Life saving skills and medical education

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Maternal mortality and injuries contribute to more than 20% of all deaths in India. These are largely preventable deaths as it requires medical interventions within a period of 6-36 hours which is mostly not available to populations with high mortality due to these causes. Prevention of anemia and puerperal sepsis, improved surgical interventions and universal access health care services are the solution to the problem. The fifth Millennium Development Goal, signed by 189 countries at the turn of this Century requires that the all signatories work to reduce maternal mortality by 75%. With appropriate interventions this is possible as was done by Sweden and USA a few decades ago and more recently by Romania, Thailand, Malaysia and Sri Lanka. Sweden had a ratio of 300 deaths per 100000 live births, and USA had 600 deaths per 100000 live births in 1935 which was reduced to 20 and 30 deaths per 100000 live births by 1960. Today India has MMR of 440 per 100000 livebirths compared to 50 for Thailand and 120 for Sri Lanka. In South Asia, Afghanistan with a higher MMR is no consolation for India if the political and economic situation of the two countries are compared.

In a similar way injures as a cause of death and disability is shockingly high for a country which boasts of health care facilities which attract medical tourists. More than 170,00,000 hospitalizations in this country are due to injuries and 11% all deaths are trauma related. Poor access to health care facilities for a majority of the population particularly the poor, is a major cause.

Emergency Surgical Care Services

Lack of health care services in large part of India particularly rural India is well documented. A deeper look at the problem will reveal that even the services that are available are suboptimal. If deaths due to surgical causes are to be reduced the policies and programs should aim at making available, sustainable basic surgical services in rural resource poor health care centers.

Some of the key issues for suboptimal emergency surgical services in rural areas are:

- Poor rural health care infrastructure
- In adequate health care personnel in rural areas
- Lack of emergency life saving skills among health care personnel
- Lack of appropriate legislation to protect health care personnel in emergency situations

Excessive reliance of medical manpower for providing even basic health care needs has been a flaw in our policy. Even in developed countries like USA, rural health practitioners are from a stream different from the medical practitioners. A radical new thinking is required in health manpower development of India. This includes development of skills that are required in emergency situations.

Some essential skills that are required for all rural healthcare personnel are:

- Central venous access
- Endotracheal indtubation
- Cricothyriodotomy
- Recognition and management of pneumothorax
- Control of bleeding- uterine, trauma
- Basic life support
- Prevention of sepsis
- Patient safety

Medical Education and Patient care Skills

The present levels of IMR and MMR were achieved in India nearly 20 years back. There have been several interventions to reduce these health indices without much success. During this period more than 100 medical colleges have been added to the country producing an additional 10,000 medical graduates per year. Even though we are adding 28,000 new medical graduates every year to existing numbers we are not making any difference to the poor health care indices of the country as a whole. There has been no study or evaluation of the medical education system in the country such as the Flexner Study undertaken by Carnegie Foundation in 1908, to evaluate the skills of medical graduates from medical schools of USA and Canada. One of the substantial observations for the study was " for the past twenty five years there has been an over production of ill trained and uneducated medical practitioners. This has been in absolute disregard to the public welfare and without any serious thought to the interests of the public". It is this kind of evaluation that has led to the improvement of medical education standards in USA and Canada.

In the absence of an evidenced based evaluation one has to go by circumstantial

evidence which by and large points to the production of large number of medical graduates and postgraduates with inadequate life saving skills. The system of medical education in this country which prepares the students to pass examinations with very little focus on patient care skills and competencies has led to a situation where medical graduates lack confidence to work independently especially in rural areas. Medical graduates continue to spend time with their books to prepare for postgraduate entrance examinations beyond their graduation and seek practical knowledge much later, which becomes an illusion as facilities for learning skills are limited. They are frustrated and represent a lost opportunity to provide a service and a threat to the health of the nation.

A New Paradigm of Skills Training

Reforms to medical education in India are long over due If the Milleneum Development Goal of reducing Maternal Mortality by 75% is to achieved, we need other strategies to activate our health human power. Multi skill training, IT based learning techniques are a few suggestions. Many success stories of bringing down MMR especially Thailand, Sri Lanka, Malaysia are due to innovations. Attempts at innovation in training health care manpower have had limited success in countries like Mozambique.

NBE response

The National board of Examinations has introduced public health related courses in three essential disciplines. The DNB Family Medicine envisages to develop family physician concept which has been lost after specialization has become the career ambition of medical graduates. The DNB in Rural Surgery hopes to create surgical specialist for rural emergency surgical needs. The training of the Rural Surgeon would ensure that he functions as a versatile surgeon dealing with obstetrical emergencies, orthopedic, abdominal and other emergencies. A one year certificate training program in Aneasthesia for medical graduates will provide for the anesthetic services in the rural hospitals.

WHO and Emergency, Essential Surgical Care

Surgery has come into the public health domain with the creation of the Emergency and Essential Surgical Care Project under the Essential Technologies Department (www.who.int/su rgery). This department will support countries in capacity building to reduce death and disability as a result of injuries, pregnancy related complications and HIV through strengthening basic skills of health providers to manage essential emergency and surgical procedures at resource limited health care facilities.

