reduction and expert nutritional counseling).
- Annual foot examination with referral to a foot specialist when indicated.
- Aspirin therapy for patients with evidence of macrovascular disease, a family history of coronary heart disease, or a history of cigarette smoking and as secondary prevention after vascular events.

Conclusion-HAART drugs in the therapy of AIDS have improved the management of HIV, but at the cost of side effects. One important side effect of some of these drugs is hyperglycemia, insulin resistance and lipid abnormality. Hyperglycemia is related to insulin resistance and pancreatic damage. Hence in the management of HIV, one should be cautious and detect the presence of diabetes and it should be managed in the same way as type 2 diabetes with special attention to drugs which may deteriorate glucose homeostasis.

Table-1, Antiretroviral medications and their adverse effects				
Drug	Abbreviation	Dosage	Most common adverse effects	Comments
Nucleoside reverse transcriptase inhibitors (NRTIS)				
Zidovudine	AZT	400-600 mg/d divided (i.e., administered bid)	Nausea, headache, rash, anemia, leukopenia, elevation of liver enzyme levels, elevation of lactic acid level elevation (rare)	Should not be combined with d4T.
Lamivudine	3TC	150 mg bid	Neutropenia (rare)	
Didanosine	ddl	Body weight 35-49 kg: 100 mg bid Body weight > 50 kg: 200 mg bid	GI intolerance, pancreatitis, gout, reversible, peripheral, neuropathy	Should be taken separately from food. Full daily dose be given once daily.
Didanosine-EC	ddl-EC	Body weight > 50 kg: 400 mg once daily		
Zalcitabine	ddC	0.75 mg tid	Reversible peripheral neuropathy, mouth ulcers pancreatitis	Should no be combined with d4T or ddl. Relatively weak risk-benefit ratio limits usefulness.
Stavudine	d4T	Body weight 40-60 kg: 30 mg bid Body weight > 60 kg: 40 mg bid	Reversible peripheral neuropathy, lactic acid elevation (rarely fatal)	Should not be combined with d4T.
Tenafavir	TDF	300 mg once daily	GI upset, low phosphate levels	
Abacavir	ABC	300 mg bid	Hypersensitivity reaction, which may be characterized by fever, rash myalgias, arthralgias, malaise.	Reaction may be fatal if medication is continued or patient is rechallenged.
Non-nucleoside reverse transcriptase inhibitors (NNRTIs)				
Nevirapine	NNP	200 mg once daily for 2 wk, then increase to 200 mg bid	Rash, elevation of liver enzyme levels	Full daily dose can be given once daily
Delavirdine	DLV	400 mg tid	Rash, elevation of liver enzyme levels	

Table-1, Antiretroviral medications and their adverse effects				
Drug	Abbreviation	Dosage	Most common adverse effects	Comments
Efavirenz	EFV	600 mg once daily (or 300 mg bid)	Central nervous system toxicity ("hangover," drowsiness), rash	
Protease inhibitors (PIs)*				
Saquinavir SQV				
Brand invirase	INV	Administer with RTV, with SQV/RTV ratio as follows: 400 mg/400 mg bid or 1000 mg/100 mg bid or 1600 mg/100 mg once daily	Elevation of liver enzyme levels	Very poor bioavailability unless combined with RTV. Better tolerability (e.g. GI) and similar pharmacokinetics to FTV when used with RTV boosting
Brand Fortovase	RTV	1200 mg tid. Alternatively, administer with RTV, with SQV/RTV ratio as follows: 1000 mg/100 mg bid or 1600 mg/100 mg once daily	GI toxic effects, elevation of liver enzyme levels	Better bioavailability than INV in the absence of RTV
Ritonavir	RTV	600 mg bid	GI upset, diarrhea, circumoral paresthesias, elevation of liver enzyme levels, hypertriglyceridemia.	Most common use at present is as a PI booster at low doses (e.g. 100-400 mg/d)
Indinavir	IDV	800 mg tid. Can be given with RTV boosting, IDV 800 mg/RTV 100 mg bid	Elevation of liver enzymes levels, nephrolithiasis, hypertension, ingrown toenails, benign hyperbilirubinemia	
Lopinavir/ritonavir	LPV/RTV	3 capsules bid	GI Upset	Two drugs combined in a single capsule. Dose should be increased to 4 capsules bid if

Drug	Abbreviation	Dosage	Most common adverse effects	Comments
				used EFZ or NVP and in the presence of moderately to highly PI-resistant HIV virus
Ampnenavir	APV	1200 mg bid. Can be given with RTV boosting: APV 600 mg/RTV 100 mg bid	Rash, GI upset	
Nelfinavir	NFV	750 mg	GI upset, mostly diarrhea	

Adapted from: Valentina Montessori, Natasha Press, Marianne Harris, Linda Akagi and Julio S.G. Montaner: Adverse effects of antiretroviral therapy for HIV infection. *CMAJ*

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Review Article

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Thyroid cancer comprises of 1.5% of all cancer. Malignant tumors of thyroid follicular cell origin have traditionally been classified as either well-differentiated thyroid carcinoma (WDTC), which is composed of papillary (75-85% of cases) and follicular carcinoma (10-20%), medullary (5%) or undifferentiated / anaplastic thyroid carcinoma (ATC) (<5%). The vast majority of patients with WDTC have an excellent prognosis regardless of the types of treatment used, whereas patients with ATC uniformly have a poor prognosis. There is growing evidence for the existence of a group of tumors that fall between WDTC and ATC in terms of both morphologic appearance and biologic behavior. These tumors, classified as poorly differentiated thyroid carcinoma (PDTC), may represent *intermediate* entities in the progression of WDTC to ATC. Within this spectrum from differentiated to undifferentiated, there are Hurthle-cell tumours and insular carcinoma. Insular carcinoma is a poorly differentiated tumour, probably part of a continuum from differentiated to anaplastic thyroid cancer. Medullary thyroid carcinoma originates from the C cells, and these cancers are, therefore, aetiologically, pathologically and clinically distinct from those arising from the follicular cells. The management

of thyroid cancer is primarily influenced by histological type, and for differentiated cancer, age and extent of disease. In locally advanced ca thyroid treatment is multimodal.

Locally advanced differentiated thyroid cancer (DTC)-

It accounts for 54-94% of all locally advanced thyroid cancers. Local invasion of the upper aerodigestive tract by well-differentiated thyroid cancer although uncommon is a major source of serious morbidity and mortality. Invasion of the upper aerodigestive tract occurs in 5% (1-13%) of patients with well-differentiated thyroid cancer. The mortality rate when this occurs is 30%. Of those who die from thyroid cancer 50% will die as a result of upper airway haemorrhage or asphyxiation. Suspect locally advanced disease if there is hoarseness of voice, respiratory insufficiency, dysphagia and hemoptysis. Removal of all gross disease has been associated with an improved long-term survival. DTC invasion of the recurrent laryngeal nerve, strap muscles and trachea are the most common followed by invasion of the esophagus, internal jugular vein and carotid artery. Locally advanced thyroid cancer invading the tracheal cartilage represents a difficult treatment dilemma during thyroidectomy. Incidence of various structures involved in advanced carcinoma are- Muscles

- 53%, RLN - 47%, Trachea- 37%, Oesophagus-21%, Larynx-12%, Other sites - 30%.

Locally advanced disease is defined as the presence of extrathyroidal extension (T4a and T4b by UICC 6th edition), recurrent disease in the thyroid bed, metastatic disease in the lung that does not take up iodine, and bone and other metastases. The goals of treatment for invasive thyroid carcinoma include - prevention of hemorrhage and airway obstruction, preservation of a functional upper aerodigestive tract, prevention of loco-regional recurrence, and long-term survival. The current treatment policy of surgical excision followed by radioactive iodine and thyroid stimulating hormone (TSH) suppression, as recommended by the British Thyroid Association and the Royal College of Physicians¹ and described by Vini and Harmer, results in cure for most patients with differentiated thyroid cancer. Recurrence rates are highest at extremes of age, survival with treatment may be excellent in younger patients.

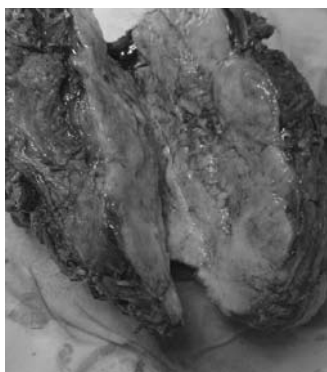
Treatment of advanced differentiated thyroid cancer- Surgical resection is the primary treatment for locally advanced DTC. Although the optimal surgical approach (ranging from conservative shave excision to aggressive en bloc resection of tumor and vital structures) in patients with locally advanced

DTC is controversial, a curative resection should be the goal unless complete tumor resection results in unwanted perioperative morbidity and mortality or widely metastatic disease is present. Some surgeons prefer conservative procedures with partial preservation of the anatomical structures and laryngotracheal functions, stating that conservative surgery is possible in most patients with adequate local control may go for complete removal of organ ie total laryngectomy.

Surgery in Involvement of Recurrent Laryngeal Nerve



CT scan shows locally advanced well differentiated carcinoma thyroid



Total thyroidectomy with laryngectomy specimen

(RLN) in locally invasive Well-Differentiated Thyroid Carcinoma (WDTC)-Identification of involvement of RLN is important as to sacrifice or preserve the nerve. If pre operative there is no involvement of RLN then dissect the tumor from the nerve. If there is pre op involvement of RLN and pre-operative examination indicates paralysis of the RLN then attempts to save the nerve at the time of surgery should not be pursued. Primary thyroplasty may be considered in this scenario. In case surgeon comes across intra operative nerve

involvement then if there is u/l nerve involvement with extensive disease, then, nerve may be sacrificed to achieve R0 resection. If both nerves are involved with extensive tumor growth and it is not possible to dissect entire tumor without damaging both RLN, small tumor may be left behind to protect both the nerve. Surgery should be followed by RI ablation and thyroid supplementation.

Surgery in case of tracheal involvement-If there is limited tracheal involvement but gross intraluminal spread of tumor, then window and sleeve resections are necessary. For larger defects, up to one third the circumference of the tracheal, Use of sternocleidomastoid and pectoralis major myoperiosteal flaps over T-tubes. For very larger defects, tracheal resection with re-anastomosis with release procedures while preserving at least one recurrent laryngeal nerve has been described with favorable results.

Laryngeal invasion of locally invasive WDTC-The goal of surgery in advanced WDTC is maximum disease removal with maximum functional preservation of larynx. In case of unilateral disease, surgeon can do a vertical partial laryngectomy. if there is extensive anterior invasion, a supra-cricoid partial laryngectomy is proffered. Indications for total laryngectomy are-Extensive laryngeal spread beyond the scope of organ-preservation surgery and involvement of more than 1/3rd of the cricoid ring.

Esophageal invasion in locally invasive WDTC-WTDC tends to invade only the outer muscular layers of the esophagus. Surgical resection will depend on the extent of the disease i.e if there is superficial disease then limited resection without intraluminal entry should be done. In case of minimal invasion, primary closure of the defect after resection is the preferred surgery. If there is extensive invasion – Reconstruction with pedicled and free tissue transfer.

Arguments for Total Thyroidectomy in Well-Differentiated Thyroid Carcinoma

- Higher survival rate for lesion > 1.5 cm in diameter
- Lower recurrent rate in all patients
- Prevention of recurrence in the contralateral lobe
- Reduces the risk of developing pulmonary metastasis
- Can be performed with the same morbidity and mortality as thyroid lobectomy
- Improved sensitivity of serum thyroglobulin as a marker for persistent or recurrent disease
- Radioactive iodine can be used to detect and treat persistent or recurrent disease
- Reduces possibility of residual tumor in contralateral lobe undergoing transformation to anaplastic carcinoma

Locoregional disease-Ideally, treatment should be a thyroidectomy and the removal of all gross disease followed by adjuvant ¹³¹Iodine therapy. Complete surgical resection is important because survival is adversely affected by gross

residual disease (R2 resection) compared with no (R0), or microscopic (R1) residual disease.² Using the 6th edition of UICC staging classification, all tumours with extrathyroidal extension are no longer classified purely as T4 disease. A distinction is made on the basis of the extent and site of extrathyroid extension. If the tumour has minimal extension to the sternothyroid muscle or perithyroid tissues, it is classified as T3. Tumours that invade the subcutaneous soft tissues, the larynx, trachea, oesophagus or recurrent laryngeal nerve are classified as category T4a, but, if there is invasion of prevertebral fascia, mediastinal vessels or encasement of the carotid artery, the tumour is classified as T4b. A T4a tumour may be resected and successfully shaved or dissected off the involved structures, But with the assumption of residual microscopic disease. Invasion of the cartilage or intraluminal involvement may require more extensive resection, although ideally, the extent of surgery should be balanced with preservation of function. Gross residual disease after resection of

T4b tumours is inevitable. ¹³¹I therapy is unlikely to eradicate gross residual tumour unless a high absorbed dose of Radiation is achieved. Further radiation in the form of radical external beam radiotherapy (EBRT) may improve local control. Management of locally invasive thyroid cancer should aim to remove all gross disease. Resection of the trachea can be performed with good functional results and quality of life. Clear surgical margins can usually be achieved by segmental resection or circumferential resection of the trachea. The use of EBRT is controversial for those patients with microscopic residual disease. All reports on the use of EBRT have been retrospective, with varying criteria for patient selection, resulting in contradictory conclusions. Several studies³ have described either no or a deleterious effect for EBRT, but many others have described benefit.⁴ In the absence of randomised data, we believe there is sufficient evidence from this study and the other retrospective studies (Table-1) to recommend EBRT in addition to standard therapy in high-risk patients.

Table 1 – Results of adjuvant external radiotherapy in high-risk disease from retrospective studies: 10-year local recurrence

	Surgery with and without ¹³¹ Iodine (%)	Surgery and radiotherapy with and without ¹³¹ Iodine
Tubiana <i>et al.</i> [12]	21	14
Simpson <i>et al.</i> * [11]	18	14
Esik <i>et al.</i> [23]	52†	11†
Ford <i>et al.</i> [26]	63†	18†
Philips <i>et al.</i> [25]	21	3
Farahani <i>et al.</i> ‡ [24]	50‡	15‡
Tsang <i>et al.</i> * [8]	22	7
Kim <i>et al.</i> [91]	37.5	4.8

*Surgery alone group had local recurrence rate of 74%.
 †Compares low dose vs higher dose.
 ‡Local and distant failures.
 §Papillary only.
 || 5-year locoregional relapse rate.

The British Thyroid Association and the Royal College of Physicians guidelines recommend EBRT in patients with gross evidence of local invasion at surgery and significant macro or microscopic residual disease, particularly if there is residual tumour that fails to concentrate ¹³¹I and is apparent only by raised thyroglobulin. However, after radioactive iodine, even if there is demonstrated uptake in the neck, it is uncertain whether this uptake is by residual normal thyroid tissue or residual disease. EBRT is given in younger patients if the extrathyroid extension is extensive or if there is gross residual disease after resection (R2 resection). Patients with gross residual disease receive 50 Gy in 20 fractions or its equivalent. The dose may be reduced to 40 Gy in 15 fractions or its equivalent in the presence of microscopic residual disease. If the decision is made to treat a large volume, including the cervical nodes for instance, or if there is extracapsular extension and local invasion of cervical nodes, fractionation is changed to 2 Gy fractions.

Locoregional relapse-Locoregional Relapse IS treated in the same way as locally advanced primary disease. The main treatment modality should be surgery, if possible, followed by ¹³¹I therapy and TSH suppression. Relapses tend to be in the cervical lymph nodes (regional relapse) rather than in the thyroid bed (local recurrence). Patients with nodal recurrence

should have a neck dissection followed by ¹³¹I, with a high expectation of tumour control. However, if the tumour burden is low (i.e. nodes ! 2 cm) then radioactive iodine without surgery may be adequate. If there is extracapsular lymph-node involvement with infiltration of the soft tissues of the neck or persistent or recurrent nodal disease despite full neck dissection and ¹³¹I, then additional EBRT may be given to maximise the chance of local control. Locally recurrent disease in the thyroid bed is usually more ominous than lymph-node recurrence. This generally occurs in older Patients with T4 lesions at initial diagnosis. The probability of the disease at this point concentrating radioiodine may be lower than with cervical nodal recurrence. Despite this, the management at the time of recurrence remains the same: a combination of surgical resection, if possible, followed by routine postoperative ¹³¹I and consideration of EBRT.

Distant metastatic disease-The mainstay of therapy for metastatic disease is radioiodine, but this will only be effective if a total or near total thyroidectomy has been carried out. Failure to achieve a complete remission from metastatic disease is predicted by the following factors: failure to concentrate ¹³¹I, age above 40 years and the presence of bone metastases.⁵ People with bone metastases in general do not respond well to ¹³¹I⁵ and therefore, surgical

resection of a solitary lesion may be appropriate. In patients with a solitary metastasis in whom a prolonged survival is expected and surgical excision is not possible, a high dose of EBRT may be given to maximise the duration of local control. Even patients who present with distant metastatic disease may have a prolonged survival.