This team will be responsible for ensuring efficacy, safety and equity in the provision of clinical procedures in surgery, anaesthetics, obstetrics and orthopaedics, particularly at the district hospital level

New Initiatives, innovations for change

The coordinated model system for surgical services in peripheral/rural hospitals suggested by World Bank requires the coordination and integration of the following:

- Wireless communication
- Continuing education programs
- Regionalised supply system for essential drugs, equipment and surgical material
- Ambulance services
- Uniform data collection system
- Coordinated ongoing monitoring of quality and outcomes

Wireless communication in India has reached many remote parts of the country. With this infrastructure already in place, putting together a continuing education program based on adult learning pedagogies and methods, Information Technology based tools like virtual libraries and simulation laboratories for skills training will not be too difficult. Much of these material is already available on the internet (www.who.int/surgery). Training programs for trainers and training centres in district hospitals, should be quickly added particularly in states and regions where the health indices are poor. Legislations and regulations to empower the local governments to generate appropriate health care manpower to provide healthcare services in their region is another dire need. The present centralized regulatory structure is to the disadvantage of rural areas.

Surgery has an important role as public health strategy in atleast four important areas:

- In the prevention of death and disability in injured patients by the provision of timely expert and complete initial treatment
- In the timely intervention in obstructed labor, in pre and post partum heamorhage and the other obstetrical complications
- In the provision of competent surgery to treat a wide range of abdominal and non-abdominal emergencies
- In the surgical care of several elective surgical conditions that have a significant effect on quality of life, such as cataract, otitis media, clubfoot, hernias and hydroceles.

Post graduate medical education in India needs a radical change perspective. A public health approach is essential if the number of preventable deaths are to be reduced in our lifetime.

National Board of Examinations- its role in Postgraduate Medical Education in the Country

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The National Board of Examinations was established in 1975 on the basis of the Report of a Working Group set up by the then Prime Minister of India Smt. Indira Gandhi. The terms of reference of the Working Group were as follows:

"• To examine the need for uniformity in the standard of examination for the award of postgraduate degrees and diplomas.

• To suggest ways and means of achieving it either through one or more national examining bodies, in replacement of or in addition to the existing system.

• To recommend the nature, composition, scope, functions and power of such national examining body/bodies……."

The Working Group recommended that

"There is an urgent need for an organization that could conduct postgraduate examinations at national level of high academic standards to ensure:

- A high quality of medical services given to the people by doctors certified by such examinations;
- Raising of standards of medical education in general;
- Availability of prestigious qualifications within the country comparable to similar qualifications given in foreign countries and thus minimize the tendency of medical graduates to go abroad to acquire these degrees;
- National integration."

The National Board functioned as a wing of the National Academy of Medical Sciences from 1975 to 1982. The Government of India, after a review, took a policy decision to make it an independent autonomous body with effect from March 1, 1982 under the Ministry of Health and Family Welfare as a registered society.

Objectives of National Board of Examinations

The main objectives of the National Board of Examinations are as follows:

- The conduct of post-graduate examinations in the discipline of Modern Medicine and other allied sciences at the national level.
- To maintain a high standard of examinations to ensure that candidates have received adequate training both theoretical and practical, and are competent in every way to practice as specialists in their respective fields.
- To determine the general principles for the examinations, and the specialities in which the examinations will be conducted.
- To develop patterns of teaching in Post-graduate Medical Education in all its branches, other allied sciences including physical and biological sciences, so as to achieve high standard of medical education in all medical colleges and other allied institutions in India.
- To conduct experiments in new methods of medical education in order to arrive at satisfactory standards of education.
- To prescribe courses and curricula for post-graduate studies.
- To determine the nature of qualification to be awarded, hold examinations and grant such degrees, diplomas and other academic distinctions and titles in Post-graduate medical education and other allied sciences as may be laid down in the regulations.
- To organize Post-graduate courses, workshops, seminars and symposia and training programme of specialized nature.
- To undertake and provide for the publication of journals, research papers, leaflets and textbooks and to augments and maintain library information services for the furtherance of the objects of the Board.
- To collect, organize, disseminate and publish knowledge about medical and allied sciences.
- To institute offers and grants, prizes, awards, scholarships, research grants and stipends in furtherance of the objects of the Board.
- To undertake, aid, promote, guide and coordinate research of a high caliber in medical and other allied sciences including physical and biological sciences.
- To provide and promote effective linkages on a continuing basis between various scientific and research agencies/laboratories and other organizations working in the country in the field of medicine and other allied sciences.

National Board of Examinations super-structures

The various super structures for the Board are as follows:

Governing Board- for overall policy guidelines and monitoring.

Accreditation Committee- to establish & review the minimum criteria for hospitals; review the inspection reports and grant accreditation to hospitals; review the infrastructure and facilities and advice re-inspection of accredited hospitals.

Examination Monitoring & Review Committee.

Fellowship Committee.

Activities of National Board of Examinations

The main activities of the National Board of Examinations are as follows:

Accreditation of hospitals for DNB programmes

- Hospitals/ Institutions apply to National Board of Examinations for Accreditation
- Eminent experts in various fields are appointed by National Board of Examinations for inspection
- Report submitted to the high level accreditation committee of NBE
- Once approved the institution/ hospital is granted accreditation for 3 years
- Trainee(s) Admission Guidelines, Curriculum of the speciality, Thesis guidelines and other instructions are provided to the accredited speciality.

Maintenance of standards of training in hospitals

- Quarterly report of training sent by accredited hospital to National Board of Examinations is evaluated
- Periodic surprise visit by experts from National Board of Examinations is required
- Six monthly appraisal of Hospital, Trainees (Thesis, Log book, Concurrent assessment) and feedback for corrections is conducted
- Online monitoring of each candidate is being designed for near future

National Board of Examinations' training programmes

- **3 years DNB programmes in Broad specialities**-Anatomy, Biochemistry, Physiology, Pharmacology, Pathology, Microbiology, Forensic Medicine, General Medicine, Pediatrics, Psychiatry, Radio-therapy, Radio-diagnosis, Anesthesiology, Dermatology and Venereology, Respiratory Diseases, Nuclear Medicine, General Surgery, Orthopedic Surgery, Obstetrics & Gynecology, Ophthalmology, Oto-rhinolaryngology (ENT), Physical Medicine and Rehabilitation, Social and Preventive Medicine, Maternal and Child Health, Health Administration including Hospital Administration, Family Medicine, (General Practice), Immuno-haematology and Transfusion Medicine
- **3 years DNB programmes in Super-specialities**-Cardiology, Endocrinology, Nephrology, Neurology, Neonatology, Gastroenterology, Medical Oncology, Plastic Surgery, Paediatric Surgery, Peripheral Vascular Surgery, Neuro-Surgery, Genito-Urinary Surgery (Urology), Rheumatology, Surgical Gastroenterology, Surgical Oncology, Cardio-Thoracic Surgery, Clinical Pharmacology and Therapeutic.
- **Two years Post Doctoral Fellowship Programmes**-Critical Care Medicine, Reproductive Medicine, Cardiac Anesthesia, Minimal Access Surgery, Interventional Cardiology, Pediatric Cardiology, Vitero-Rentinal Diseases, Pediatric Intensive Care, Pediatric Hemato Oncology, Spinal Surgery, Hand and Micro Surgery, Trauma Care.
- **3 years DNB in Family Medicine (New Rules)**- Clinical skills in effective managements of common health problems (medical, surgical, obstetrics and gynecology, pediatrics, ophthalmology, ENT and medical emergencies) in the family.
- **3 years DNB in Rural Surgery**- After qualifying the final examinations the candidate should be able to function as a consultant (specialist) in Rural Surgery (multiple surgical disciplines) within the constraints of limited resources in the areas of - Basic & general surgery with emphasis on open surgeries; Basic orthopedics including trauma care; Obstetrics and Gynecology; Basics of anesthesia, ultrasound and X-Ray; Emergency care.
- **One year PG certificate courses in future**- Diabetes, Anesthesia, Emergency medicine, Reproductive and Child health, Gynecological endoscopy, Gynae urology, Rheumatology, Geriatrics, Pain and palliative care, Cranio-facial surgery, electro-physiology (cardiology), Embryology (ART Lab Technology), Sleep medicine, Sports medicine, Arthroscopy, Neuro-electrophysiology.
- **DNB Dental specialties**- Prostho-dontics, Oral and Maxillo-facial Surgery, Orthodontics and Conservative Dentistry, Peri-odontics, Oral Medicine, Oral Pathology, Community dentistry, Pedontics and Preventive dentistry.

Maintenance of standards for DNB training

- **Structured competency based**

curriculum-Aim & Objectives, Posting schedules, Syllabus, specification of skills/ procedures to be learnt, Methods of training, log book maintenance, reference books & journals, sample cases & sample questions, sample of log book, guidelines for thesis etc.

- **Workshops for faculty development for**-Training technology, Research methodology, Evaluation.
- **CME Programmes for DNB candidates**- in major specialties.
- **Counseling of DNB candidates**- Feed back on their performance, Guidance for attempting Theory & practical examination, Placement with other hospitals as observers.
- **Six monthly semester appraisal**- For institute infrastructure as per the given format; Concurrent assessment of DNB candidates in theory and practical skills as per the given format; Review of thesis work and log book.
- **Memorandum of Collaboration with Indira Gandhi National Open University (IGNOU) for**- developing need based post graduate medical educational programmes; development of learning materials; Joint conduction of interactive CME programmes for the students and teachers/ trainers and sharing of facilities and expertise etc.
- **Local network of DNB hospitals for joint academic activities**- In order to share the academic learning material the Board encourages the accredited hospitals to have academic networks for joint academic activities.
- **Special centers for DNB candidates who are academically weak**- Those candidates who are fail repeatedly, the Board on request places them in selected hospitals as observers for attending the academic programmes.
- **Learning material on web portal/ DVD/CDs**- Development of National Board of Examinations web portal with online- Query, chat forums, performance monitoring, feedback to candidates, and availability of technical material, examination facilities.