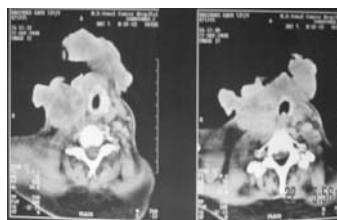
When every thing fails....then what?-Little effective therapy is available for patients who have not responded to the above treatments. Single-agent doxorubicin, with a response rate of 25–40%, is the most effective chemotherapeutic agent.⁶ There is little evidence to suggest that combination chemotherapy is more effective. In a small randomised study (84 evaluable patients), which included all thyroid cancer histologies, no difference was observed in overall response rate when doxorubicin was compared with doxorubicin and cisplatin⁷, although the complete remission rate was higher with the combination. For patients unresponsive to radioiodine, re-differentiation of their tumours with retinoid therapy or combination chemotherapy has been reported to increase uptake of ¹³¹I, but the therapeutic results have been disappointing, as have those reports on the use of lithium carbonate to increase uptake of ¹³¹I. The finding of an elevated thyroglobulin level with a negative radioiodine scan presents a difficult clinical situation. This can represent de-

differentiation of the tumour, with reduction or loss of its ability to accumulate iodine. Therefore, detection of residual tumour foci is important to allow for further surgical resection or external beam radiotherapy if appropriate. Further investigation with imaging modalities, such as ultrasound, computed tomography or magnetic resonance imaging, may be helpful but can be difficult to interpret on the background of post-surgical changes. The use of dynamic imaging for this scenario is under investigation. Use of 2-[18F]fluoro-2-deoxy-D-glucose positron emission tomography has demonstrated a sensitivity of 70–90% in identifying the source of elevated thyroglobulin, increasing sensitivity correlated with thyroglobulin levels. The diagnostic value of somatostatin receptor scintigraphy with 111Indiumoctreotide has also been evaluated. Further investigation and refinement of these non-invasive functional techniques will hopefully allow increased ability to identify residual tumour that may be amenable to surgical resection.

Medullary thyroid cancer-Nodal involvement in the neck and superior mediastinum is relatively common at presentation (about 50%), and there may be infiltrative local disease into the soft tissues of the neck. Extensive locoregional disease is not always completely resectable, resulting in postoperative microscopic or macroscopic disease. In some cases, after what was thought to be complete surgical resection and lymph-node dissection, there may be residual disease shown

only by high serum calcitonin and carcinoembryonic antigen levels.

Treatment of advanced medullary thyroid cancer-locoregional disease-The standard management is surgery, comprising a total thyroidectomy and central node dissection if the lymph nodes are thought to be involved. In addition, selective lymph-node dissection might be required if further lymph nodes are thought to be involved. Radioactive iodine has no role in the management of medullary thyroid cancer; however, after surgery for high-risk disease (gross or microscopic residual disease, or extensive regional lymphnode involvement), adjuvant EBRT to the thyroid bed and regional nodal tissue may be considered, in the absence of known distant metastatic disease, to try to reduce the local recurrence rate. Without further treatment, about half of these high-risk patients will experience recurrences in the neck.



Patient of locally recurrent medullary carcinoma

Radiation doses of 40 Gy in 2 Gy fractions to the neck and upper mediastinum, followed by a 10 Gy boost to the thyroid bed, have been associated with a locoregional control rate of 86% at 10 years. Adjuvant EBRT does not affect overall survival, but locoregional control is important because cervical relapse can have a deleterious effect on the patient's quality of life. For patients with high-risk disease, extrathyroid extension or multiple-nodal involvement, with hypercalcitoninemia and no evidence of metastatic disease, radiation should be considered to improve local relapse free rate. For patients with gross residual disease after surgery, the local control rate after EBRT is as low as 20% ; therefore, every attempt should be made to completely extirpate disease surgically. When this is not possible, external radiation may result in long-term local control in a few patients. There is no role for adjuvant chemotherapy.

Distant metastatic disease-The most frequent sites of metastatic disease are liver, lung and bone. Treatment intent is palliative and includes supportive measures, analgesic drugs and consideration of the potential benefits of chemotherapy, hormonal therapy and local radiation. Chemotherapy is documented to have a response rate of 15–30%. Regimens may include doxorubicin, either as single agent or with cisplatin⁵, 5-fluorouracil containing combinations and others. Hormonal therapy consists of Somatostatin analogues (e.g. octreotide), which have been reported to lessen

symptoms, reduce calcitonin levels, but generally do not induce tumour shrinkage. A higher response rate has been reported with a combination of octreotide and interferon alpha. Local radiation can be used for symptomatic bone metastases. Experimental therapies with targeted radiation and monoclonal antibodies conjugated to radionucleotides (e.g. anti-carcinoembryonic antigen, or ¹¹¹Indium-octreotide, ¹³¹I-MIBG) are being studied⁸ as are gene therapeutic approaches.

Anaplastic thyroid cancer (ATC)-It is more common in females with a peak incidence- 6th to 7th decade. The mean age of diagnosis is 55 – 65 yrs. One should suspect ATC if there is rapid growth, hard and fixed masses, vocal cord paralysis, neck nodes and compromised airway. All patients with anaplastic thyroid cancer (ATC) are considered to have advanced cancer (6th edition UICC T4a or T4b disease), because the prognosis is invariably poor. Some ATC have been found to co-exist with areas of differentiated thyroid carcinoma in the gland, suggesting that the anaplastic component arose from pre-existing differentiated disease (de-differentiation).⁹ The prognosis of patients with any element of anaplasia within a differentiated thyroid cancer was no different from patients with anaplastic tumour throughout, with a 1-year survival of 10%. Airway management is very important and one should secure airway by fiber optic intubations, tracheostomy or cricothyroidotomy. Tracheostomy is not to be done prophylactically

Treatment of Anaplastic Thyroid Cancer- Locoregional Disease-Complete surgical resection gives the best chance of cure; however, this is only possible in a few patients.¹⁰ Those most amenable to this approach are patients with predominantly differentiated thyroid carcinoma and only a small focus of ATC, in whom the surgery can be carried out without undue morbidity. Radical surgery is not warranted in patients with more extensive invasion of adjacent structures, as it has a significantly negative effect on quality of life and no survival benefit. Unfortunately, most patients with ATC are unresectable at the time of diagnosis. A surgical biopsy may be necessary to confirm the diagnosis, and a tracheostomy can alleviate critical upper airway obstruction. ATC does not concentrate ¹³¹I, and so radiotherapy is the mainstay treatment for local control and palliation of symptoms to try to maintain quality of life. The ineffectiveness of radiation alone in this disease has led to the development of both novel fractionation schedules and concurrent chemotherapy regimens. Because anaplastic thyroid cancer grows quickly, hyperfractionated and accelerated radiation have been used, sometimes in combination with chemotherapy and surgical resection. The most successful regimen in obtaining local control is that described by the Swedish group,^{11,12} which involves combined preoperative hyperfractionated radiation and chemotherapy followed by surgical resection. After Resection, further radiation and chemotherapy are given. Other

approaches to intensify radiotherapy have met with limited success owing to increased morbidity of normal tissues. Invariably, the median survival is between 3 and 6 months.



Patient of anaplastic carcinoma

Patients with good performance status with no evidence of distant metastatic disease may benefit from an aggressive approach with high-dose radiotherapy with or without concurrent chemotherapy or altered fractionation, such as accelerated hyperfractionated radiotherapy, otherwise a palliative approach is warranted. Even if local control is achieved with EBRT, death still occurs from distant metastatic disease. Chemotherapy for metastatic disease has not been effective. The expected 5-year survival is about 5% with any of the currently available treatment approaches. Although doxorubicin and cisplatin have been

the most common drugs used, there have been recent reports of activity of other drugs. Ain et al.¹³ reported a response rate of 53% to paclitaxel; however, there remains little evidence that anaplastic carcinoma of the thyroid is chemosensitive.

Distant metastatic disease-The main goal of treatment is to palliate symptoms, with the expectation of a short survival. Chemotherapy is frequently ineffective, and local radiation may be used for pain control. Anaplastic thyroid cancer remains an extremely lethal disease, and innovative approaches are needed, as presently available therapies are seldom effective.

Surgical complications in Locally Advanced Thyroid Cancer-The various complications of thyroid surgery are Hemorrhage, Airway obstruction, Pneumothorax, Hypocalcemia, Chyle leak, Hypothyroidism, Injuries to the superior laryngeal nerve or recurrent laryngeal nerve. These complications should be avoided as far as possible with precise surgical techniques and if they happen, should be managed accordingly. **Conclusion-**Most patients with thyroid cancer have an excellent prognosis; however, as we have discussed within this review, there are a small but significant number with advanced disease in whom prognosis may be very poor. Radiotherapy continues to have a role in the improvement of local control and palliation. There are, however, no effective chemotherapeutic agents for any of the histologies of advanced thyroid cancer; therefore, the development of novel therapies, such as biological modifiers or

new chemotherapy agents, are needed. These patients could be incorporated into phase I and II studies.

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Hepatitis B is a major public health hazard caused by hepatitis B virus. Blood is the main source of infection, therefore sexual contact and blood transfusion are common mode of spread. Disease can be transmitted by transplacental route from infected mother to newborn. Apart from these, parenteral drug abuse, tattooing and acupuncture can also spread this disease if inadequately sterilised needles are used. Mode of transmission of HB is very much similar to HIV, but it is several time more infectious than AIDS. Unlike HIV it can be prevented by proper immunization. Persistence of disease after six months can developed chronic form of hepatitis i.e chronic HB that further progress into cirrhosis and liver cancer with poor outcome. Now a day's, number of antiviral drugs are available as anti-hepatitis agents. Although treatment is suppressive rather than curative, the high prevalence of this infection worldwide with their concomitant morbidity and mortality reflect a critical need for improved therapeutics.

Virus-Hepatitis B is caused by Hepatitis-B virus belongs to family hepadnaviridae. HBV is complex double layered sphere. Outer surface or envelope contain surface antigen (HBsAg) and inner dense core contain core antigen (HBcAg) with

nucleocapsid (HBeAg). A single circular double stranded DNA with DNA dependent polymerase is present inside the core. Person suffering from acute hepatitis are highly infectious for at least as long the HBsAg is in the blood. Chronic HB by definition is persistence of HBsAg in serum for more than six months. Individual with chronic HB may carry virus for life, these carrier are at high risk of cirrhosis and hepatocellular carcinoma.

Hepatitis B Vaccination- Immunization with Hepatitis B vaccine is most cost effective preventive measure. Infection with HBV may occur perinatally (vertical transmission) and during early childhood from child to child (horizontal spread). Younger the age of acquisition of HBV infection higher the chances of becoming a chronic carrier. As HBV infection is one of the most important cause of chronic hepatitis, cirrhosis and hepatocellular carcinoma, these are all preventable by early childhood immunization. It is for this reason that World Health Organisation (WHO) has recommended universal Hepatitis B vaccination. HB vaccine is highly purified recombinant DNA vaccine. The usual paediatric dose in less than 12 years of age is 0.5 ml corresponding to 10 microgram of antigenic component. Route

of administration is intramuscular at anterolateral aspect of thigh. Adult dose is twice the paediatrics dose. The vaccine is highly immunogenic and seroconversion rate are greater than 95% after a three dose schedule-

- Birth, 1 and 6 months.
- Birth, 6 and 14 weeks.
- 6, 10 and 14 weeks.

(In practice, one can still use, 0, 6 week and 6 months schedule.) If mother is HBsAg positive, the baby should be given HB immunoglobulin (HBIG) within 24 hours along with HB vaccine using two separate syringe and site for injection (3 dose schedule). If HBIG not available or unaffordable than HB vaccine may be given at 0, 1 and 2 months with additional dose between 9-12 months (4 dose schedule).

Anti-Hepatitis B Drugs- To date, three anti-viral drugs are approved for treatment of chronic HB infection- Adefovir, Lamivudine, Interferon. Adefovir and lamivudine are given orally therefore patient compliance is good. Interferon is injected by parenteral route and costly at present. In addition to three approved anti-viral, several other are being evaluated in clinical trial. Overall outcome depends on age of patient, liver status as well as duration of therapy.

Pharmacological Aspect of Anti-Hepatitis B Drugs- The aims of anti-viral therapy are to

control infectivity, eradicate the virus and prevent the development of cirrhosis. As adefovir, lamivudine and interferon are currently use anti-hepatitis B agents, their pharmacological aspects are briefly discussed under following heads-structure, pharmacokinetic, mechanism of action, adverse effects, preparation, dose and indication.

Adefovir-The unique feature of adefovir is the near absence of resistance. Adefovir dipivoxil is a diester prodrug of adefovir. It is an acyclic phosphonate nucleotide analog of adenosine monophosphate. Adefovir as enters inside cells is phosphorylated by kinases into the active metabolite diphosphate, which act as a competitive inhibitor of viral DNA polymerase and reverse transcriptase with respect to deoxy-adenosine triphosphate and also serve as chain terminator of viral DNA synthesis. Its selectivity relates to a higher affinity for HBV-DNA polymerase compared with cellular polymerases. The parent compound has low oral bioavailability whereas prodrug is absorbed rapidly and hydrolyzed by esterases in the intestine and blood to adefovir with liberation of pivalic acid. Food does not affect absorption. Adefovir has low protein binding capacity and circulated mostly in free form. Pivalic acid is product of metabolism. Adefovir is eliminated unchanged by renal excretion. Adefovir is available for oral therapy. Half life is prolonged and ranging from five to eighteen hours so once-daily

dosing is feasible. Recommended dose is 10 mg per day. Adefovir therapy can result headache, asthenia and abdominal discomfort in usual dose. It can also result dose related tubular dysfunction in few subjects manifested as azotemia, Hypophosphatemia, glycosuria and proteinuria. Adefovir is genotoxic therefore high dosage can cause nephrotoxicity and hepatotoxicity. No clinically important drug interaction have been recognized. An increased risk of lactic acidosis and steatosis may exist when adefovir is used in conjunction with nucleoside analogues or other anti retroviral agents. Adefovir is approved for treatment of chronic hepatitis B. Its therapy result in over one hundred fold reduced serum HBV-DNA level, improved hepatic histology and normalization of aminotransferase levels by 48 weeks. Continued therapy is associated with increasing frequencies of HBeAg seroconversion. Regression of cirrhosis may occur in some patient.

Lamivudine-Lamivudine is a anti-retroviral of nucleoside reverse transcriptase inhibitor group. Chemically, lamivudine is a cytidine analog presented by 2-3 di-deoxy 3-thiacytidine. Lamivudine inhibit both HBV-DNA polymerase as well as HIV reverse transcriptase. Cellular enzymes convert lamivudine to triphosphate and cause chain termination. Lamivudine triphosphate is potent inhibitor of DNA polymerase of HBV. Following oral administration, lamivudine is absorbed rapidly with a bioavailability of about

80%. It is distributed widely in a volume comparable with total body water. The plasma half life of elimination is about nine hour and approximately 70% of the dose is excreted unchanged in the urine. Lamivudine is formulated for oral therapy. Usual adult dose is 100 mg daily and in children it is given as 3 mg per kilogram. Lamivudine is generally well tolerated at recommended dose. Its administration can result headache, malaise, fatigue and GI disturbance. Rarely it can cause lactic acidosis and hepatotoxicity. Dose reduction is indicated in renal insufficiency. Lamivudine can be used safely in patient with decompensated liver disorder. Overall, it has excellent safety profile as anti hepatitis dose. Lamivudine is approved for the treatment of chronic hepatitis B in children and adult. In children aged two to seventeen years, lamivudine in dose of 3 mg per kg per day for one year duration is associated with normalization of aminotransferase level in about half and seroconversion to Anti HBe in about one-fifth of cases. Adult dose of 100 mg per day for one year cause suppression of HBV-DNA level, normalization of aminotransferase level and reduction in hepatic inflammation in over half of patients. HBV-DNA level decrease approximately 98% after one year. Seroconversion of HBeAg from positive to negative occur in about 20% of patients. Such therapy is also associated with an halving of the risk of clinical progression and development of hepatocellular carcinoma in those with advanced fibrosis or cirrhosis.

Administration of lamivudine before and after liver transplantation may suppress recurrent HBV infection.

Interferon- Interferons are endogenous cytokines that possess complex antiviral, antiproliferative and immunomodulating activities. These proteins are synthesized by host cells in response to various inducers and in turn cause biochemical changes leading to a potent antiviral state in cells. Three major classes of human interferons are recognized alpha, beta and gamma. Pegylated alpha interferon is under clinical trial. Each of these can be produced by recombinant DNA technology. Interferon alpha consists of 166 amino acids. Interferon alpha is not a single substance but a family of approximately 20 proteins with similar activities. Interferon alpha is used in treatment of chronic HB infection. Interferon appears to function by binding to specific membrane receptors on the cell surface and initiating a series of intracellular events that include enzyme induction, suppression of cell proliferation, immunomodulating activities and inhibition of viral replication. Interferon is not absorbed orally. Absorption is about 80% after parenteral administration. Maximum concentration occurs approximately four hours after intramuscular and seven hours after subcutaneous administration. It induces long-lasting cellular effects. Elimination time is two to five hours depending upon route of administration. Interferon injection is associated with acute influenza like

syndrome manifested as fever, chills, headache, nausea, vomiting, diarrhea, myalgia and arthralgia, but tolerance develops gradually in most patients. Alopecia, pneumonia, interstitial nephritis and hepatic toxicity are also reported. Elevation of hepatic enzymes and triglycerides may occur. All adverse effects are reversible upon dose lowering or cessation of therapy. The principal dose-limiting toxicities are myelosuppression with granulocytopenia and thrombocytopenia. Some of the rare reported manifestations are autoimmune disorder, neurotoxicity and cardiovascular effects such as hypotension and tachycardia. Interferon reduces the metabolism of various drugs by hepatic cytochrome and significantly increases the level of drug such as theophylline. It can increase the cardiotoxicity, neurotoxicity and hematologic toxicity of other drugs. It is abortifacient and should not be administered in pregnancy. Interferon alpha is available for parenteral therapy. It is given preferably by SC or IM injection. Usual dose is 5 million units daily or 10 million units three times weekly. Interferon administration is associated with loss of HBeAg, loss of HBeAg and development of anti-HBe antibody. It leads to normalization of serum aminotransferase and sustained histologic improvement thus reducing risk of progressive liver disease.

Newer Anti Hepatitis-B agents- In addition to three approved anti-hepatitis B agents some of the other antiviral agents like reverse transcriptase

inhibitors (RTI) are being evaluated in clinical development. Based upon their structure, RTIs are both nucleoside and nucleotide inhibitors.

- Nucleoside RTI-Entecavir, Clevudine, Emtricitabine, Telbivudine

- Nucleotide RTI-Tenofovir

These nucleoside and nucleotide agents are reverse transcriptase as well as DNA polymerase inhibitors. Route of administration of these drugs is oral.

Special situation- Lamivudine monotherapy after long term can result universally in the rapid emergence of YMDD variants in persons with HIV infection. It is methionine to valine or methionine to isoleucine mutation in YMDD (tyrosine-methionine-aspartate-aspartate) motif of HBV-DNA polymerase analog to mutation that occurs in patients with HIV infection treated with lamivudine. Therefore, patients with chronic HB should be tested for anti-HIV prior to therapy. Lamivudine monotherapy is contraindicated and these patients should be treated with triple drug antiretroviral including lamivudine 300 mg daily (usual dose is 100 mg). Adefovir is effective against lamivudine-associated YMDD variant HBV and can be used when such lamivudine-induced variants emerge. Its major advantage is the near absence of resistance. Interferon requires relatively brief duration therapy but repeated injections and cost is associated with intolerance. Although children can respond as well as adults, interferon therapy has not been effective in very

young children infected at birth. Similarly interferon therapy has not been effective in immunosuppressed person. Improved long term and complication free survival as well as reduction in the frequency of hepatocellular carcinoma have been documented among responder supporting the conclusion that successful interferon therapy improve the natural history of chronic HB. Relapse after successful therapy is rare.

Either lamivudine or adefovir is recommended for interferon refractory patients, where as patient with decompensated chronic HB are not candidate for interferon therapy, they may respond to lamivudine or adefovir with reversal of the sign of decompensation.

Conclusion-Chronic hepatitis-B is common liver disorder that can lead to cirrhosis and hepatocellular carcinoma. Immunization is the only cost effective measure till date. Management of chronic HB is directed at suppressing the level of viral replication. Now a days, three antiviral agents- adefovir, lamivudine and interferon are use as first line therapy. Each drug has own advantages and disadvantages. Lamivudine require long term therapy but foster the emergence of viral variant. Adefovir can be used when lamivudine variant emerge and also in interferon non responder. Interferon require relatively short duration therapy with rare chances of relapse, but only limitation is repeated parenteral administration and cost. Apart from these approved antiviral, some of the newer agents are under clinical development.

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History of cancer chemotherapy

The beginnings of the modern era of cancer chemotherapy can be traced directly to the discovery of nitrogen mustard,

a chemical warfare agent, as an effective treatment for cancer. Two pharmacologists, Louis S. Goodman and Alfred Gilman were recruited by the United States Department of Defense to investigate potential therapeutic applications of chemical warfare agents. Autopsy observations of people exposed to mustard gas had revealed profound lymphoid and myeloid suppression. Goodman and Gilman reasoned that this agent could be used to treat lymphoma, since lymphoma is a tumor of lymphoid cells. They first set up an animal model - they established lymphomas in mice and demonstrated they could treat them with mustard agents. Next, in collaboration with a thoracic surgeon, Gustav Linskog, they injected a related agent, mustine (the prototype nitrogen mustard anticancer chemotherapeutic), into a patient with non-Hodgkin's lymphoma. They observed a dramatic reduction in the patient's tumour masses. Although this effect lasted only a few weeks, this was the first step to the realization that cancer could be treated by pharmacological agents (Goodman et al 1946).The antifolates- Shortly after World War II, a second approach to drug therapy of cancer began. Sidney Farber, a pathologist at Harvard Medical School, studied the effects of folic acid on leukemia patients. Folic acid (citrovorum factor), a vitamin crucial for DNA metabolism (he did not know the significance of DNA had been discovered by Lucy Wills, when she was working in India, in 1937.

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Disasters have existed ever since the existence of mankind and no community is immune to the emergencies caused by disasters. The disaster affects not only health & well being of the community but also large number of people are displaced, killed, injured and/or subjected to a greater risk of epidemics.¹ Major emergencies, disasters and other crises are social, economic and political events.

Magnitude of the problem- In the past decade the total number of catastrophic events has almost doubled, showing a trend line from approximately 450 to 800 major emergencies per year. The increase is most marked in middle and low income countries, where emergency preparedness is often insufficient. Because of improved response and rescue in many countries, fewer people are dying from catastrophic events, but the number of people affected by them is still increasing, with important long-term implications. An estimated 157,000,000 people were directly affected by natural disasters alone in 2005.² India has been traditionally vulnerable to natural disasters on account of its unique geo-climatic conditions. Floods, droughts, cyclones, earthquakes and landslides have been recurrent phenomena. About

60% of the landmass is prone to earthquakes of various intensities; over 40 million hectares is prone to floods; about 8% of the total area is prone to cyclones and 68% of the area is susceptible to drought. In the decade 1990-2000, an average of about 4344 people lost their lives and about 30 million people were affected by disasters every year. The super cyclone in Orissa in October, 1999 and the Bhuj earthquake in Gujarat in January, 2001 underscored the need to adopt a multi dimensional endeavor involving diverse scientific, engineering, financial and social processes; the need to adopt multi disciplinary and multisectoral approach and incorporation of risk reduction in the developmental plans and strategies.³

Definition- Commonly used definition that are used to describe disaster are

- A serious disruption of the functioning of a community or a society causing widespread human, material, economic or environmental losses that exceed the ability of the affected community or society to cope using its own resources. A disaster is a function of the risk process. It results from the combination of hazards, conditions of vulnerability

and insufficient capacity or measures to reduce the potential negative consequences of risk.⁴

- Any occurrence that causes damage, ecological disruption, loss of human life or deterioration of health and health services on a scale sufficient to warrant an extraordinary response from outside the affected community or area.⁵

Types of disaster⁶ Disaster may be classified into two groups, 'natural' and 'man-made' and again sometime be sub-divided into those of 'slow' and 'sudden' onset. To illustrate, certain disasters caused by "fires" may be both 'natural' and/or 'man-made' according to the circumstances.

Natural Disaster

- Natural phenomenon beneath earth's surface: Earthquake, volcanic eruption
- Natural phenomenon at earth's surface: Landslide, avalanches
- Meteorological/hydrological phenomenon: windstorms [cyclone, typhoon, hurricane]; Tornadoes; Hailstorms & Snowstorms; Seasurges; Floods; Droughts
- Biological phenomenon: Locust swarms; Epidemics of diseases

Man-made Disasters

- Caused by warfare/terrorist activities: Conventional warfare; Nuclear, Biological, Physical and Chemical warfare
- Caused by accidents: vehicular [plane, ship, train, car etc.]; Drowning; Collapse of building; Explosions; Fires; Biological; Chemical including poisoning

The general belief that disaster causes only surgical problem is not true. The example of chemical poisoning due to leakage of MIC in Bhopal and subsequent epidemics of diseases are both medical and public health problems.

Disaster Process ⁷-Disaster situation has been conceptualized as a process with different phases. In each different phase, the information, the problem encountered, the action required, and the people involved may be quite different. The interrelationship of different phases [warning, threat, and

impact] and activities [assessment, rescue, immediate action, initial recovery and rehabilitation] are important for its management. The disaster and its management have been considered as a continuum of inter-linked activities in which the cyclical nature of various stages of disaster management [prevention, mitigation, preparedness, response and recovery] has been conceptualized as a disaster cycle.

Special characteristics-Disasters are considered a phenomenon in themselves with some common characteristics. One such characteristic is the geographical distribution of disaster that has been divided into three main 'area':

- **Impact area**- Area in which the impact of disaster is seen to its full capacity for destruction. The area will vary with the type of disaster like in aircraft or train accident the area will be relatively small. But in floods,

dam burst, typhoons and storms, the area will be very large.

- **Filter area**- it is virtually the undamaged zone from which the reserves enter the area and through which evacuees and rescue workers must pass. Serious traffic confusion often occurs in this area.
- **Community aid area**- the area outside the filter area from where the community, institutions and organized teams operate for performing the rescue and rehabilitation roles.

Short-term effects of major natural disaster⁸-After a major disaster initially the only behaviour exhibited is either generalized panic or stunned waiting. Spontaneous yet highly organized individual actions occur as survivors rapidly recover from their initial shock which may be just minutes after an earthquake.

The short-term effects of major natural disaster are:

Effects	Earthquake	High winds without floods	Tidal wind with flash floods	Floods
Deaths	Many	Few	Many	Few
Severe injuries requiring extensive care	Overwhelming	Moderate	Few	Few
Food scarcity	Rare	Rare	Common	Common
Population displacement	Rare	Rare	Common	Common
Increased communicable diseases	Potential risk following all major disaster [probability rises with overcrowding and deteriorating sanitation]			

Principles of Disaster Planning ⁹- Disaster management means a planned and systematic approach towards understanding and solving problems in the wake of disasters. The effects of disaster could be minimized, if there is pre-disaster preparedness and properly drawn up disaster plans. The disaster management plan may be applicable at the national, state or district level and/or at the level of an organization/institution say hospital.

General principles of disaster planning

- It should be a continuous process
- Analyze the risk and hazards in the geographic location concerned
- Carry out vulnerability analysis of the community exposed to the risk and hazard
- Assess the resources available and determine response capabilities
- Plan must evoke appropriate response
- Plan should serve as an educational activity
- Planning should adjust to people rather than expecting people to change their behaviour in order to conform with the planning
- Plan must be realistic and adaptable
- Plan must use existing structure rather create new ones
- Plans must be clearly written at each level and should be

harmonized with those of the level above.

There can be no tailor made plan for all situations but as most elements of response are common to all disasters, a general preparedness plan will help in a more rational response in various emergency situations.

Government of India approach in management of disasters^{3,10} -States are primarily responsible for handling disasters and Government of India provides assistance depending upon the magnitude and scale of disaster. Government of India provides 75% of Calamity Relief Fund [CRF] as a corpus money that is available at state level and used for provision of immediate relief, restoration of essential infrastructure for the provision of immediate relief & restoration of public assets in the social sector. On the similar ground, National Calamity Contingency Fund [NCCF] has been constituted at the Central level which provides additional resources in case the magnitude of disaster is of disproportionate scale. The Government of India approach has been translated into a National Disaster Framework [a roadmap] covering institutional mechanisms, disaster prevention strategy, early warning system, disaster mitigation, preparedness & response, partnership with voluntary sector, monitoring & impact assessment of natural disaster, establishment of disaster knowledge management, disaster warning system, and human resource development. The expected inputs, areas of

intervention and agencies to be involved at the National, State and district levels have been identified and listed in the roadmap. The roadmap has been shared with all the State Governments and Union Territory Administrations. Ministries and Departments of Government of India, and the State Governments/UT Administrations have been advised to develop their respective roadmaps taking the national roadmap as a broad guideline.

The framework is being put into effect through

- Institutional changes
- Enunciation of policy
- legal and techno-legal framework
- Mainstreaming mitigation into developmental process
- funding mechanism
- Specific schemes addressing mitigation
- Preparedness measure
- Capacity building
- Human resource development
- Community participation

Nodal ministry at Government of India level for management of disaster ¹¹

Every ministry/department provide their share of support and assistance in wake of occurrence of disaster, however, for efficient management, nodal ministries have been identified for better coordination of various activities. These are as follows:

Disasters	Nodal ministry/Department
Earthquakes and Tsunami	MHA/Earth Sciences/IMD
Floods	-do-
Cyclone	-do-
Drought	Ministry of Agriculture
Biological disasters	Ministry of Health and Family Welfare
Chemical disasters	Ministry of Environment and Forests
Nuclear disasters	Ministry of Atomic Energy
Air accidents	Ministry of Civil Aviation
Railway accidents	Ministry of Railways

In the Ministry of Health & Family Welfare, Emergency Medical Relief [EMR] Division is the technical unit exclusively meant for management of crisis situations. The division is headed by Director, Emergency Medical Services and Relief. For the purpose of crisis situations, he reports/receives instructions directly from the technical chief (Director General of Health Services) and Administrative Head (Secretary Health & FW). The Director, EMR coordinates with other health sector partners like director of Health Services of the state governments, medical store divisions under central government, vaccine producing institutes, central government hospitals and national institute of communicable diseases and director, malaria unit. The objective of the coordination is to review crisis situations from time to time and meet those needs, which State Governments cannot meet.¹²

Management of disaster from the perspective of a Hospital -The disaster planning should aim at preparing a written hospital disaster manual. The

hospital disaster manual is written statement of disaster plan, which is activated during disaster. It can be divided into following six sections: Introduction; Distribution of responsibilities with authority; Disaster containment; Chronological action plan: initial alert, activate hospital action plan, formulation of command nucleus, management of casualties, and hospital management; [5] Checklist of personnel and items; Rehearsal and conclusion.

Managerial issues in disaster management ^{6, 13, 14}

These issues could be clinical or administrative:

Clinical issues: After a massive disaster the quantity and severity of injuries will overwhelm the handling capacity of health facilities. Triage is the only approach that can provide maximum benefit to the greatest number of injured in a disaster situation. It is a means of rapidly classifying the injured on the basis of the severity of their injuries and the likelihood of their survival with prompt medical intervention. Higher

priority is granted to victims whose immediate or long-term prognosis can be dramatically affected by simple intensive care.¹⁵ All Health personnel should be able to reach health premises in the shortest possible time. Hospital administrator needs to ensure the continuity of logistic supply such that there is no break down of essential services.

Administrative issues: For proper execution of disaster management, a disaster management team should be formed under the chairmanship of disaster control officer who should be a senior hospital administrator. Administrative issues involved are:

- **Documentation:** Proper documentation on previously structured forms should be done to save time. The unconscious patients and those dead on arrival may pose some problems but M.L.C papers should also be prepared for these patients. The list may be computerized and one may be kept with medical records, second with

casualty, third with PRO and one may be sent to police/district collection for revenue records in case the question of compensation arises in future.

- **Police documentation**
- **Communication and coordination:** Central command nucleus should be made functional round the clock and all messages to be written down in a log book in details for follow up. All issues raised that need attention should be brought to notice of nodal persons for coordination with all stakeholders.
- **Friends and relatives:** The anxious, excited friends and relatives want to know the welfare of their kith and kin and hospital authorities should calm them down, console and give them all possible details from time to time from information booth.
- **Crowd control:** Large crowds of curious people gather in hospital premises and even in reception and treatment areas. They should be controlled, evacuated and only person with authorized passes be allowed to enter hospital. There should be one entry guarded by the police.
- **Involvement of voluntary workers:** The requirement of voluntary workers and their disposition should be decided by the hospital

administrator and if these are not required, they may be politely told that they will be called when required by the hospital. No organization should be shown favour as others will be hurt. Their contact numbers and names of contact person should be kept on record.

- **Blood donation:** There is usually over response to disaster and lots of people rush to donate blood. Blood donation camps can be arranged as & when blood is required and should have low priority in other disasters except where surgical injuries are more and blood is necessary.
- **Donation of foods, clothes, drugs etc:** Similarly response of food material should be regularized and controlled as many times the food go waste. The medicine samples of various kinds and drugs, which are not wanted, are also donated in assorted quantities. This creates problems in inventory, storage, utilization as well as quality control. It has been observed that sub-standard drug or even near expiry drugs have been donated. A buffer stock of all medical and surgical items should be readily available in the emergency department and replenished every day.
- **Patient's property:** the normal procedure of listing every single item of patient's

property is not practicable in disaster. The property of each admitted patient with identification tags should be kept in a large polythene bag. It can be later sorted and listed in the wards ensuring that valuables and cash are not pilfered.

- **Press and broadcasting:** There should be only one person to give press release in hospital. People should be discouraged to give interviews and their personal opinions, as it can create confusion and mislead the lay people and even authorities.
- **Ambulance services:** Ambulance van of hospital should be maintained in order and additional van can be requisitioned from nearby hospital and social organization. These are to be kept under control of one person stationed in control room who would only authorize their trips.
- **Emergency lights :** arrangement for additional lights in triage area, treatment areas and maintenance of continuous supply to x-ray department, OT and blood bank should be ensured. Generators should be installed immediately. Reception area and approach road for ambulance should be well lighted.
- **Disposal of dead:** The arrangement for prompt disposal of dead should be

made since at times the hospital mortuary may not be able to cope with the large number of dead bodies and which may pose public relations and public health problems.

- **VIP visits:** As far as possible, these should be avoided during the first few days as it interferes with hospital work and entails additional security problems.
- **Team of doctors and other professional:** The world should be passed that unless asked for or appealed such teams should not on their own rush to the site. As it hampers rescue works and may times they no work and get dissatisfied.

Disasters strike without warning and have been known to recur and thus integrated training to cope with disasters is always needed. The objectives of training should be to familiarize all staff concerned with strategy of the disaster plan and their individual roles. In the training some parts of the plans needs to be tested frequently. A disaster management drill in part may also be carried out and deficiency can be identified and solved before full-scale exercise are undertaken. It is apt to conclude that 'prevention is better than cure' especially applicable in a situation like disaster with its far-reaching consequences.

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Hospital acquired infection [HAI] or nosocomial infection is a global phenomenon with important contributor to increased morbidity and mortality. Recently, a newer term is increasingly being used i.e. Health care-associated infection [HAI]¹ instead of rather 'restricted' "hospital" acquired infection. The incidence of HAI varies not only from one hospital to another but with primary disease condition of the patients and nature of treatment. With increasing awareness regarding prevention and control of infections both in the community and hospital, the health care provider is under greater pressure than ever before to meet the demands of modern medical practice. Litigation's and consumer protection acts make practitioners accountable to patients, and any deficiency in good clinical practice renders them vulnerable.²

Definition-An infection originating in a patient while in the hospital or other health care facility in whom the infection was not present or incubating at the time of admission. It includes infection acquired in the hospital but appearing after discharge and also includes such infection amongst staff.³

Historical milestones-⁴ One of the earliest records of hospital

infections are perhaps those found in an Egyptian papyrus written around 3000 BC. Needless to say, mere absence of documentation of bacterial infection does not exclude its prevalence prior to this time.