Maintenance of standards for DNB examinations

- **Standard procedures for examinations**- This is ensured by the actions such as- all new examiners are sensitized in the examiners workshops; independent non-examiner co-ordinator for each centre; independent appraiser appointed for new centers; confidential report by appraiser; written standard guidelines for examiners; individual DNB candidate is marked for various sub components of the examination like long case, short case, ward round, viva, instruments etc. on standard worksheet
- **OSCE (Objective Structure Clinical Examination)**-This is an innovation for uniformity and objectivity in practical examination. It is currently operational in Pediatrics, Ophthalmology, and ENT. It is being introduced in 2006-07 in Orthopedics, Dermatology, Psychiatry, Anesthesia
- **Standing Examination Monitoring and Review committee**- For analysis of results; review of test development and delivery; suggestions for policy change
- **DNB Vs MD/MS examination**- In DNB examination theory examination is first screening level of DNB candidates. Only those who qualify theory appear for practical examination. Different examiner assesses each theory paper. There are no internal examiners. The marks are given and minimum score of 50% in aggregate is required for passing the examination. The candidates appear in practical centers which are different than the place of their MBBS and DNB training Only those who qualify theory appear for practical examination

Students Support Services (SSS)

The following Students Support Services are available:

Student Support Services at the accredited hospitals

DNB-Coordinator cum Academic In charge /Director- Each National Board of Examinations accredited hospitals has one senior consultant designated as a DNB-Coordinator cum Academic In charge /Director. He /She is the intermediary between the hospital, DNB trainee and National Board of Examinations. His/her primary responsibility is to communicate and co-ordinate with National Board of Examinations in all respects pertaining to accreditation, training of DNB candidates, six monthly appraisals and examination. The name, phone numbers etc. of these Coordinators are available on the National Board of Examinations website (www.natboard.nic.in). All the latest circulars related to DNB programmes are sent by National Board of Examinations to DNB coordinators. The DNB Coordinator is supported by Academic In charge/Director for proper implementation of training programmes. He/she is expected to draw details of posting schedules, seminars, guest lectures and coordinate with various units or departments for DNB training programmes as per the National Board of Examinations curriculum. He/she also ensures that the speciality library has standard textbooks, reference books, at least one Indian and International Journal

in the all the specialities in which DNB programmes are being carried out. He also ensures Internet and Online Library facilities are provided to DNB candidates.

Thesis & Protocol Review Committee
Each accredited hospital has a Thesis Protocol Review Committee comprising of consultants from various accredited specialities to ensure that the thesis protocol of the DNB candidates are properly reviewed, and duly certified before they are sent to National Board of Examinations. The committee also periodically review thesis progress of the DNB candidates and makes suggestions for completion of the research studies. The committee is supported by a clinical ethical committee for research involving patients in clinical specialities.

Independent Local Appraiser- Since January 2006 independent local appraiser from the same city selected by National Board of Examinations conducts independent review of the accredited speciality every six months for the followings activities:

- **Review of Thesis protocol/ progress**- the appraiser participates in thesis protocol/ progress presentation & discussion; assist the DNB candidates in their thesis work by monitoring their progress and giving them suggestions. He/she gives specific remarks to improve the Thesis work after reviewing the objectives, methodology (sample size, sampling technique, data collection tools etc.), data analysis plan and statistical tests, results and discussion plan etc. of thesis of each candidate. These remarks are communicated in writing to the supervisor and the concerned candidate by the appraiser and a copy is sent to National Board of Examinations.
- **Review of Log Books maintained by DNB candidate**- He/she is expected to examine the log book maintained by the candidates and give specific remarks to improve the log book maintenance after reviewing the contents of the log book (name of procedure, details of the case, salient findings, remarks of the supervisor for the improvement of the candidate etc). These remarks are communicated in writing to the supervisor and the concerned candidate by the appraiser and a copy be sent to National Board of Examinations.
- **Conduction of theory assessment**- He/She prepares question paper containing ten short structured questions in the speciality on the topics covered during the preceding six months and evaluates the answer sheets. He/she also maintains total confidentiality in these activities. The arrangements for six monthly theory and practical examination are made by local accredited hospitals/ institutions.
- **Conduction of practical assessment**- He/she formally conducts practical examination (On the topics/areas covered in preceding six months). The practical has long case, short cases; ward round, spots and viva voce as per the DNB format. He/she communicates the result of assessment to the concerned candidates along with detailed feed back on their performance. He/she also gives detailed suggestions to each candidate in writing for improving his/her performance. He/she acts as counselor and gives specific remarks for improving the overall performance level of the candidate. These remarks are communicated in writing to the supervisor and the concerned candidate by the appraiser and a copy is sent to National Board of Examinations. He/she prepares the Examination worksheet for each candidate and submits the same to the concerned hospital for records with a copy of the same to the National Board of Examinations.
- **Verification of training Infrastructure**, Man Power, Library and Other Facilities: He/she sends six monthly report on the infrastructure, patient load and manpower in the concerned speciality of the accredited hospital, to Executive Director, National Board of Examinations, Ring Road, Ansari Nagar, New Delhi-110029. The reports are reviewed by the National Board of Examinations and deficiencies are communicated in writing to the Head of the hospitals for compliance.
- **Feedback from DNB candidates**- Independent and Confidential feedback from DNB candidates is obtained by the Board on training activities conducted by the hospitals in terms of lectures, case presentations, seminars, journals clubs, thesis progress discussions, library facilities, internet facilities, clinical procedures conducted by DNB candidates under supervision/ independently, difficulties/ deficiencies/suggestions for improving training etc. The format of the feedback is available on the National Board of Examinations website (www.natboard.nic.in).