- In the Indian context, an account of hospital infection is available in the ancient Ayurvedic literature (600 BC) Again the famous Hindu physician Charaka and surgeon Sushuruta (400 BC) have also emphasized the need for prevention of infection in clinical practice. Else where in the world, records of Herodatus on the conditions that prevailed in Greek and Roman hospitals in the period 1000 to 600 BC, and the Hippocrates treatise (400 BC) testifies existence of infection.
- For several subsequent centuries that followed it was generally believed that the disease was caused by the contagion and spread by wind & various other types of air currents. In 1856 Louis Pasteur conclusively demonstrated that bacteria were responsible for fermentation of wine, which could be prevented by gentle heating whereby the microorganisms were destroyed. He proved the

existences of such microorganism in the atmosphere in 1864.

- In 1869 Simpson provided further evidence by the survey of sequelae of amputation, which established that sepsis, gangrene and pyaemia were very much common in large urban hospitals than in rural practice.
- At about this time Lister introduced his antiseptic theory, following the extensive use of carbolic acid to pack wounds, especially of compound fractures, sterilize instruments and sutures, decontaminating his hands and as an air spray. He observed that these practices could greatly reduce the incidence of suppuration and gangrene, which quite commonly occurred otherwise.
- In 1883 Gustao Neubar introduced the use of masks and gowns in surgery, and Halsted in 1890 introduced the use of rubber gloves in surgery. Von Bergman discovered steam sterilization in 1896 and all these measures further increased the safety of surgery and contributed greatly in bringing down rates of

infection by use of aseptic and antiseptic techniques. During the period, when many fundamental discoveries in bacteriology were being made, other principles of hospital infection control were also simultaneously established.

- Flugge (1897, 1899) showed the importance of droplet and aerial spread in tuberculosis. By 1894, Hutinel and others had established basic isolation systems for diphtheria and other infectious diseases in children and fever hospitals.
- National Nosocomial Infections Surveillance (NNIS) system was developed by Centre for Disease Control [CDC] and hospitals in USA in early 1970s to monitor the incidence of healthcare-associated (nosocomial) infections (HAIs) and their associated risk factors and pathogens. It is now called as National Healthcare Safety Network [NHSN].⁵

Magnitude of problem statement-It is estimated that at any given time, more than 1.4 million people worldwide are suffering from infections acquired in hospital. In developed countries, between 5% and 10% of patients acquire one or more infections and 15%–40% of patients admitted to critical care are thought to be affected with HAI. In resource-poor settings, rates of infection can exceed 20% but available data are scanty and more research is urgently

needed to assess the burden of disease in developing and transitional countries.⁶ Prevalence survey conducted under the auspices of WHO in 55 hospitals of 14 countries representing 4 WHO Regions [Europe, Eastern Mediterranean, South-East Asia and Western Pacific] showed an average of 9% of hospital patients suffering from nosocomial infections.⁷ In a prevalence survey (1996) surgical wound infection accounted for 12.3% of all hospital-acquired infections.⁷ In United States of America (USA), one in every 136 patients becomes severely ill as a result of acquiring an infection in hospital and it is estimated that over two millions of HAI occur annually with an extra cost of 4 billion dollar and causing 80,000 deaths.⁸ In England it is estimated that there are at least 1,00,000 cases of HAI causing 5000 deaths each year with an annual extra cost estimated about 930 million pounds.⁹ Unsafe injection practices are a major source of transmission of HBV and other blood-borne pathogens (e.g. Hepatitis C virus, HIV) but also the leading cause of abscess and septicemia in many countries. WHO estimates that over 23 million infections of Hepatitis B, C and HIV occur yearly due to unsafe injection practices (reuse of syringes/needles in the absence of sterilization). In many developing countries, upto 50% of injections are administered with needles and syringes that are reused without sterilization.^{10, 11, 12} In a nation wide study carried out by

AIIMS (2002-04), it was observed that out of the total administered injections, 31.6% had potential risk of transmission of blood borne viruses like HBV, HCV and HIV.¹³

Types of HAI- The most common types of nosocomial infections that could occur in the hospital set up are - surgical wounds and other soft tissue infections; Urinary Tract Infection; Respiratory Infection; Gastroenteritis; Septicemia.

Sources of HAI-The prerequisite for an infection to occur in the hospital setting are [a] susceptible host [b] a microbe capable of producing an infection [c] an environment that is congenial for multiplication of the microbe. These factors interplay with each other resulting in HAI. The infecting organism may spontaneously invade the tissue of the patient or may be introduced by some intervention. The sources of such infections could be endogenous or exogenous.^{14, 15}

Endogenous- When the infection [microorganisms] is derived from the patient's own body, it is termed as endogenous, auto or opportunistic infection. It occurs as a consequence of debilitated condition of the patient; Extremes of age-very young and old; Compromising the persons immune system [genetically, by disease, or following immunosuppressive therapy; Breach of individual's skin/mucous membrane barrier [following severe burns, widespread dermatoses, surgical wounds, catheterization,

intubation etc.]; Following diagnostic/treatment procedure [e.g. pulmonary infection developing in a patient on respirator]

Exogenous- When the source of infection is external, it is termed as exogenous or cross-infection. This occurs as a result of Improper asepsis of environment, equipment and/or instruments; Poor sterilization/disinfection techniques; Invasive monitoring and therapeutic procedures; Transmission of infection by staff carriers; Consumption of infected food/water; An epidemic arising in the community and spreading to the hospital;

Pathogens- Many different bacteria, viruses, fungi and parasites may cause nosocomial infections. Infact any microbe may have the capacity/ability to cause an infection in the hospitalized patient. Infections by Staphylococcus aureus, Group B Streptococci, Enterobacteriaceae and Pseudomonas aeruginosa could either be acquired from other persons (exogenous source) or by self-infections (endogenous/auto-infection) whereas most infections by Group A Streptococci are from other persons. Again while most infections caused by Enterococci and other non-haemolytic streptococci, anaerobic cocci, histotoxic clostridia, Bacteroides and Acinetobacter species are self infections; infections with Clostridium tetani, Pseudomonas cepacia, Flavobacterium meningosepticum are nearly always

and infections by Pseudomonas aeruginosa and members of the Klebsiella-Enterobacter-Serratia group are often, acquired from independent environmental sources (exogenous). Patients and hospital personnel may acquire infection by HIV and Hepatitis B, C, D viruses through contact with blood positive for these viruses form patients and blood donors.¹⁶ Three of the most troublesome forms of bacteria that cause HAIs include Methicillin-resistant Staphylococcus aureus (MRSA); Vancomycin-resistant enterococci (VRE); and Clostridium difficile (C. Diff.). Candida, fungi, now ranks as the fourth most common cause of systemic nosocomial infection in the United States.¹⁷ Multi-resistant bacteria (MRB) are involved in 1/5th of nosocomial infections and the 3/4th of MRB are methicillin resistant Staphylococcus aureus and extended-spectrum-beta-lactamase-producing Enterobacteriaceae.¹⁸

Prevention of hospital/health care-associated acquired infections-Infection control is the responsibility of all health care professionals, hospital staff including managers, nurses, technician's, orderlies and also consumer of hospital services. We may be 'aware' of correct practices but it's the right attitude & mindset that makes a big difference in providing quality services. An effective infection control programme would benefit patients and ensure considerable health care

resources are made available for alternative use.^{1, 6,14,15, 19, 20}

- **Hand washing:** The greatest single factor in the spread of nosocomial infections is the failure of health care workers to wash their hands often enough. Conscientious washing of hands between patient's contacts effectively prevents most of the cross infections, which tends to occur between patients.
- **Disinfection and sterilized material:** Disinfection of the environment and provision of properly sterilized materials for all diagnostic and treatment procedures is a necessity. Sterilization of instruments and consumable is more effective when carried out in a central sterile supply department [CSSD]. Use of pre-sterilized packs, disposable and routine disinfection of wards, equipment, furniture, linen etc. is important in preventing nosocomial infection and should be easily made available at patient care areas. The use of a large number of disinfectants, especially without knowing the proper concentration and anti microbial spectrum should, however, be discouraged. In situations when the use of disinfectant is indicated, it is important to ensure that choice of disinfectant is appropriate with adequate concentration and enough contact time.

- **Aseptic technique:** Adhere strictly to aseptic techniques while performing various surgical and instrumentation procedures including injections. These include a strict “no touch” technique while changing surgical dressing, insertion or removal of a drain, catheterization, etc; use of adequately sterilized packs; periodical removal and re-insertion of sterilized catheters drains, etc; proper handling of catheter and suction tubing’s and related equipments.
- **Segregate contaminated instruments:** keep them aside for disinfection, cleaning, repackaging and re-sterilization. Infected material should be discarded and soiled infected linen should be sluiced, washed separately using steam and sterilized. Sputum cups to be incinerated; bedpans and urinals to be washed and disinfected between uses.
- **Segregation, isolation facilities and procedures:** must exist in all critical care areas intensive care, burns, surgical units, newborn nursery, etc. both for the patients with communicable infection [source isolation] and for those who are particularly vulnerable to infection [protective isolation].
- **Indiscriminate use of antibiotics:** should be discouraged as it leads to spread of drug resistant strains of bacteria. This could be worked out after due consultative process within the organization and then strictly implemented as per guidelines.
- **Staff precautions:** Immunize staff against Hepatitis B. Screening of staff working in dietary and canteen is essential to rule out carriers of organism causing amoebiasis, typhoid and diarrhea. Staff with overt infections should be discouraged from operating on a patient or employed in nursery.
- **Surveillance:** of nosocomial infection entails an ongoing scrutiny of hospital patients and procedures to determine the types of nosocomial infection occurring and why & how they are occurring. It requires the active follow up of specific infections in terms of morbidity and mortality in time and place, keeping track of the sources and spread of the infecting agent and study of conditions that may favor or inhibit the spread of infection in the hospital and ensuring adequate documentation. Outcome surveillance focuses on results of practices and procedures, provides a profile of endemic infection rates and pinpoint increases. Process surveillance involves on the spot checks to see whether or not these infection control policies and procedures are being carried out. Beyond taking swabs for culture on a monthly basis from the environment, equipment, instruments and consumables from critical areas of the hospital for the checking the bacterial load, type and antibiotic resistance, it is important to check the sterility of fluids prepared or used in these areas.
- **Safe management of Bio Medical Waste:** according to Bio Medical Waste [Management and Handling] Rule, 1998 which involves all persons/organization involved with generation, collection, receipt, transportation, treatment, disposal, storage or handling of bio-medical waste in any form. Guidelines for each of the above including recording, reporting, appeal and nomination of prescribed authority has been detailed.
- **Orientation and sensitization training of health personnel:** all staff needs to be regularly oriented on universal precautions, risk & magnitude of infections and its control strategies, practice and processes. Standard Operating Procedures [SOPs] should be developed for all procedures and checklists & educational material be made available at strategic locations for ready reference & reminder.
- **Patient and family involvement:** Inform and educate patients, family and visitors at each opportunity of interactions about importance of hand hygiene, safe waste management,

avoiding unnecessary injections and their role in supporting infection control activities.

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Review Article

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The Idiopathic Interstitial Pneumonia covers large number of condition that involve parenchyma of lung - Alveoli, Alveolar Epithelium, Capillaries Endothelium and space between these structures and perivascular and lymphatic tissue.¹ These lesions are classified together, as there is Clinical, Radiological, Pathological and Physiological similarities between these entities. These disorders are associated with considerable mortality and morbidity. Exact classification and diagnosis of these disorder is very much essential for proper management. Considerable overlap is seen between these disorders. Exact diagnosis often requires Clinical, Radiological and Pathological correlation.² Interstitial Lung Disease are classified broadly into two categories.¹

Where cause is known (Secondary)-Known causes of Interstitial Lung Disease include Occupation and Environmental exposure, Inhalation of organic and inorganic dust, fumes and toxic agents. Connective tissue disorders like SLE, Sarcoidosis, Langerhan's cell granulomata. Eosinophilic granuloma, Wegener's granulomatosis.³

Where the cause is unknown (Idiopathic)-Where the cause is unknown : Idiopathic Interstitial Pneumonia. (IIP) Before the

diagnosis of Idiopathic Interstitial Pneumonia is entertained, all the known causes of Interstitial Pneumonia should be excluded.² Diagnosis and classification of Idiopathic Interstitial Pneumonia is often confusing and is dependent on Clinical, Radiological and Histological features. In 2002, American Thoracic Society and European Respiration Society (ATS-ERS) standardized the classification of Idiopathic Interstitial pneumonia into seven distinct entities. This classification is now universally followed. This classification is based on Clinical, Radiological and Pathological manifestation.⁴ Accurate diagnosis is very important before initiating the appropriate line of management. With recent advances in management accurate diagnosis is very much essential and it is not a mere Academic Exercise.

Broadly Idiopathic Interstitial Pneumonia (IIP) can be classified as² -Idiopathic pulmonary Fibrosis (IPF); Idiopathic Pneumonia other than IPF-This is further categorized in 6 distinct entities with different Clinical, Radiological and Pathological findings but with considerable overlap.

Idiopathic Interstitial Pneumonia other than IPF

- Desquamative Interstitial Pneumonia. (DIP)

- Respiratory Bronchiolitis Associated Interstitial lung disease. (RB-ILD)
- Acute Interstitial Pneumonia (AIP)
- Cryptogenic Organizing pneumonia (COP – OP) - formerly called
- Bronchiolitis obliterating organizing pneumonia. (BOOP)
- Non specific Interstitial Pneumonia (NSIP).
- Lymphoid Interstitial Pneumonia. (LIP)

IIP are very rare but secondary Interstitial Pneumonia are relatively common, like Sarcoidosis, Vasculitis and connective tissue disorders. Morphological changes in both Secondary and Idiopathic Interstitial pneumonia are identical. Imaging plays a very important role in diagnosis of these conditions.³ Radiologists must be familiar with the Morphological and Clinical manifestation of these disorders. Ultimate classification and diagnosis of IIP's is based on Histological criteria and each disease entity has got specific imaging pattern and radiologist play a key role in the work up of IIP's.

Methods of Investigations

- Chest X-ray – is usually starting point of

investigation, may be normal in early diseases.(Fig-1)

- HRCT - scanning is done at 1 mm slice thickness at 10 mm intervals in deep inspiration. High spatial frequency algorithm as bone algorithm is used for reconstruction. High spatial algorithm sharpens the resolution of the linear structures with improvement in fine details even though there is increase in visible noise. Further increase in spatial resolution can be obtained by targeting reconstruction of the images, which effectively reduces the pixel size.^{5,6}

HRCT sections should be obtained in prone and supine positions. Dependent areas show increased attenuations in 35% healthy Individuals and may obscure or mimic Early Interstitial fibrosis if scans are not obtained in prone position. Asbestosis involves sub pleural and dependent portions of Lung. Early changes of Asbestosis may be obscured if scanning is done only in supine position.³HRCT should be part of general CT of Thorax with contrast, to document the mediastinal pathology. For follow up study just to document lung changes HRCT alone can be done. Contrast study can be avoided. In our centre we usually do HRCT only in supine position and repeat HRCT is done in prone position if there is suspicion of any doubtful opacity in the dependent part. Approximate lab investigations, detailed history

and physical examination is done to rule out secondary interstitial pneumonia.

Pulmonary Function tests¹ -

Most ILD produce restrictive pattern with reduced total lung capacities (TLC), Functional residual capacities and residual lung volume. Forced expiration volume on 1 sec (FEV1) and forced vital capacities (FVC) are reduced. FEV1/FVC ratio is normal or increased.¹Diffusion capacity of lung is reduced in most ILD. Diffusion capacity of lung for carbon monoxide is reduced (DLCO). Ventilation and perfusion mismatch is seen. Lung is poorly ventilated but adequately perfused.¹Arterial blood gas may be normal or show hypoxemia. Cardiac pulmonary exercise testing may reveal severe exercised induced hypoxemia. Serial assessment of resting and exercise gas exchange can be used to monitor the response to therapy in patient with IPF.¹ Fibro optic bronchoscopy with multiple transbronchial biopsy is usually necessary for initial work up. Multiple lung biopsy from multiple sites from both lobes may be necessary for final diagnosis in difficult cases.² HRCT findings usually help in choosing the appropriate site of biopsy. Radiological work up plays an important and significant part in initial work up. But final diagnosis and classification depends on Clinical, Radiological and Pathological correlation.²

Idiopathic interstitial fibrosis-

This is the most common form of Idiopathy Interstitial Pneumonia. Morphology is that

of usual interstitial pneumonia. Age incidence is 50 yrs or older. Common in male, presents with progressively worsening Dyspnoea and non productive cough. Has got very poor prognosis with a Median survival time from 2 to 4 years. IPF has got poorest prognosis compared to other forms of IIP. Do not respond to Corticosteroids. Relation with cigarette smoking is not exactly known and is currently under discussion. Steroids are contra indicated. Patient should be considered for early Lung transplantation.

Imaging

Chest X-ray – Normal in Early disease. Advanced disease show Decrease in lung volume and sub pleural reticular opacities. Opacities increase from apex to basal regions.(Fig-1)

HRCT show – sub pleural reticular opacities. Macro cystic honeycombing and traction Bronchiectasis. These lesion have got apico basal gradient i.e.lesions gradually increase from apex and are seen maximally at the base of lungs. (Fig-2 &3)Ground glass opacities are also present but are limited in extension. Typically lesions show temporal and special heterogeneity with intervening normal Lung parenchyma.If the lesion show characteristic distribution and morphology on HRCT, in appropriate clinical settings, diagnosis can be made on HRCT evidence alone without biopsy.² ATS and ERS has defined eight major and minor criteria for diagnosis of IPF without Lung biopsy. However it is necessary to obtain

Histopathological confirmation if imaging findings are atypical, like Extensive ground glass opacities, Nodules, consolidation or predominantly perivascular, peri Bronchovascular distribution.²

ATS and ERS criteria for IPF without surgical Lung biopsy²

Major Criteria

- Exclusion of other cause of ILD - toxic effect, environmental exposure and
- connective tissue diseases.
- Abnormal results of Pulmonary function tests
- Bibasilar reticular abnormalities with minimal ground glass opacity on HRCT
- No features to support alternative diagnosis in Transbronchial lung biopsy or bronchio-alveolar lavage.

Minor Criteria

- Age more than 50 years.
- Insidious onset of unexplained Dyspnoea on exertion.
- Duration of illness more than 3 months.
- Bibasilar inspiratory crackles.

Non specific interstitial pneumonia (NSIP)-NSIP is less common than UIP. Distinction from UIP is very important as NSIP responds to corticosteroids and prognosis is better than of UIP.

Typically NSIP presents a decade earlier than UIP and the symptoms are similar but milder. There is no gender predilection and cigarette smoker is not an obvious risk factor.

Before diagnosis secondary form of NSIP should be ruled out.²

Imaging

Chest X-ray – normal in early disease. Bilateral pulmonary infiltrates are seen in advanced disease. Lower lobes are frequently involved.

HRCT – shows sub pleural and symmetrical abnormalities. Obvious apico basal gradient is missing. More common manifestation is patchy ground glass opacities combined with scattered reticular, linear and micronodular opacities. (Fig-4&5)Advanced disease shows traction Bronchiectasis and consolidation. Ground glass opacity is the predominant radiological features. (Fig-3)In contrast to UIP temporal and spatial homogeneity of the lesion is seen. Advanced disease shows honeycombing, in contrast to honeycombing in UIP, these cysts are smaller and limited in extent, so called microcystic honeycombing. Above features help to differentiate NSIP from UIP, if the Radiological features are typical. However there is considerable overlap in atypical case, surgical lung biopsy is often required to differentiate between UIP and NSIP. In NSIP ground glass opacities do not usually progress to areas of Honeycombing. In UIP ground glass opacities progress to honeycombing and ultimately lead to lung fibrosis.

Cryptogenic organising pneumonia(COP) -Characteristic histological features of COP is organizing pneumonia, formerly it was referred to as

BOOP – Bronchiolitis Obliterans Organizing Pneumonia. Currently the Term BOOP has now been omitted. Mean age of presentation is 55 yrs with no specific gender predilection . Presents with cough, Dyspnoea, and fever usually over a few weeks. There is no relation with cigarette smoking, response to corticosteroids. For diagnosis of COP other causes of organized pneumonia like infection, Drug induced pneumonias and collagen vascular disorders have to be excluded. ⁽²⁾

Imaging features

Chest X-ray – Unilateral or bilateral patchy consolidation – that resemble pneumonia. Some patients present with nodular opacities. Lung volumes are preserved in most cases.

CT findings, as expected are far more extensive than plain Radiograph.

Abnormalities are seen more frequently in lower lobes, have peripheral or peri bronchial distribution. No special predilection for sub pleural region is seen. In some cases outer most sub pleural area is spared. Typical appearance is ground glass haziness or consolidation. Air bronchogram or cylindrical bronchial dilatation is seen. (Fig -6 & 7)The opacities may vary in size and distribution and have a tendency to migrate. Consolidation which increases over several weeks, despite adequate antibiotics will suggest possibilities of COP in appropriate clinical settings.² Atypical imaging features – include irregular linear opacities, solitary nodules or multiple

nodules with cavities. Diagnosis needs to be confirmed by surgical lung biopsy. Role of transbronchial lung biopsy is currently not clear and is being evaluated.

Respiratory Bronchiolitis Associated with Interstitial Lung disease (RB-ILD)-It is related to smoking and presents in younger age group (30 to 40 yrs) Men are affected twice as often as women. Response to corticosteroid and cessation of smoking. Chest x-ray is often normal. Many show bronchial wall thickening and reticular opacities. HRCT shows diffuse distribution of abnormalities. Centrilobular nodules, ground glass opacities and bronchial wall thickness. (Fig -8)In consistence with the history of smoking associated findings is Centrilobular emphysema. Changes are prominently seen in upper lobes.

Desquamative interstitial pneumonia (DIP)-It is also strongly associated with cigarette smoking and is considered as end spectrum of RB-ILD. Age of Presentation is 30 to 40 yrs, more common in male. M:F ratio 2:1. Response to corticosteroid and cessation of smoking is good. However disease can progress in some cases especially in patients who continue to smoke.

Imaging

Chest X-ray – non specific and may show hazy opacities.

HRCT – shows diffuse ground glass opacities. Distribution is peripheral and lower lobe predominance. Other findings include irregular linear opacities, small cystic spaces suggestive of fibrosis.(Fig-9) Lung biopsy

required to differentiate between RB-ILD and DIP

Lymphoid interstitial pneumonia (LIP)- Primary Idiopathic form of LIP is extremely rare. Secondary LIP is common and seen in associated with Sjogren's Syndrome and HIV infections. More common in women. Age of presentation is 5th and 6th decade. Presents with slowly progressive Dyspnoea over a period of 3 to 4 years. Response to steroid is unpredictable. LIP was considered as a pulmonary lymphoproliferative disorder in the past with subsequent progression to malignant lymphoma. However many of these case were reclassified as Lymphoma from the outset. Now it is believed that very small number of cases undergo malignant transformation.

Imaging

Chest X-ray – Nonspecific reticular, reticulonodular and alveolar opacities.

HRCT – shows bilateral diffuse abnormalities with lower lobe predominance.

Ground glass opacity is the dominant radiological presentation. Thin walled perivascular cysts are seen. Cysts in LIP are seen in lung parenchyma through out mid zone. Probably results from air trapping. Ground glass opacity with cysts is highly suggestive of LIP. (Fig -10 & 11). Centrilobular nodules and septal thickening are also seen occasionally.

Acute interstitial pneumonia (AIP) -This is the only IIP with acute onset of symptoms.

Mean age of presentation is 50 years. Presentation is acute.

Develop severe Dyspnoea and need mechanical ventilation within 3 weeks of presentation. Men and women are equally affected. No relation with cigarette smoking is documented. Corticosteroids are effective in early stages. Progress is poor with mortality more than 50%. Most patients who survive acute phase progress to lung fibrosis For definite diagnosis Histopathological investigation is necessary but most of the patient are sick and cannot tolerate surgical lung biopsy. Transbronchial biopsy is seen to be sufficient.

Imaging

X-ray and HRCT findings are similar to Acute respiratory distress syndrome.

Changes are seen bilaterally. They are symmetrical and predominantly seen in lower lobes. C P Angles are usually preserved. Ground glass opacity is the predominant CT pattern. (Fig-8) Areas of consolidation are also seen, usually limited to dependent area of lung. Radiological findings result from alveolar oedema and hyaline membrane. Early changes are seen in basal dependent region. (Fig 12) Late phase of AIP are usually seen in non dependent areas of lung. Changes are characterized by architectural distortion, traction, Bronchiectasis and Honeycombing. (Fig-13). Late changes are seen in non dependent areas, as dependent areas which predominantly show acute changes, are protected from late changes. Acute changes protect the dependent area of lung from potential damage associated with mechanical ventilation.

Conclusion-Idiopathic Interstitial Pneumonias are rare but they are prototypes of much commonly encountered Secondary Interstitial pneumonias. Though exact classification of Idiopathic Interstitial pneumonia require Clinical, Radiological and Pathological correlation. Radiology especially HRCT plays a very important role in diagnosis and classification of IIP according to ATS-ERS conscientious statement of 2002. Diagnosis of IIP requires close communication between Clinician, Radiologist and Pathologists. HRCT is indicated in all cases suspected IIP's.²Careful attention should be paid to HRCT technique. Radiologist should differentiate UIP from other form of Interstitial Pneumonia as UIP has very poor prognosis compared to other IIP's. Only patient who have typical clinical and radiological features of UIP do not require surgical lung biopsy.² All other patient need surgical lung biopsy for exact classification of IIP's. Multiple biopsies from both lobes should be taken. HRCT acts as a guiding tool to select the appropriate biopsy site. Diagnosis of NSIP should be considered provisional until further characterization of the disease entities is achieved. To some extent HRCT appearance of COP may be diagnostic in appropriate clinical settings.

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Fig-1, Early IPF showing reticular and reticulonodular opacities predominantly in basal region



Fig-2, IPF showing sub pleural reticular opacities, macrocystic honeycombing and traction bronchiectasis

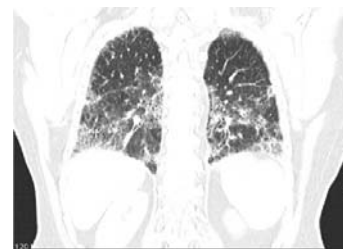


Fig 3 IPF showing Apicobasal gradient



Fig -4, NSIP-subpleural, symmetrical, reticular opacities, microcystic honeycombing

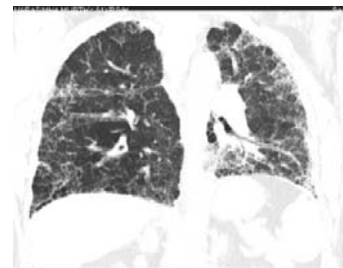


Fig-5, NSIP subpleural opacities with ground glass haziness without obvious apicobasal gradient



Fig 6, COP showing consolidation with ground glass haziness

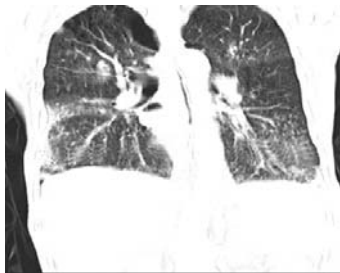


Fig-7, COP showing patchy air space consolidation with ground glass haziness with peribronchial distribution



Fig-8, RB-ILD showing ground glass opacity centrilobular nodules and bronchial thickening



Fig-9, DIP showing diffuse ground glass opacity and irregular linear opacities



Fig-10, LIP showing bilateral diffuse reticulonodular opacities with ground glass opacity

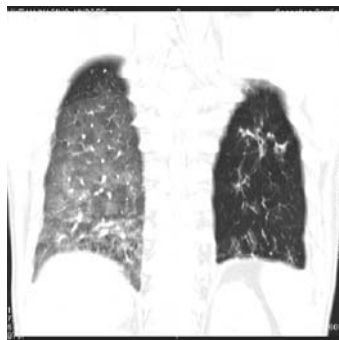


Fig-11, LIP –showing ground glass opacity with perivascular cysts

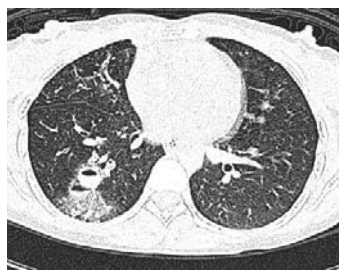


Fig-12, Early AIP Showing basal consolidation and ground glass opacity in dependent area



Fig-13, late AIP Showing traction Bronchiectasis ,architectural distortion and honey combing in non dependent area

Combination chemotherapy in cancer

In 1965, a major break-through in cancer therapy occurred. James Holland, Emil Freireich, and Emil Frei hypothesized that cancer chemotherapy should follow the strategy of antibiotic therapy for tuberculosis with combinations of drugs, each with a different mechanism of action. Cancer cells could conceivably mutate to become resistant to a single agent, but by using different drugs *concurrently* it would be more difficult for the tumor to develop resistance to the combination. Holland, Freireich, and Frei simultaneously administered methotrexate (an antifolate), vincristine (a Vinca alkaloid), 6-mercaptopurine (6-MP) and prednisone together referred to as the POMP regimen and induced long-term remissions in children with acute lymphoblastic leukaemia (ALL).

Case Reports of Abdominal Cocoon

The sclerosing encapsulating peritonitis (SEP) is a rare cause of intestinal obstruction which is characterized by the encasement of the small bowel by a fibro-collagenic cocoon like sac.^[1,2] It was first observed by Owtschinnikow in 1907 and was called *peritonitis chronica fibrosa Incapsulata* and termed "Abdominal cocoon" by Foo in 1978.^[1,2] SEP can be classified as idiopathic or secondary. The idiopathic form is also known as abdominal cocoon.^[1] The exact etiology is unclear. Herein, we present two cases of SEP causing intestinal obstruction.

Case - 1

Mrs.P.D, an 18 year old married, nulliparous women was admitted with complaints of colicky abdominal pain and vomiting for three days. The patient had attained menarche four years ago and was having regular cycles. She has been diagnosed as having abdominal tuberculosis and was on irregular treatment. She has had similar episodes previously and was treated conservatively. On general examination patient was anxious, thin built and severely dehydrated. Her pulse rate was 112/minute, temperature was 98.4°F and BP was

100/60 mmHg. There was no cyanosis, jaundice or lymphadenopathy. Systemic examination was normal. Local examination of the abdomen revealed a vague mass occupying the epigastrium and the umbilical region. The mass was tender, firm, not mobile, had indefinite margins and resonant on percussion. There was no free fluid in the abdomen. The bowel sounds were hyperactive. Per rectal and per vaginal examinations were normal. A provisional diagnosis of intestinal obstruction was made. Routine biochemical and hematological investigations were normal. Chest X-ray was normal but plain X-ray of abdomen revealed multiple air fluid levels, with no free gas under the diaphragm. Exploratory laparotomy revealed that the whole small bowel was adherent together like a cocoon from duodeno-jejunal flexure to the ileo-caecal region, encapsulated within a thick grayish white, opaque covering. It was free from the parietal wall and we were able to deliver the whole mass outside the laparotomy wound (Figure-1). Since we were not able to see the free small bowel we started tracing the small bowel from the ileo-caecal junction. While tracing we incised and peeled off the membrane from the mass which exposed the coils of intestine. The small bowel within this

membrane was seen coiled up in a concertina like fashion and these coils were separated easily from each other with the serosa intact. The entire small bowel was delivered from the cocoon and their adhesions released. Peritoneal toileting and mass closure of abdomen was done leaving an intraperitoneal drain. The patient had uneventful post operative period, discharged on 12th post-operative day and was started on anti-tuberculous treatment. She is attending follow-up clinics regularly for the past one year and is symptom free. The peeled off membrane was sent for biopsy and revealed fibrosis and hyalinization suggesting sclerosing peritonitis.

Case -2

Miss.S.G a 13 year old girl was admitted with complaints of abdominal pain and vomiting for two days. She had no similar episodes previously. She had not attained menarche and family history was non-contributory. On examination she was averagely built and nourished. Her vitals were normal and she had no pallor or lymphadenopathy. Abdomen was mildly distended and tenderness was present all over. No mass was palpable because of tenderness and distension. Bowel sounds were absent. Per rectal examination was normal. Routine investigations were normal. Plain X-ray

abdomen showed multiple air-fluid levels. Sonogram of abdomen showed gas filled loops of small bowel suggestive of small bowel obstruction. Exploratory laparotomy was performed and the whole small bowel was found encapsulated in a thick fibrous covering forming a huge swelling occupying the central abdomen. There was no mesenteric lymphadenopathy. She underwent adhesiolysis as described in case-1 (Figure-2 & Figure-3). She is doing well on follow-up. Biopsy report from the membrane revealed abdominal cocoon showing sclerosing fibrocollagenous tissue.

Discussion- Sclerosing encapsulating peritonitis (SEP) is a rare condition of unknown etiology, which is characterized by a thick grayish white fibrotic membrane that wraps the small bowel in a concertina like fashion. Clinically it presents with recurrent episodes of acute, sub-acute or chronic small bowel obstruction, weight loss, nausea, anorexia and at times with a palpable abdominal mass, but some patients may be asymptomatic. SEP can be classified as idiopathic (primary) or secondary. The secondary form of SEP has been reported in association with continuous ambulatory peritoneal dialysis.^[3] Other rare causes include abdominal tuberculosis,^[4] beta-blocker praxolol intake,^[5] ventriculoperitoneal and peritoneovenous shunts,^[6,7] orthotopic liver transplantation and

recurrent peritonitis.^[8] Abdominal tuberculosis could be the cause in our first case, although the biopsy did not support it. Idiopathic form has been classically described in young adolescent females from tropical and subtropical countries. The etiology has remained relatively unknown. To explain the etiology a number of hypothesis have been proposed. These include retrograde menstruation with a superimposed viral infection,^[1] retrograde peritonitis and cell mediated immunological tissue damage incited by gynecological infection.^[9] However, since it is also seen in males and children, there seems to be little support for these theories. Our second case is probably idiopathic. Although, preoperative diagnosis is difficult and most cases are diagnosed at laparotomy, better awareness and careful interpretation of imaging studies may facilitate diagnosis. Management of SEP is debated. But most authors agree that surgical treatment is required. Surgery includes freeing the bowel from the thick encasing membrane and the release of obstruction. Finger dissection is done with minimal blood loss without injuring the bowel serosa. Extensive surgery and unnecessary bowel resections are associated with high incidence of anastomotic failure and should be avoided unless the bowel is non-viable. No surgical treatment is required in asymptomatic SEP.^[10] This condition should be suspected in young adolescent girls who

present with small intestinal obstruction with no obvious cause.

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Figure-1, Intraoperative photograph, A fibrotic, cocoon like membrane covering enteric loops, delivered outside the laparotomy wound.



Figure-2, Intraoperative photograph: Membrane being peeled off from the serosa of the small bowel.



Figure-3, Intraoperative photograph: Ileum delivered from cocoon, jejunum still encased within the cocoon

Vaginal delivery in monoamniotic-monochorionic twins: a case report

Multifetal gestation though fascinating has always been a great challenge to concerned obstetricians. The incidence of twin pregnancy is approximately 1 in 90 of which 30% are monozygotic and 70% are dizygotic. Monozygotic twins have a higher complication rate than dizygotic.¹ Amongst monozygotic twins also monochorionic-monoamniotic twins are the rarest. Incidence of monoamniotic twins is approximately 1 in 10000 pregnancies.² Cord entanglement, structural malformations, twin-twin transfusion syndrome, and prematurity are responsible for their high perinatal morbidity and mortality.