Student Support Services available at National Board of Examinations website (www.natboard.nic.in)

General information- Circulars/letters related to policy matters like payment of stipend to the DNB Candidates, Annual Fee Structure under various heads to be paid by DNB Candidates, Thesis Status, Dates of Interactive CME Programmes

using IGNOU nation Dates, Theory and Practical Results etc. are displayed on the National Board of Examinations website.

Information related to accredited hospitals- The availability of DNB Seats in various institutions, Names and Phone Numbers of DNB Coordinators, details of minimum criteria for patients, support services, operative procedures, infrastructure, number of consultants, library facilities, support staff, details of guidelines for six monthly appraisals etc. are displayed on the website for the benefit of DNB Candidates.

Learning material for DNB candidates- The Board website has key points for practical case presentations and technical material for major specialities, curriculum details, exercises and handouts on research matters, sample questions for theory, National Board of Examinations Journal of Post-Graduate Medical education, Training and Research (which contains theme based review articles prepared by experts)

Information details related to National Board of Examinations as required under Right for Information Act- The website contains all the information related various administrative units, committees, officers and staff members etc. as required under the Act for the benefit of general public as well as DNB Students.

Online facilities for handling queries from DNB candidates- the email-id nbefellow@yahoo.com given on the website where the DNB Candidates can send their queries by email. These queries are replied through email / telephone/ mail.

Student Support Services available at National Board of Examinations, Ansari Nagar, New Delhi Office

- Telephone Queries are handled by the staff at the reception by directing the calls received to the concerned officers/staff members.(Phone Number– 011-26589517)
- FAX Queries are received on FAX Number 011-26589781.
- The DNB candidates/visitors visiting the office fill up the query form and submit to the staff at the reception. These queries are either answered immediately or in case detailed record review is required these are answered on the phone number given on the query format by the candidates/visitors.
- The Notice Board at the reception displays the latest circulars / dates related to DNB Examination.
- Counseling services: The candidates have the access to counseling services if requested. The requests are to be sent to the Executive Director National Board of Examinations, Ring Road, Ansari Nagar New Delhi-110029
- Special placement of DNB candidates in hospitals as observers for participating in academic activities are also available to candidates on request.

Strengths of National Board of Examinations

- Autonomous body with clear mandate to act as an apex body for post graduate medical education and training.
- National perspective of the activities
- Well defined, uniform standardized mechanisms for training and examination
- Quality and standard of the DNB programmes and examination well accepted within and out side the country
- DNB alumni well respected abroad
- More than 1500 experts from all over the country are involved in examination and accreditation activities every year
- More than 455 hospitals and institutions in the private sector with patient load, facilities and more than 5000 specialists provide training opportunities to less privileged but meritorious students from all over the country
- Nearly 20,000 candidates have passed National Board of Examinations till date
- Networking with other organizations and institutions like IGNOU and other primer post graduate medical institutions etc, would further enhance the reach of the Board' activities.
- Regular capacity building programmes in the form of CME, workshops, consultations with experts etc. ensures the continues updating and modifications of the training and examination mechanisms
- With wide variety of post graduate medical training programmes (43 Medical specialties, 9 Dental specialties, 14 post doctoral programmes etc.) Available in the country, the Board is preventing "Brain Drain" of medical manpower.
- The need based medical manpower in the form of DNB (Family medicine), DNB (Rural Surgery), and in future short term post graduate certificate courses etc. would help in meeting the current challenges of the health services.
- Currently, nearly 3500 DNB seats are available every year in Broad & Super Speciality (2000 CET and 1500 post diploma)

- Current capacity of DNB training seats can be further enhanced by nearly 6000, if the directure of the Ministry of Health & Family Welfare, GOI, for starting DNB course in medical colleges with surplus capacity of post graduates teachers (1:1) are followed by all medical colleges
- National Board of Examinations thus has the potential for training nearly 10,000 post graduate medical students each year, which exceeds the capacity of any other organization in the country (even all medical colleges)
- DNB degrees being equated with M.D/MS/DM/MCh for all purposes

National Board of Examinations requires the statuary status as an apex Post graduate Medical Education body, with powers to promote the post graduate medical education in the country. This would ensure development of need based quality postgraduate medical manpower in the country.

History of ophthalmology

The eye, its structure and mechanism, has fascinated all since ancient times.

Sushruta wrote *Sushruta Samhita* in about 5th Century BC in India, describing about 72 eye diseases, fine ophthalmological surgical instruments & eye surgery and was the first ophthalmic surgeon. Arab scientists wrote about and drawn the anatomy of the eye- the earliest known diagram being in Hunain ibn Is-hâq's *Book of the Ten Treatises on the Eye.*

The pre-Hippocratics based their anatomical conceptions of the eye on speculation. They recognised the sclera and transparent cornea running flushly as the outer coating of the eye, with an inner layer with pupil, and a fluid at the centre. Alcamaeon and others believed that this fluid was the medium of vision and flowed from the eye to the brain via a tube. Aristotle dissected the eyes of animals, and discovering three layers, found that the fluid was of a constant consistency with the lens forming after death, and the surrounding layers were seen to be juxtaposed & explained the existence of 3 tubes from the eye, not one. One tube from each eye met within the skull.

Aëtius tells us that Herophilus dedicated study to the eye which no longer exists. No mss. from the region and time are known to have survived, leading us to rely on Celsius' account- which is seen as a confused statement not knowing the subject. From Celsius it is known that the lens had been recognised, and they no longer saw a fluid flowing to the brain through some hollow tube, but likely a continuation of layers of tissue into the brain. Celsius failed to recognise the retina's role.

Rufus recognised a modern eye, with conjunctiva, extending as a fourth epithelial layer. Rufus was the first to recognise a two chambered eye - with one chamber from cornea to lens (filled with water), the other from lens to retina (filled with an egg-white-like substance). Galen remedied some mistakes including the curvature of the cornea and lens, the nature of the optic nerve, and the existence of a posterior chamber. Yet it was not advanced upon again until after Vesalius. A ciliary body was then discovered and the sclera, retina, choroid and cornea were seen to meet at the same point. The two chambers were seen to hold the same fluid and the lens attached to the choroid. Galen had the notion of a central canal, though he dissected the optic nerve, and saw it was solid. He mistakenly counted seven optical muscles, one too many. He also knew of the tear ducts.

Understanding of the eye was slow to develop as the lens was perceived to be the seat of vision. It was corrected when Fabricius and his successors correctly placed the lens and developed the notion of the eye's structure. They removed the idea of Galen's 7th muscle (the *retractor bulbi*) and reinstated the correct curvatures of the lens and cornea & stating the ciliary body as a connective structure between the lens and the choroid.

The 17th and 18th century saw the use of hand-lenses (by Malpighi), microscopes (van Leeuwenhoek), preparations for fixing the eye for study (Ruysch) and the freezing of the eye (Petit). Some mistakes persisted: the changed size of pupil, the existence of the posterior chamber, and the nature of the retina. In 1722 Leeuwenhoek noted the existence of rods and cones though they were not properly discovered.

The establishment of the first dedicated ophthalmic hospital in 1805 - now called Moorfields Eye Hospital in London, England was a transforming event in modern ophthalmology. Clinical developments at Moorfields and the founding of the Institute of Ophthalmology by Sir Stewart Duke-Elder established the site as the largest eye hospital in the world and a nexus for ophthalmic research.

Breast Cancer and Pregnancy

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Breast cancer occurring within pregnancy or within 1st year after delivery is considered as pregnancy associated breast cancer (PABC). It is the most common cancer associated with pregnancy. 1.5% of the women are pregnant at the time of diagnosis of breast cancer. Its incidence is 1: 3000 deliveries, but because of late child bearing it can go up to 1 in 1000 deliveries. An obstetrician having experience of 250 deliveries per year will require 40 years of experience to see 2 – 3 cases of PABC.

Breast cancer pathology is similar in age–matched pregnant and non pregnant women. Hormone receptors are usually negative in pregnant breast cancer patients, but this may be the result of receptor binding by high serum estrogen levels associated with pregnancy.

The natural tenderness and enlargement of the breast of pregnant & lactating women may hinder detection of discrete masses and therefore early diagnosis of breast cancer. The weight of breast approximately doubles, increases in vascularity by 180% and also density increases by proliferation of mammary epithelium. As a result there is delay in diagnosis, with an average reported delay of 5 to 15 months from the onset of symptoms. Because of this delay cases are detected in late stages then in a non pregnant, age matched population. To detect the cancer early, women should be encouraged to practice breast self examination & undergo a regular breast examination as a part of prenatal examination by the doctor.

If any abnormality is found diagnostic approaches such as ultrasound and mammography may be used. With proper shielding mammography poses little risk of radiation exposure to the fetus. Accuracy of mammography is reported to be >80%. Ultrasound is frequently used to asses the extent of the disease and also to guide the biopsy of the mass and lymph nodes. Specificity of ultrasound is reported to be 100% in breast cancer occurring during pregnancy. Biopsies for cytological evaluation may be done with a fine needle aspiration (FNA) from suspicious breast mass or/ and suspicious nodes. However the preferred technique is core needle biopsy.This provides tissue for histological confirmation of the invasive disease as well as provides adequate tissue for hormone receptors and HER-2-Neu analysis. To avoid a false positive diagnosis as a result of misinterpretation of pregnancy related changes, the pathologist should be informed that the patient is pregnant.