Case report

A 24 year old primigravida with 1 year married life with history of 32 weeks 4 days amenorrhoea and twin pregnancy and Rh negative blood group came to the outpatient department of Obstetrics and Gynecology with complain of spotting per vaginum and backache since 2 hours. The patient had been registered antenatally at the institution and had been coming for regular checkups and had been diagnosed as having monochorionic-monoamniotic twins at ultrasonography at 18 weeks gestation. Her antenatal period had been uneventful

except for once when she was admitted for excessive vomiting at 30 weeks gestation. There was no history of drug intake prior to conception and this was a spontaneous conception. Neither was there a family history of twinning. On examination her vitals were stable, no pallor or edema or cyanosis was noted. Respiratory system and cardiovascular system revealed no abnormality. On abdominal examination uterus was term size, relaxed, multiple fetal parts were felt. First of the twins was cephalic with a regular heart rate of 140 bpm. The lie of the second could not be made out exactly but seemed to be cephalic with a heart rate of 130 bpm. On per speculum examination cervix and vagina were healthy, no bleeding or leaking demonstrable. On per vaginal examination cervix was central, early effaced, 2.5 cm dilated, membranes were present, cephalic presentation, and pelvis seemed adequate. In her previous investigation record all hematological, urine reports were within normal limits, and Indirect coombs test negative at 24, 28 weeks gestation. A haemogram, blood sugar were sent and an urgent ultrasound was done. Haemoglobin level was found to be 11.9 gm%, and blood sugar was normal. Ultrasound report revealed twin pregnancy with both cephalic in presentation. First of the twins corresponded to 30 weeks 2 days gestation with expected fetal weight of 1599 kg, and second corresponded to 30 weeks 3 days with expected weight of 1688gm. A single placenta (monochorionic) in upper segment

anterior wall was noted (not low lying). Amniotic fluid index was found to be 12.5 cm, good fetal movements noted. The patient and her kin were explained the risks involved in the case however they refused for cesarean section and hence patient was kept under observation, started on antibiotics, steroids administered. No augmentation was done initially. The patient went into spontaneous labour, during which continuous fetal monitoring was resorted to and patient kept hydrated. During second stage of labour syntocinon drip was started to establish good contactions. Patient delivered the first baby a male child by outlet forceps applied due to fetal distress and non descent at 8.31 pm, methergin was withheld. After delivery of first baby heart rate of second was rechecked and repeat per vaginal examination revealed vertex presentation with no intervening membranes. The second baby delivered at 8.38 pm also a male. Injection methergin was administered after delivery of second twin. A single placenta was delivered intact with membranes, both the cords were intertwined with one another (6 turns), the first cord had 2 true knots. Monochorionicity was confirmed at delivery and placenta sent for histopathological examination which confirmed monoamniocity and monochorionicity. Both babies had same blood group AB positive, and so anti D injection administered to mother. Both babies were admitted to the neonatal intensive care unit where they progressed nicely and

were discharged after 15 days. The mother also had an uneventful post partum stay and was discharged on day 3

Discussion-Monoamniotic wins occur only in 1% of twin pregnancies.³ The late embryo division (> 8 days after fertilization) results in two embryos within a common amniotic sac, or a monoamniotic-monochorionic-monozygotic twin pregnancy and is also at risk of developing specific complications related to this condition. Monoamniotic twins are at a greatly increased risk of perinatal complications with a mortality of 28-60% reported in literature.⁴ The most specific include entanglement and (or) knotting of cords, leading to intrauterine death of both (more often) or one of the fetuses; twin-twin transfusion syndrome; prematurity. Ultrasound represents the corner stone in the management of these pregnancies, firstly in diagnosis of monochorionicity in first trimester; and second by screening and monitoring of their specific complications. In the case presented above cord entanglement and knots were diagnosed post delivery only, fortunately no mortality occurred. However the early diagnosis of entanglement enables forecasting possible complications, for which management of such cases should be performed in tertiary medical centres only. Management of this unpredictable condition is controversial. Intense monitoring of fetal growth and well being is recommended and may

necessitate hospitalization as early as 28-30 weeks of gestation.⁵ However even with the best of surveillance sudden catastrophies have occurred. Most authors^{3,5,6-8} prefer abdominal delivery upon reaching fetal maturity in case of known monoamniotic twins, although this management is not validated by available studies. However Tensen et al found labour and vaginal delivery were not associated with increased risk of fetal death.⁹ They found that no fetal death occurred after 32 weeks, suggested that prophylactic preterm delivery was not required in all cases to overcome complications of cord entanglement. Similar results have been obtained by others.^{9,10} Monoamniotic twins the most precarious of twin pregnancies, though have a high neonatal morbidity and mortality outcomes for survival may be better than anticipated.

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Ultrasound during second trimester at Lok Nayak Hospital Delhi (29.10.07)

Twin A	Twin B
BPD= 4.7 H" 21 WKS	BPD= 4.89H"21 WKS
FL= 3.2H" 20 WKS	FL= 3.19
H"20 WKS	
FHS + REGULAR	FHS +
REGULAR	
Cephalic at presentation	Breech at present
Single placenta anterior grade I	
No obvious membrane made out	
Imp: 20-21 wks twin gestation monochorionic, most probably monoamniotic	

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Appendicectomy by Small Incision and Comparing it With Laparoscopic Technique

Appendix is a small organ of large gut and very much prone to develop an 'acute abdomen'. Medical students all over the world are much fascinated about its nature. All most all young surgeons are passionate in doing a smooth flawless appendicectomy without much difficulty. Though the skin is the best dressing and most powerful biological guard, we do not like to make a minimum scar or blemish on the abdomen. '*Big surgeons make big incision*' an aphorism to be reviewed when we are in the peak of using the minimal access laparoscope in the wide field of surgery for maximum benefit and minimum morbidity. In our previous series (*Surgery, Vol.5No, 1 2001*)¹⁰ We operated upon 54 patients by the small transverse incision in between 1997 and 2000. Post operative scar was small and more towards the right anterior superior iliac spine hiding behind the garment. In our old series three patients (out of 54) needed extension of incision to deliver the appendix. In this present series, we performed appendicectomy in the same method in two pregnant women and in two children. In between 1997 and February 2005, we performed a total of 209 appendicectomy (54 in the old series + 155 in the present). We selected the patients at random. There were 33 women

and 122 men including 2 children of 5 and 6 years. We also performed appendicectomy in 2 women of 2 and 3 months pregnancy (16yrs and 25yrs). We operated under spinal and general anesthesia with equal comfort. When the patient became anaesthetized. The operation table was tilted towards left allowing the shift of the intestine to get the advantage of smooth delivery of the appendix in many cases. The surgeon retracts the skin over right iliac fossa with the left thumb forcefully to words the left iliac fossa. A transverse skin incision (<2.5cm) was made on the right iliac fossa over the skin while the traction to wards the medial side pointing to the umbilicus was maintained by the thumb. The incision reseeds back to wards the anterior superior iliac spine again when the thumb was withdrawn. The assistant coordinately moves his hands with the two Langenbeke's retractors in the peritoneal cavity and maintaining a steady pull upwards and towards the umbilicus. We thus got the maximum advantage to deliver the appendix. We used the cord light source when it was available, through the small opening to illuminate the area. (Fig-3) This light source helped us detecting appendix easily even placing outside the skin of abdominal wall. The incised peritoneum was not sutured. Splitting muscles were allowed to appose spontaneously or by figure of eight apposing suture in need. External oblique apponeurosis was apposed by the 1/0 vicryl. Skin apposition was made by the vicryl or cyanoarylate glue. The

skin scar returns to the right anterior superior iliac spine. Intra venous fluid was continued for 12 hours in patients without any complications like high temperature, nausea and vomiting. It was also observed that nausea subsided in most of the patients when sips of cold milk were offered after 12 hours along with the oral proton pump inhibitors. After 24 hours, we served light meals as over boiled rice and curd for next 2-3 days.

Results analysis-We operated upon the 209 patients in between 1997 and 2005. Fifty-four patients were operated by small incision appendicectomy in the first series in between 1997 and 2000. We followed up 198 patients in the out patient department in between 1997 and 2005. However, the 11 patients did not turn up in the clinic. All the patients excepting six were discharged in between 2nd and 3rd postoperative day. Some of them suffered from mild postoperative nausea and vomiting. These symptoms were controlled by oral PPIs and cold milk within 12 hours. All patents except six were discharged in between 2nd and 3rd day with an instruction to stay in the near by *lodge* and to attend the out patient clinic positively by the 3rd day after discharge for follow up or if necessary, any time earlier at the emergency room. Since the skin wound was closed by the vicryl or cyanoacrylate glue. One patient developed keloid over the scar. Nine out of 198 followed up patients attended our out patient department (OPD) with the complaints of postoperative pain or numbness over the scar,

nausea and indigestions. They were treated by the assurance and oral drugs like metronidazole, omeprazole and albendazole in combinations. We also performed appendicectomy by this method in two patients with the history of previous laparotomy. One patient had herniotomy about 20 years back and the other underwent laparotomy for peptic perforation about 12 years back. There were adhesions around the inflamed appendix in about >50 % patients. Careful dissection by finger and forceps enabled us to deliver appendix in those situations. Invagination of the stump was not done in any patient in this series. Most of the procedures were well controlled by tying the inflamed or gangrenous base of the appendix first. The inflamed and edematous meso appendix was tied with the silk or by the vicryl. The diathermy was not always readily available in our theatre. A small opening was made first through the mesoappendix close to the wall of the appendix. The appendix was tied with vicryl by transfixing through the serosal coat. We tied the base along with the meso appendix in five patients due to difficulty and danger of caecal injury following dissection.

Discussion-Minimal access abdominal surgery is always preferable to laparotomy but not at the cost of major unacceptable risks. We discuss the small incision appendicectomy and tried to justify its advantages and disadvantages over the laparoscopy. Mc. Burney's incision at times was the most accepted skin incision for appendicectomy.

Many schools still continue to believe it. It is a time tested world wide accepted procedure by both surgeons and the patients. It is known to us that laparoscope is costly. Special training and set up is essential. A team, at least five members including paramedical staff, is essential for laparoscopy. "LAP took longer to perform (57 minutes vs 34.5 minutes) at higher cost (\$3718 vs \$1858) than OAP. Overall complications were lower in the LAP group (17% vs 29%), and LAP for RA had significantly fewer total complications (25% vs 62.5%). Intra-abdominal abscess increased following LAP: 9.2 per cent versus 3.6 per cent. Length of stay was shorter for LAP versus OAP in both AA (2.0 vs 2.5 days) and RA (5.5 vs 7 days)".⁶ Laparoscope was introduced for appendicectomy due to some major benefit over open technique by Grid iron incision or improvised Lanz incision. Laparoscopic appendicectomy is important for clear anatomical dissection by minimal access, short hospital stay and minimum scar. Laparoscopic approach is excellent especially who is obese and in women whose diagnosis is doubtful.⁵ In the laparoscopic appendicectomy the ports are thrust through the skin over the pubis, below umbilicus and on the skin of various right upper quadrant points. Therefore, skin scar marks are at least two. Right quadrant skin blemishes are difficult to hide. Sub umbilical skin blemishes might also be visible over anterior abdominal wall. A side table should be kept ready for laparotomy in failure-laparoscopy. General anaesthesia

is essential in the conventional laparoscopy. Use of harmonic knife, staples and use of sutures are all costly. Defined, skilled as well as precise technique is essential in laparoscopy. Incidence of adhesions after laparoscopic procedures is less (10%) than the laparotomy (18%) as described in a study, supported by the Research Council of Norway.⁴⁰ However, in our series the adhesion after surgery was only assessed clinically. Pain over the site of operation or around it was observed in about <20 % of post-operative patients. They did not require definite treatment in the followed up period. Laparoscopy is considered to be a good diagnostic tool in suspected appendicitis especially in the child-bearing age, where as post operative intra abdominal sepsis in case of grossly inflamed and gangrenous appendix is higher in laparoscopic appendicectomy.³⁰ Appendicectomy in patients with pregnancy and in children by the laparoscopic procedure is suitable but many schools do not recommend unanimously because of the risks following pneumo peritoneum and sepsis. In children, use of metal clips in broad base is yet to be considered after evaluations. One-quarter of seemingly normal appendix show microscopic evidence of inflammation.³⁰ However, appendicectomy in clinically acute appendicitis is justified without the diagnostic laparoscopy. Time for operation after anaesthesia in our technique was approximately in between 20 and 40 minutes. It is almost equal, if not less, to the laparoscopic

procedure. Spinal or epidural anaesthesia was satisfactory for adequate relaxation.

We performed the operations in our rural set up. General surgeons, not accustomed to do laparoscopy, can comfortably perform appendicectomy in a rural hospital set up. One surgeon with a trained theatre nursing staff may comfortably complete the appendicectomy. Duration of hospital stay was 2-3 days in most of the patients. We omitted the intra venous fluid line by 12 to 48 hours and allowed patients to go home or near by *lodge* or *dharamsala* (like a hotel) to stay and report on the *third* post operative day especially about fever, discomfort, nausea, vomiting and pain. Dr. Rajesh Chandulal Saha also performed 500 appendicectomy by random selection of patients. He opined as the small transverse incision (1.5 to 2cm) was comfortable for 'key-hole' appendicectomy in a normal set up. Skin incision returns to wards the right anterior superior iliac spine leaving the muscle wound behind the skin as contrast to the wound by the puncture of ports in laparoscopy. Port site hernia, though rare, may occur in 0.3% of cases. We did not find any incisional hernia as yet. In our technique skin wound and the muscle wound are in two different sites and planes. This might be a guard against herniation. 'No significant difference between the groups was found in the use of narcotic analgesia, length of stay or incidence of wound infection. However, operating time was significantly longer in the

laparoscopic group'. In experienced hands using a meticulous technique, LA provides diagnostic and therapeutic options, decreased operative time, rapid recovery, short hospital stay, fewer postoperative complications, and no intra-abdominal abscesses. Appendicectomy has cured right iliac fossa pain in almost all the patients.⁸

Comparing laparoscope with open technique is just an attempt of comparing lime with milk. Laparoscope is no doubt an instrument, which advanced our surgical technique and knowledge of dimensional anatomy. Minimal access offered maximum benefit to both surgeons and patients when used rationally. Laparoscope is a viewing tool and its diminution is wide. However, in appendicectomy by small transverse incision is equally good and cost effective. Incisional hernia after appendicectomy by Lanz incision is uncommon (<0.2%). In our series, we did not find any hernia. But the period (1997 to 2005) is short to make any comment. Our procedure is not a new one. The technique is good enough to accept both by the patients and the surgeons in all set up. 'Laparoscopic appendicectomy on an unselected group of patients does not confer many advantages but laparoscopy may be beneficial in certain subgroups'⁷

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Fig-1, Incision



Fig-2, Delivery of Appendix



Fig-3, Skin back towards iliac spine



Fig-4, Day 4 after surgery

Recent trends in cancer therapy

Targeted therapy-Molecular and genetic approaches to understanding cell biology uncovered entirely new signaling networks that regulate cellular activities such as proliferation and survival. Many of these networks were found to be radically altered in cancer cells, and these alterations had a genetic basis caused by a chance somatic mutation.

Tyrosine kinase inhibitors-The classic example of targeted development is imatinib mesylate (Gleevec), a small molecule which inhibits a signaling molecule kinase. The

genetic abnormality causing chronic myelogenous leukemia (CML) has been known for a long time to be a chromosomal translocation creating an abnormal fusion protein, kinase BCR-ABL, which signals aberrantly, leading to uncontrolled proliferation of the leukemia cells. Imatinib precisely inhibits this kinase. Unlike so many other anti-cancer agents, this pharmaceutical was no accident. Brian Druker, working in Oregon Health Science University, had extensively researched the abnormal enzyme kinase in CML. He reasoned that precisely inhibiting this kinase with a drug would control the disease and have little effect on normal cells. Druker collaborated with Novartis chemist Nick Lydon, who developed several candidate inhibitors. From these, imatinib was found to have the most promise in laboratory experiments. First Druker and then other groups worldwide demonstrated that when this small molecule is used to treat patients with chronic-phase CML, 90% achieve complete haematological remission. It is hoped that molecular targeting of similar defects in other cancers will have the same effect.

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Esophageal cancer is unique among the gastrointestinal tract malignancies because it has two distinct histopathologic types, squamous cell carcinoma and adenocarcinoma. Which type of cancer occurs in a given patient or predominates in a given geographic area depends on many variables, including individual lifestyle, socioeconomic status, race and environmental factors. The United States, along with many other Western countries, has witnessed in recent decades a profound increase in incidence rates of adenocarcinoma, whereas squamous cell carcinoma continues to predominate worldwide. Although it would seem appropriate to individualize treatment of these tumors, often they are managed as a single entity. Present-day therapeutic interventions have limited impact on survival, as evidenced by fatality rate of 90%. However, a more thorough understanding of the initiating events, the molecular biologic basis, and treatment results has begun to spawn a new era of therapy aimed at targeting both adenocarcinoma and squamous cell carcinoma of the esophagus. Carcinoma Esophagus is the 9th most common cancer in the world. It causes 2% of all cancer related deaths. Although squamous cell

carcinoma is the most common variety in endemic regions, the incidence of adenocarcinoma has shown a dramatic increase in recent times due to the well established associations among gastroesophageal reflux disease (GERD). Squamous cell carcinoma is 2 to 3 times and adenocarcinoma is 7 to 10 times more common in males. Squamous cell carcinoma is mainly associated with tobacco and alcohol abuse. According to ICMR cancer registry 2001 – 2003 carcinoma oesophagus is ranked 1st as the 5th leading cancers. Esophageal cancer is relatively uncommon in the United States, and the life time risk of being diagnosed with the disease is less than 1%. It was estimated that 15,560 new cases were identified in 2007, with nearly 14,000 patients died of the disease, which emphasizes its virulence. Mortality rates for esophageal cancer in the United States also are race-dependent. Although survival rates for all esophageal cancer patients are uniformly dismal, regardless of race or gender, 5-year relative survival rates have significantly improved since the 1970s (5% if diagnosed in 1975-1977 vs. 16% if diagnosed in 1996-2002) based on Surveillance, Epidemiology, and End Results population-based tumor registry reporting. African American has poorer 5-year survival rates than white

Americans, and men fare poorly compared with women. There is no survival difference related to cell type (squamous cell carcinoma vs. adenocarcinoma). The treatment of oesophageal cancer is challenging, not only because of the heterogeneity of the disease but also due to an aggressive tumor biology and lack of consensus regarding a uniform treatment approach. Traditionally, surgery has been the mainstay therapy. However, recently more and more centers are relying on multimodality therapy to treat oesophageal cancer, using a combination of chemotherapy and / or radiotherapy with or without surgery. In addition, major progress has been made during the past decade in the fields of diagnostic imaging, molecular biology and minimally invasive surgical techniques. These developments are likely to have a major impact on the management and outcome of oesophageal cancer in the future.