After confirmation of diagnosis, patient should be staged X-ray chest with proper shielding, and US Scan abdomen is recommended. Bone scan skeletal survey is not usually done. MRI study of the spine can be done if it is indicated.

Surgery either in the form of modified radical mastectomy on conservative breast surgery is the standard of care in the early stage disease. Mastectomy can be performed in all the trimesters, 2nd and 3rd trimester usually preferred. Conservative surgery though it can be done in 2nd and 3rd trimester but 3rd late trimester is preferred.

Most of the patients in pregnancy present with locally advanced disease and 70% of the patients have lymph nodes positive. Invariably majority of the patient require chemotherapy. (CAF/ CEF/FAC) Adriamycin based chemotherapy is safe during pregnancy & can be safely used in 2nd & 3rd trimester from 15th week to 35th week.

Radiotherapy, Hormone therapy (Tamoxifen), Taxanes & Herceptin are not to be used during pregnancy but can be used post partum when indicated. Chemotherapy is avoided during lactation.

Overall survival of pregnant women with breast cancer may be worse than in non pregnant women in all the stages, however this nay be attributed primarily due to the delay in the diagnosis, big tumors, positive lymph nodes, poorly differentiated tumors, raised ER, PR negativity and increased HER-2-NEU expression (30%).

Termination of the pregnancy has not shown to have any beneficial effect on the breast cancer outcome and is not considered to be a therapeutic option. It can be considered however, based on the age of the fetus and if the treatment warrants aggressive chemotherapy / radiotherapy. The clinician can safely use any mode of therapy without bothering its effect on the fetus.

Continuation of pregnancy is safe, no teratogenic or mutagenic effect on the fetus by CEF, chemotherapy has been observed with no obvious growth retardation of fetus, premature delivery, baby is healthy with normal growth.

I have personal experience of treating 5

Patients of PABC and in two of them chemotherapy (CEF) was used, where there was no deleterious effect on mother or baby and both the deliveries were normal.

Lactation is safe from the normal breast and even 1/3rd of the patients undergoing conservative therapy can lactate.

Pregnancy after the diagnosis of breast cancer is recommended after a gap of 3-5 year, it does not have any deleterious effect on the course of fetus.

Early detection of breast cancer by frequent examination, ultrasono mammography, FNA / Core biopsy to establish the diagnosis, surgical intervention with or without chemotherapy (CEF regimen) during 2nd/3rd trimester will help to drastically & dramatically improve the prognosis in PABC and pregnancy can be safely continued without any deleterious effect on the delivery and the fetus whatsoever.

References

1. American Cancer Society, Breast Cancer Facts and Figures, Atlanta; American Cancer Socienty 2003.
2. Gwyn K, Theriault R. Breast Cancer durng pregnancy; Oncology (Huntingt) 2001; 15 (1) 39-46.
3. Merchant D. Breast Cancer in Pregnancy. Clin. Obstet Gynecol 1994;37:993-997.
4. Smith LH, Dalrymple JL, Leiserowitz GS, Obstetrical deliveries associated with maternal malignancy in California 1992 through 1997. Am. J. Obstet Gynecol Jun 2001; 184 (7): 1504-1512.
5. Elledge RM, Ciocca DR, Langone G, Estrogen receptor, progestron receptor and HER-2/ neu protein in breast cancers from pregnant patients. Cancer 1993;71 (8); 2499-506.
6. Shepherd J. Cancer in pregnancy. Preg Obstet Gynecol 1996; 12:219-234.
7. Berry DL, Thericeult RI, Holmes F A et al. Management of breast cancer during pregnancy using standardized protocol. J. Clin Oncol; 1999:17:855
8. Nicklos AH, Baker ME. "Imaging Strategies in the Pregnant Cancer Patient Seminar. Seminar Oncol 2000; 27:623.
9. Helewa M, Levisque P, Provencher D, et al. Breast Cancer, Pregnancy and Breast Feeding. J. Obstet Gynecol Can 2002; 24:164.
10. Guinee VF, Olsson, H, Moller T, et al. Effect of Pregnancy on prognosis for young women with breast cancer. Lancet 1994 343 (8913); 1587-9,.
11. Petrik JA, Dukoff R, R. ogutko A. Prognosis of pregnancy associated breast cancer. Cancer 67 1991; (4): 869-72.
12. Espic M, Cubier C. Treating breast cancer during pregnancy, what can be taken safely? Durg Safety 1998; 18:135-142.
13. Keurer HM, Gwyn K, Ames FC, Theriault RL. Conservative Surgery and Chemotherapy for Breast Cancer during pregnancy. Surgery 2002; 131 (1): 108-110.
14. Gentilini O, Cremonesi M, Trifiro G et al. Safety of Sentinel Node Biopsy in Pregnant Patient with Breast Cancer. Ann Oncol 2004; 15 (9): 1348-1351.
15. Germann N, Goffinet F, Gold Wasser F. Anthracyclins During Pregnancy. Embryofetal outcome in 160 patients. Ann Oncol. 2004; 15(1): 146-150.