Etiology-The exact cause of cancer is unknown and various factors are thought to increase the risk of development of cancer. It is more likely to occur in older age group. Tobacco, alcohol, use of caustic substances or swallowing lye that cause irritation to the lining of oesophagus increase the risk. Patients having other head &

neck cancers in the past also have chance of developing a 2nd cancer in oesophagus. Low socio economic status is associated with increased risk of oesophageal squamous cell carcinoma and to a lesser degree for adenocarcinoma. Increased BMI is a risk factor for oesophageal adenocarcinoma and individuals with highest BMI have up to 7 fold increased risk than those with low BMI. Infection with *H. pylori* and particularly with *cagA* + strains is inversely associated with oesophageal adenocarcinoma. HPV infection may also contribute to the pathogenesis of oesophageal squamous cell cancers in high incidence areas in Asia and South Africa.

Pathology-Grossly, the pathological types are fungating, ulcerating, infiltrating and polypoidal. The incidence of squamous cell carcinoma is 50% in middle third, 30% in lower third and 20% in upper third of oesophagus. Adenocarcinoma tends to be localized in the distal third of oesophagus and may be fungating or stenoting in appearance.

Clinical presentation-Early oesophageal cancers are usually

asymptomatic. Dysphagia is the most common symptom which is progressive. Initially it is to solids and then progresses to liquids. In the most extreme cases, patients can't even swallow their own saliva. Other symptoms are regurgitation, odynophagia, loss of weight, loss of appetite, dull retrosternal pain; cough with or without hemoptysis, hoarseness of voice, dyspnea, neck mass, hematemesis and black tarry stools. These are usually signs of advanced disease.

Staging modalities-Besides medical history, physical examination and routine investigations, the conventional staging for oesophageal cancer includes upper gastrointestinal endoscopy, barium swallow, bronchoscopy in upper one-third tumors, and MRI / CT scan of the chest and abdomen.

New staging modalities-Recently endoscopic ultrasound (EUS), laparoscopic ultrasonography, positron emission tomography (PET) scan, thoracoscopy, mediastino-scopy and laparoscopy are also being used by some investigators to improve the accuracy of staging. However, all these modalities have considerable limitations.

- If tumor is at or above the carina with no evidence of M1 disease, do bronchoscopy
- Endoscopic ultrasound (EUS), if no evidence of M1 disease, with FNA if indicated.
- If no evidence of M1 disease and tumor is at GE junction, laparoscopy is optional.
- Suspicion of metastatic cancer confirmed by biopsy.
- PET/CT scan if no evidence of M1 disease

Staging of oesophageal carcinoma-Accurate staging of oesophageal cancer is essential as this helps identify individuals most likely to benefit from aggressive therapy. Staging remains the most accurate method for predicting overall prognosis. Conventionally, surgical staging used to be the gold standard. However, with the advent of multimodality therapy there is a need to evolve an accurate non-surgical staging method which has the capability to accurately assess response to chemo/radiotherapy. Cancer of the oesophagus is staged according to the AJCC, TNM classification

Accuracy of staging techniques

Modality	T Accuracy %	N Accuracy %	M Accuracy %
CECT	49-60	39-74	85-90
EUS	76-92	50-88	66-86
MRI	96	56-74	—
PET	—	48-76	71-91
Thoraco/ Laparoscopy	—	90-94	—

TNM staging of esophageal cancer

Stage	Primary tumor (T)	Regional lymph Nodes* (N)	Distant metastasis (M)
0	Tis (carcinoma in situ)	N0	M0
I	T1 (invasion of lamina propria or submucosa)	N0	M0
IIA	T2 (invasion of muscularis propria) T3 (invasion of adventitia)	No	M0
IIB	T1 T2	N1 N1	M0
III	T3	N1	M0
III	T4 (invasion of adjacent structures)	Any N	M0
IV	Any T	Any N	M1

Treatment-Treatments of esophageal cancer depend on a number of factors, including size, location, extent of tumor and the general condition of the patient. It is multimodal treatment in most of the cases. The various treatment strategies are surgery, radiotherapy, chemotherapy, and laser therapy, photodynamic therapy along with supportive care.

Rationale for multimodality therapy-Oesophageal cancer is highly lethal with most patients ultimately succumbing to the disease. Early (Tis/T1, N0, M0) oesophageal cancer is extremely rare (<5%) and surgical resection alone as a single modality can cure a majority of such patients. The aim of treatment in stage IV metastatic oesophageal cancer, which continues 25% - 30% of the patients with oesophageal cancer, is palliation. The remaining 65%-70% of patients with oesophageal cancer present with locally advanced disease (stages II and III) and <60% of such patients can undergo a

resection with a curative intent, as 70%-80% of such resected specimens have metastases in the regional lymph nodes. These unfavorable outcomes may be due to early dissemination of tumour cells into the submucosal networks and lymph nodes as well as the absence of a serosal wall to limit local invasion. In these patients failure to cure or prolong survival occurs because of the inability to eradicate residual disease at the primary site and because of early systemic tumour dissemination. Since the first description of oesophagectomy by Torek in 1913, it remains the standard of care. While its role has been questioned due to the generally poor outcomes following surgical resection, improved patient selection, anesthetic and postoperative care have resulted in a significant decrease in the morbidity and mortality related to oesophagectomy during the past 2 decades. Similarly, the 5-year survival rates of patients undergoing surgical resection have also shown a modest

improvement. Currently, the reported 5-year survival rates for oesophagectomy are in the range of 20%, compared with a 5% 5-year survival reported by Earlam and Cunha-Melo in the 1980s. However, as the results of surgery alone have not improved overall hypothesis, effective systemic chemotherapy and local radiotherapy directed at micrometastases added to surgical resection has lead to increased survival.

For better patient outcome, multimodality treatment is used in many patients. There are six different multi modality protocols:

- Pre-operative radiotherapy
- Post-operative radiotherapy
- Pre-operative chemotherapy (Neo-adjuvant)
- Post-operative chemotherapy (Adjuvant)
- Pre-operative chemoradiotherapy (CRT)
- Chemotherapy (CRT) without surgery

Problems of multimodality therapy—Despite 3 decades of experience, there are many unresolved issues as far as multimodality treatment of oesophageal cancer is concerned. In the era of evidence-based medicine only high quality randomized controlled trials will provide answers to these controversies. The factors responsible for the paucity of such studies in oesophageal cancer and lacunae of currently available literature include

- Relative rarity of the disease with wide variations in geographic distribution.
- Lack of accurate non-surgical staging methods leading to inappropriate patient selection for clinical trials.
- Heterogeneous disease spectrum in relation to histology – adenocarcinoma v. SCC and location – upper, middle, lower third and gastro-oesophageal junction.
- Rapidly changing disease spectrum: Migration from SCC to adenocarcinoma and from the middle – third to the lower – third in location.
- Complex and protracted treatment protocols in nutritionally compromised patients with limited life expectancy.
- Diverse treatment philosophies ranging from an optimistic curative approach to a pessimistic palliative approach.
- Lack of consensus among treating physicians with regard to the surgical

technique (transhiatal v. transthoracic, simple v. radical en bloc oesophagectomy, 2-field v. 3- field lymphadenectomy).

- Lack of quality data regarding treatment – related toxicity, compliance, quality of life issues and cost of multimodality protocols.

Surgery—Surgical resection is the standard treatment for early esophageal cancer i.e. stage I, II and most cases of III. After surgical fitness and preoperative staging, the patient is taken up for surgery. The tumor is removed along with all or a portion of oesophagus, near by lymph nodes, and other tissues in the area. A minimum of 15 lymph nodes to be removed to achieve adequate nodal staging. Type of resection is dictated by surgeon's and patient's preference and available facilities. During the past decade, the outcomes with surgery have improved due to better staging techniques, increased rate of curative resection and decreased rate of post-operative death. However, the 5 year survival rate remains low; stage I – 30to50%, stage IIA – 15to30%, stage IIb – 5- to15%.

Resectable tumors

- T1-T3 tumors with regional nodal metastasis.
- T4 tumors involving pericardium, pleura and diaphragm only
- Stage IVA involving lower oesophagus with celiac nodes (< or = 1.5 cm) but without involvement of celiac artery, aorta or other organs

- T1a tumors limited to lamina propria can be considered for endoscopic mucosal resection (EMR) in experienced centers.

Unresectable tumors

- T4 tumors involving heart, great vessels, trachea or adjacent organs including liver, pancreas, lung & spleen.
- Stage IV a involving lower oesophagus with celiac nodes > 1.5 cm with involvement of celiac artery, aorta or other organs including liver, pancreas, lung and spleen
- Stage IV b with systemic metastasis or non-regional lymph node involvement

Types of esophagectomies—Three Most frequently used approaches for resection

- Transhiatal Oesophagectomy
- Transthoracic oesophagectomy
- Enbloc Oesophagectomy (Two Field Dissection)
- Enbloc Oesophagectomy (Three Field Dissection)
- Thoracoscopic and Laparoscopic oesophagectomy
- Transendoscopic surgery

Transhiatal Oesophagectomy

- Exposure is provided by an upper midline laparotomy and a left neck incision.
- The thoracic esophagus is bluntly dissected, and a cervical anastomosis created; thoracotomy is not required.

- Drawbacks: inability to perform a full thoracic lymphadenectomy, and lack of visualization of the midthoracic dissection.

Transthoracic Oesophagectomy

- The Ivor Lewis esophagectomy combines a laparotomy with right thoracotomy, and produces an intrathoracic anastomosis.
- This technique permits direct visualization of the thoracic esophagus, and allows the surgeon to perform a limited lymphadenectomy.
- However formal dissection of lymph nodes is not performed

Enbloc Oesophagectomy

- Diagnostic to improve staging
- Prophylactic against local recurrence
- Improve prognosis

Transthoracic oesophagectomy has been the most common surgical approach and is the standard procedure against which all other techniques are measured. The various conduits used are gastric (preferred), colon, short segment jejunum, long segment jejunum with super charged micro vascular anastomosis. Either transhiatal or trans thoracic procedures with regional lymph node resection can be performed with acceptable morbidity and mortality in experienced hands. Extended oesophagectomy is not a routine practice. It involves enbloc resection of primary tumor with its adjacent

surrounding tissue and systematic lymph node dissection encompassing two (mediastinum and abdominal) or three (cervical, mediastinum and abdominal) lymph node areas. It improves staging and may enhance loco regional control and survival.

Minimal Invasive Oesophagectomy-Minimal Invasive Oesophagectomy has been the recent trend in the surgery for carcinoma oesophagus. It is technically feasible and oncologically safe procedure with faster postop recovery. But it has steep learning curve. Techniques are-Laparoscopic Transhiatal oesophagectomy; Thoracoscopic oesophageal mobilization and laparoscopic oesophagectomy with neck anastomosis. It is highly contraindicated in patients with large bulky tumors and having previous abdominal surgeries. It still continues to gain popularity among surgeons and patients.

Surgical results-The surgical associated mortality rate is <5% and morbidity rate varies from 35% to 65%.

Definitive chemoradiotherapy (CRT)-Various organ preservation protocols using CRT without surgery were initiated for chemo and radiosensitive solid tumors in the 1980. After the publication of successful results in anal cancer, Wayne State University investigators initiated definitive CRT protocols in oesophageal cancer and have shown that it is feasible to treat oesophageal cancer with definitive CRT. CRT has been evaluated in 3 different setting: Phase II studies, studies

comparing CRT versus radiotherapy and studies comparing CRT versus CRT and surgery. CRT phase II trials. Several phase II trials were undertaken using CRT alone as definitive therapy in locally advanced inoperable oesophageal cancer patients. Coia et al. in one of the largest trials of 90 patients with SCC reported a 2-year survival of 44% using 5-FU and mitomycin along with 50-60 Gy radiation. Seitz et al. reported a median survival of 17 months and a 2-year survival of 41% using 5-FU and cisplatin along with 40 Gy radiation. Basically, phase II trials provided the learning experience for CRT in oesophageal cancer and encouraged many investigators to initiate comparative studies. CRT versus radiotherapy: Definitive CRT has also been compared with radiotherapy in localized oesophageal cancer. In a recent systematic review, 13 randomized studies were included. Eight studies used concomitant CRT in 769 patients whereas 5 used sequential CRT involving 453 patients. Pooled data from studies using concomitant CRT showed a benefit in favor of CRT over radiotherapy alone at 2 years (OR 0.53; 95% CI 0.32-0.88; $p < 0.009$), whereas sequential CRT did not show a significant survival benefit. Preoperative CRT versus definitive CRT: In a recently reported randomized study from France, 455 patients with locally advanced carcinoma of the oesophagus were treated with 2 cycles of 3-weekly 5-FU and cisplatin followed by 20 Gy radiotherapy. Subsequently, 259 patients with partial response

were randomized to surgery or an additional 3 cycles of 5-FU/ cisplatin given according to the same schedule. Similar rates of median survival (17.7 v. 19.3 months) and 2-year survival (34% v. 40%; $p=0.56$) were seen using CRT and surgery compared with definitive CRT. However, treatment-related mortality was much higher in the CRT and surgery arm compared with definitive CRT (9% v. 1%). In this study, only patients with responsive disease were randomized. Therefore, an adequately powered, carefully stratified, multi-centre comparison of preoperative CRT with definitive CRT is required to define whether surgery could be omitted in some patients. Definitive CRT is feasible in oesophageal cancer and is superior to radiotherapy alone. Definitive CRT may represent an alternative strategy to surgery especially in patients who are medically unfit to undergo oesophagectomy.

Neoadjuvant therapy-Chemoradiotherapy is the most commonly used treatment modality in Ca. Oesophagus around the world. Radiation therapy, chemotherapy may be used alone or in combination as neoadjuvant therapy in cases of unresectable tumors. It helps in down staging the disease, removes microscopic persistent disease, increases the rate of complete resection after negative circumferential margins. With this the loco regional control gets improved but the distant failure is frequent and is the cause of death. Preoperative chemo radiation is not the standard of care but with benefits outlined

and improved survival, many centers have adopted this modality for locally advanced stage (II b & III). As single agents, bleomycin, methotrexate, mitomycin-C, adriamycin, Vindesine and etoposide have shown activity against squamous cell carcinoma, but the most active and widely used agents are 5-FU and cisplatin. The overall response rate to chemotherapy varies from 30% to 50% and complete pathological response is obtained in 5% - 6%. Different regimens of radiotherapy have been used ranging from 45Gy over 4 weeks to 25 Gy over 5 days and the timing of surgery varies from 1-6 weeks after radiotherapy

Adjuvant therapy-The adjuvant therapy can also be given to decrease the risk of loco regional relapse and to improve survival. The main advantage of postoperative treatment is the selection of patients for adjuvant therapy based on the final histopathological staging. However the drawbacks include the inability to effectively irradiate the radio resistant hypoxic tumour clones embedded in scar tissue and unnecessary exposure of the gastric conduit to irradiation. The experience with postoperative chemotherapy in esophageal cancer is limited. But it has been tried to control residual microscopic locoregional disease and systemic micro metastasis.

Definitive radiation therapy and chemoradiotherapy is used for patients who are not candidates for surgical resection. Local control with this is 40-75%, median survival is 9 to 24 months and 2-year survival ranges from 18% - 35%. However

chemoradiotherapy is superior to radiotherapy alone.

Future strategies-Carcinoma oesophagus continues to challenge the oncologists and only modest survival gains have been achieved during the past 3 decades. Surgery has contributed significantly to the overall improvement in mortality due to oesophageal cancer and it still remains the mainstay of therapy for localized esophageal cancer. However, lymphadenectomy and minimally invasive oesophagectomy. As far as chemotherapy is concerned, the results with the most widely used cytotoxic agents, (cisplatin and 5-FU) have plateaued and future trials should investigate the role of newer cytotoxic agents including the taxanes (paclitaxel and docetaxel), topoisomerase inhibitors (irinotecan), oral fluoropyrimidine derivatives (capecitabine) and new generation platinum compounds (oxaliplatin).

Molecular targeted therapy-Currently, research is in progress evaluating the role of biomolecular markers in the diagnosis, prognosis and treatment of oesophageal cancer. Several biomarkers have been identified but none has fulfilled the desired needs. Collaborative research has helped in the identification of high risk individuals with severe dysplasia among patients with Barrett oesophagus, who have a higher chance of transformation to adenocarcinoma. Currently 'prophylactic oesophagectomy' in such patients is an acceptable intervention and 5-year survivals in the range of 80% have been reported. Molecular targeted therapy has shown activity in

several solid tumors and it is being investigated in oesophageal cancer also. The epidermal growth factor receptor (EGFR) signaling pathway influences cell differentiation, proliferation, migration, angiogenesis and apoptosis. Cetuximab is a monoclonal antibody directed against EGFR and it appears to have a synergistic effect with chemotherapy and radiotherapy. Studies evaluating the combination of cetuximab and chemo/radiotherapy in carcinoma of the oesophagus are currently recruiting patients. Studies have also commenced evaluating oral EGFR tyrosine kinase inhibitors include ZD1839 and OSI774 in oesophageal cancer. Epidemiological studies have also suggested the use of non-steroidal anti-inflammatory drugs (NSAIDs) which may reduce the incidence of oesophageal cancer, presumably

through inhibition of cyclooxygenase (COX)-2. Studies are being planned to investigate the use of NSAID's or COX-2 inhibitors in patients with Barrett oesophagus.

Palliative and supportive care- For those patients who are not fit for any aggressive therapy because of advanced stage, palliative supportive treatment be offered. Nutritional support in form of feeding jejunostomy can be done. The supportive measures like stents, laser, photodynamic therapy, radiotherapy (external or brachytherapy) can be used in cases of obstruction.

- Endoscopic placed stent to provide palliation of dysphagia
- Radiation therapy with or without intraluminal intubation

- Intraluminal brachytherapy to provide palliation of dysphagia.
- Nd:Yag - endoluminal tumors destruction
- Radiotherapy can be used for analgesia along with medications.
- Bleeding can be control with endoscopic therapy.
- Oesophageal dilatation can be done, if needed and possible.

Follow-up- Follow-up care after treatment for esophageal cancer is important to ensure that any changes in health are found. Proper history and physical examination 4 monthly in 1st year, 6 monthly in 2nd year followed by yearly visit. Investigations are done, if indicated clinically like CBC, SMA-12, Endoscopy, Chest X-ray, CT Scan etc. Nutritional counseling should also be done.

AJCC stage grouping recommended treatment and predicted 5 yr survival

Stage	TNM designation	Treatment	5-yr survival (%)
0	Tis, N0	Surgery alone	95
I	T1, N0	Surgery alone	75
IIA	T2, N0, M0	Surgery alone	30
IIB	T1, N1, M0	Surgery along or surgery +/- preop chemo / XRT under	20
	T2, N1, M0	Surgery along or surgery +/- preop chemo/XRT under investigation	
III	T3, N1, M0	Surgery for T3 lesions with or without preoperative chemo/XRT under investigation	10-15
	T4, any N,	Palliation (chemo, XRT stenting, or combination)	
IVA	Any T, any N	Palliation (chemo, XRT, stenting, or combination)	5
IV B	Any T, any N	Palliation (chemo, XRT, stenting, or combination)	1

Recommendations

- Surgery remains the standard of treatment in esophageal carcinoma. Oesophagectomy is an appropriate method for treating patients with stage I, II, III and selective stage IV patients.
- preoperative chemotherapy remains an attractive approach where there is resectable disease and should be considered to be examined in well designated clinical trials.
- Alternative chemoradiation is therapeutic option for loco regional disease, particularly if patient is medically unfit for surgery.
- Post operative RT is reserved for adenocarcinoma of GE junction.
- All patients with stage IV disease are ideally suited for clinical trials exploring novel therapeutic agents and approaches.
- Supportive therapy is given in patients with locally advanced and metastatic disease.

Oswal approach-Oswal cancer hospital is a high volume center, registering nearly 150 new oesophageal cancer patients annually. The mainstay of staging is CT scan. As far as patients with localized oesophageal cancer are concerned, we usually recommend surgical excision. Transhiatal is done for lower end lesion and Transthoracic for mid oesophagus & lower thoracic regions with complete abdominal and limited mediastinal lymph node dissection. Adjuvant

radiotherapy and chemotherapy is used in lymph node positive patients or T3 disease. Definitive radiotherapy and chemotherapy is used for patients refusing surgery or patients who are poor candidates for surgery. For locally advanced lesions, 2-3 cycles of neo-adjuvant chemotherapy (5-FU / cisplatin \pm taxane) followed by surgery and post operative chemotherapy and radiotherapy. For metastatic disease, chemotherapy is the mainstay of treatment with or without local radiotherapy. At times, stenting or feeding jejunostomy is done in stage IV disease as a part of palliative treatment. Once patient's general condition improves with palliative treatment local radiotherapy and chemotherapy \pm surgery is given to cancer patients.

Adjuvant therapy in cancer

As predicted by studies in animal models, drugs were most effective when used in patients with tumours of smaller volume. Another important strategy developed from this - if the tumour burden could be reduced first by surgery, then chemotherapy may be able to clear away any remaining malignant cells, even if it would not have been potent enough to destroy the tumor in its entirety. This approach was termed "adjuvant therapy". Emil Frei first demonstrated this effect - high doses of methotrexate prevented recurrence of osteosarcoma following surgical removal of the primary tumour.

5-fluorouracil, an inhibitor of DNA synthesis, was later shown to improve survival when used as an adjuvant to surgery in treating patients with colon cancer. Similarly, the landmark trials of Bernard Fisher, chair of the National Surgical Adjuvant Breast and Bowel Project, and of Gianni Bonadonna, working in the Istituto Nazionale Tumori di Milano, Italy, proved that adjuvant chemotherapy after complete surgical resection of breast tumours significantly extended survival — particularly in more advanced cancer. Patients receiving these agents experienced severe side-effects that limited the doses which could be administered, and hence limited the beneficial effects. Clinical investigators realized that the ability to manage these toxicities was crucial to the success of cancer chemotherapy. Several examples are noteworthy. Many chemotherapeutic agents cause profound suppression of the bone marrow. This is reversible, but takes time to recover. Support with platelet and red-cell transfusions as well as broad-spectrum antibiotics in case of infection during this period is crucial to allow the patient to recover. Several practical factors are also worth mentioning. Most of these agents caused very severe nausea (termed chemotherapy-induced nausea and vomiting (CINV) in the literature) which, while not directly causing patient deaths, was unbearable at higher doses.

A Comparative Study of Effects of Transcendental Meditation (TM) And Yogaasnas on Autonomic Activity

Original
Article

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Present day lifestyle is the major contributing factor towards stressful living, both at mental and physical levels. Stress is known to cause imbalance in neuroendocrinal mechanisms (responsible for maintaining physiological stability during environmental change), resulting in ill health.¹ Over a few decades, non-pharmacological "self induced relaxation techniques" have gained popularity in 'stress management' over drugs. These techniques might be having an influence on adaptive mechanisms, such as autonomic activity. Beneficial effects of yogaasnas and T.M on physical and mental health are reported in literature and these practices are advocated in psychosomatic illnesses arising out of stressful situations. T.M as introduced by Maharishi Mahesh Yogi² is a widely studied meditation technique as it is systematic and easy to study. It involves neither concentration nor contemplation. Yogaasnas are alleged to enhance parasympathetic activity and TM to suppress sympathetic activity. No published data regarding the effects of a combined practice of the two techniques is available. To study the effects of a combined practice of yogaasnas and TM on autonomic function a comparative study was done in 24 young healthy females.

Material and methods-Subjects of the study were 24 female healthy resident medical students, 17-20 years of age. It was conducted in the Department of Physiology, Lady Harding Medical College, New Delhi, India. After recording the basal data, subjects were randomly divided in four groups (6 subjects in each. Subjects were novice and were taught yogaasnas and TM by teachers from ashram of Mahesh Yogi. They practised these techniques twice a day (morning and evening) in the department (except for Sundays and holidays, when they practised at home)

Group I – Subjects sat with closed eyes for 20 minutes (Control group)

Group II – Practiced TM for 20 minutes

Group III – Practiced yogaasnas for 20 minutes followed by Shavasna practice for 20 minutes
Group IV – Practiced yogaasnas for 20 minutes followed by TM for 20 minutes

Groups III and IV performed following yogaasnas : Vajrasna, Ushtrasna, Janusir, Sarvangasna, Halasna, Paschimothan, Bhujangasna, Shalbhasna, Aradhmatyandra and Padhasthana.

Group III performed Shavasna in addition.

The parameters studied to assess activity of the Autonomic Nervous System were-Heart rate

(HR) calculated from ECG, Galvanic skin resistance (GSR); Electroencephalogram (EEG), They were recorded over a Polygraph (Polyrite.INCO), Blood Pressure (BP) using sphygmomanometer, Lipid profile by standard biochemical methods (Total lipids by Folch et al³; Serum cholesterol – Zak⁴; Free fattyacids – Itaya⁵; Blood glucose – Folin⁶; Urinary VMA – Pisano⁷ Polygraphic recordings were taken during morning session. For initial base line data ECG and GSR were recorded during quiet sitting with eyes closed for 20 minutes. ECG and GSR were recorded before eyes-closing, every 5 – minute during sitting with closed eyes till 20 minutes and again 5 minutes after opening the eyes labeled as 0-min, 5 min, 10 min, 15 min, 20 min and 25 min. This was repeated after 6 and 12 weeks. In control group polygraphic recording was done during quiet sitting and in groups II and IV during TM practice and in group III during Shavasna.

Collection of blood samples - For basal data a fasting blood sample was collected before and just after 20 min of quiet sitting in all the subjects.

After 6 and 12 weeks

Group I – Before and just after 20 minutes quiet sitting

Group II – Before and after TM practice session (within 5 minutes)

Group III- Before and just after Shavasna practice

Group IV – As in group II

The 2 blood samples were labeled as 0 – min and 25-min samples respectively.

Urine for VMA estimation - Morning sample was collected at the beginning of the study and then after 6 and 12 weeks of various practices (before the morning practice session). The essential dietary restrictions for VMA estimation were imposed on the subjects.

All parameters were repeated after 6 weeks and again after 12 weeks of study.

Results were analysed by student's 't' test to know the significance using MS Excel.

Results-No statistically significant changes were observed in subjects of control group during the study period. A progressive fall in HR (Fig 1), and BP (Fig 2 & Fig 3) and rise in GSR was observed in all practising groups (II, III & IV). In comparison to control group decrease in HR and systolic blood pressure (SBP) were statistically significant only in group IV after 12 weeks of practice. Decline in diastolic blood pressure (DBP) was statistically significant in group practising TM alone (Group II) after 12 weeks and in group practising TM along with yoga after 6 weeks and it declined further after 12 weeks, but it was insignificant in group III (Tables 1 & 2). A significant increase in GSR occurred in all practicing groups after 6 weeks and it increased further after 12 weeks, being maximal in group IV. In addition a significant increase in GSR also occurred during the practice of

TM in groups II and IV (Tables 1 & 2). A fall in blood glucose level (0 min) was observed in practicing groups (Fig 4) when compared to control group. It was significant in groups practicing TM and yoga along with TM (groups II & IV) after 6 weeks and persisted after 12 weeks (Tables 1 & 2), whereas in yoga group fall was not significant. In comparison to controls a significant fall in levels (0 min) of total lipids and cholesterol occurred in yoga along with TM group after 6 weeks and persisted till 12 weeks. In the group practicing TM alone the changes were significant only after 12 weeks of practice (Tables 1 and 2, Fig 5) only and insignificant in the group practicing yoga alone. A significant decline in levels of FFA was also observed in groups II and IV (Fig 6). In addition a significant decrease in FFA levels occurred during the practice of TM technique in these groups (a significant change in levels before and after the practice session was observed). A significant fall in urinary VMA also occurred in practitioners of TM along with yoga after 6 weeks and in practitioners of TM alone after 12 weeks (Fig 7, Tables 1 & 2). Decline in yoga group was statistically insignificant.

Discussion-In this study a decrease in HR, BP, total blood lipids, cholesterol, FFA, Glucose, VMA (major excretory product of catecholamines) and a progressive increase in GSR is observed in all study groups. When compared to control group, changes are significant in the group practicing TM alone

(Group II) after 12 weeks. In group IV the changes are significant after 6 weeks, and are more pronounced after 12 weeks and were statistically more significant than group II after 12 weeks (Tables 1 & 2). In group III (practicing yoga alone) the changes were statistically insignificant. In addition a significant rise in GSR and a fall in FFA levels were observed during the practice of TM technique in groups II and IV. Possibly, a 12 week duration for practice of yoga is inadequate to produce a significant variation in the parameters studied. At the same time yoga practice has a definite influence, as the changes are more pronounced in TM along with yoga group than in the group practicing yoga alone. These changes are suggestive of decreased sympathetic activity and / or enhanced parasympathetic activity due to these practices. Benson⁸ also observed similar results in subjects practicing TM technique and opined that the findings are akin to the "relaxation response" consistent with generalized decrease in sympathetic activity and are different from physiological changes occurring during sleep and quiet sitting. Similar changes in HR and in BP have been reported by a number of researchers in practitioners of TM.^{8-11,2} Some authors observed a fall in BP in volunteers performing various yoga asanas for 3-6 months.¹²⁻¹⁵ Skin resistance reflects the level of anxiety in an individual. There is an inverse relationship between basal skin resistance and

emotional arousal.^{9-10,2} As in the present study a number of authors^{9-10,2} reported a highly significant increase in GSR in practitioners of TM and suggested that TM produces a deeper relaxation than other techniques such as reading, sitting with closed eyes or listening to music. Fewer spontaneous changes in skin resistance and rapid habituation to stressful stimuli in TM practitioners suggests autonomic stability.^{16,2,10} Catecholamines are released during sympathetic stimulation and their activity is also related to mood, social stress and the psychic status¹⁷⁻¹⁸. Frankenhaeuser¹⁹ opined that epinephrine level increased under circumstances of novelty, anticipation, unpredictability and general emotional arousal. An increase level of catecholamines in public speakers²⁰⁻²¹ and during examination stress²² has been reported. Von Euler²³ recorded enhanced excretion of catecholamines in pilots and passengers during flight. Mitcheals²⁴ has reported a decline in catecholamine levels in subjects practising TM. In the present study a significant fall in urinary VMA, the major excretory product of catecholamine was observed in subjects who practised TM (groups II & IV). There has been a reported decrease in excretion of VMA in subjects practicing yogaasnas including Shavasna.¹² Sympathetic stimulation raises blood lipid levels as it enhances the activity of hormone sensitive lipase by releasing catecholamine. Stress also enhances the lipase activity.²⁵ Some authors²⁵⁻²⁷ have

observed increased level of cholesterol under varying stressful situations. In our study a significant fall occurred in cholesterol level in subjects practicing TM. Cooper²⁸ has reported a decrease in cholesterol level in subjects after TM practice, who were initially hypercholesteremic whereas some have recorded a decrease in blood cholesterol level in volunteers performing yogaasnas.¹²⁻¹³ FFA level is also closely related to sympathetic activity and hence level of emotional stimulation. Taggart²¹ observed increased levels during the stress of racing and Michael²⁹ during pneumoencephalography. A significant decrease in FFA during and outside TM practice in our study is suggestive of reduced sympathetic activity in the subjects, thereby, stabilizing autonomic nervous system. Present observations suggest that TM and yogaasnas practice bring about autonomic stability by decreasing responsiveness to sympathetic stimuli and are thus beneficial in releasing stress. In this respect TM is a better tool than yogaasnas. A combined practice by inducing balance is more effective in bringing about autonomic stability and then greater harmony with the environment. As such no published report is available on the influence of a combined practice of TM and yoga on autonomic activity which we have attempted to investigate.

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Table- 1

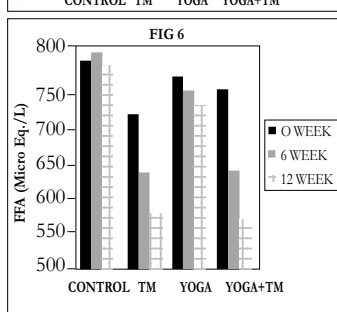
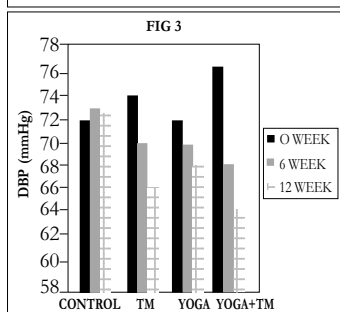
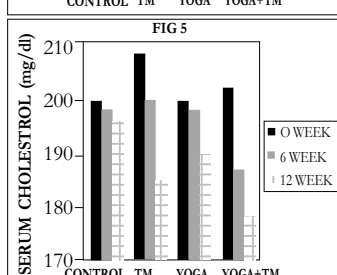
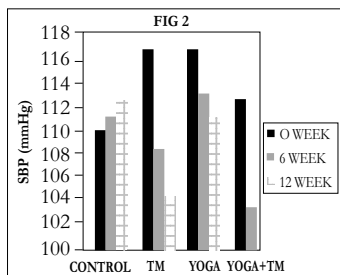
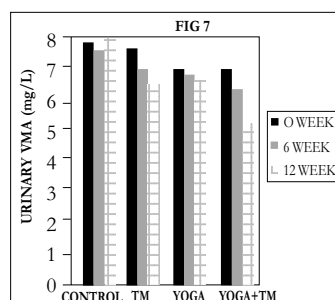
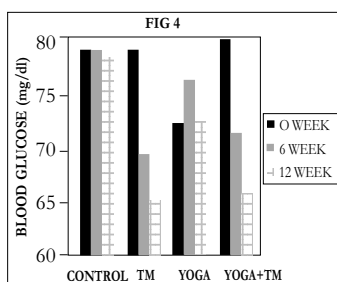
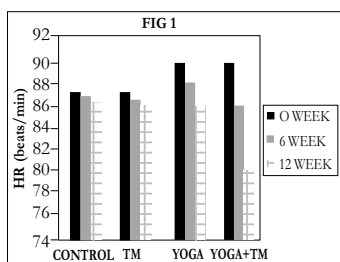
PARAMETER	HR	SBP	DBP	GSR	GLU.	LIPIDS	CHOLES.	VMA
TM	>0.10	>0.10	>0.10	<0.01**	<0.05*	>0.10	>0.10	>0.10
YOGA	>0.10	>0.10	>0.10	<0.05*	>0.05	>0.10	>0.10	>0.10
TM + YOGA	>0.10	>0.05	<0.05*	<0.001***	<0.05*	>0.05	>0.05	<0.05*

* – ‘p’ value < 0.05 – significant; ** – ‘p’ value < 0.01 – highly significant; *** – ‘p’ value < 0.001 – very highly significant

Table- 2

PARAMETER	HR	SBP	DBP	GSR	GLU.	LIPIDS	CHOLE	VMA
TM	>0.05	>0.05	<0.05*	<0.001***	<0.05*	<0.01**	<0.05*	<0.05*
YOGA	>0.10	>0.10	>0.10	<0.05*	>0.05	>0.05	>0.10	>0.10
TM + YOGA	<0.05*	<0.05*	<0.001***	<0.001***	<0.01**	<0.01**	<0.05*	<0.01*

* – ‘p’ value < 0.05 – significant; ** – ‘p’ value < 0.01 – highly significant; *** – ‘p’ value < 0.001 – very highly significant



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