Artificial Heart

AbioCor Total Artificial Heart is the first electro-hydraulic heart implanted in a human. Approved by the United States Food and Drug Administration for clinical trails, the AbioCor was implanted in Robert Tools by cardiac surgeons Laman Gray and Robert Dowling on July 2, 2001, at Jewish Hospital in Louisville, Kentucky. The historic operation marked the first time an artificial was used as a permanent replacement for a human heart since the air-powered Jarvik-7 artificial heart was implanted more than fifteen years before.

The AbioCor is a two-chamber pump designed to perform like a natural human heart. It is powered by batteries, and pumps more than 2.5 gallons of blood a minute to the lungs and then to the rest of the body.

Tools, who suffered from irreversible congestive heart failure, chose to have his diseased heart removed and replaced with the plastic and titanium pump. He lived for five months, well beyond the clinical trials goal of sixty days.

The development of the AbioCor involved a team of engineers, scientists, and physicians from across the United States. Completely contained within the body, no tubes protrude through the skin, nor is the patient tethered to a noisy bedside console, as with air-powered hearts. Instead the heart is powered by rechargeable batteries & microcomputer technology that regulates the heartbeat according to the patient's activities.

Foreign Bodies of the Airway

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Foreign body aspiration is a major cause of morbidity and mortality, especially in children. The diagnosis of foreign body aspiration is a dilemma for otolaryngologists and pediatricians as often there is no history of foreign body aspiration. A high index of suspicion and prompt treatment alone can help in managing the condition successfully and preventing complications. Until the late 1800s, foreign bodies were removed by bronchotomy. Gustav Killian, in 1897, was the first to remove a foreign body from the lower air passages with a rigid bronchoscope. In the early 1900s, Chevalier Jackson revolutionized foreign body removal with his per oral endoscopes. Subsequently, the evolution of the rod-lens system and improvements in anesthesia have made foreign body removal from the airway a very safe procedure.

Incidence

Foreign body aspiration has two peaks: in children under the age of 3 years and in adults above the age of 70 years. It is more common in infants and young children as they are curious, tend to explore the surroundings, have a tendency to put everything in their mouth , lack molars for proper grinding of food, lack coordination of swallowing and glottic closure and tend to run or play while eating leading to aspiration. Adults who are unable to protect the airway, such as those who lack molars for grinding food or have mental retardation, alcoholism, psychoses and neurologic disorders are at risk of aspiration due to decreased airway protective mechanisms (Kavanagh, 1999). Foreign body aspiration is more common in boys than in girls with a male to female ratio of 2:1 (Rothman, 1980), although the cause for this is not known.

Nature of foreign bodies

Airway foreign bodies are commonly food items; peanuts are the commonest, followed by carrots, popcorn, beans and fruit seeds. Dried foods and vegetable foreign bodies swell up and cause a reaction leading to congestion and oedema of the respiratory mucosa. Other non food items are rubber balloons, plastic toys, teeth, dentures, glass or metal (pins, needles, battery cells etc.)

Pathophysiology

The human airway has been provided with a number of protective mechanisms. These include the epiglottis and the arytenoid cartilages which protect the laryngeal inlet; intense spasm of the true and false vocal cords whenever any objects touch the vocal cords and a highly sensitive cough reflex with afferent impulses generated throughout the larynx, trachea, and the entire proximal tracheobronchial tree. Despite these protective reflexes foreign bodies are aspirated. Large foreign bodies can lodge in the supraglottic area, while the smaller ones will pass down through the larynx into the trachea or bronchi. Sharp foreign bodies (e.g pins, needles, fish bones etc.) can lodge anywhere in the laryngobronchial tree. Most foreign bodies get lodged distal to the larynx and trachea in the right main stem bronchus as (1) the diameter of the right main bronchus is larger than the left (2) the angle of divergence from the trachea is smaller on the right and (3) airflow through the right lung is greater than through the left.

Clinical features

There are three phases of foreign body aspiration: the initial phase of choking, gagging and wheezing while eating a meal followed by a symptom -less middle stage and finally the late symptoms of obstruction (recurrent attacks of pneumonia) and inflammation (hemoptysis). In case of a large laryngeal foreign body there may be cyanosis and acute respiratory distress leading to even death or hypoxic brain damage unless resuscitative measures are undertaken. Typically such patients place their thumbs and index fingers around their neck and are unable to speak or cough. However in many cases, the choking episode is not seen or sometimes not remembered. A partially obstructing foreign body will cause aphonia, change in voice, pain in throat, croupy cough, dyspnoea, wheezing and haemoptysis. A loose foreign body in the trachea may move up and down between the carina and the undersurface of the vocal cords causing "audible slap" and "palpatory thud". Occasionally, asthmatoid wheeze may be heard at the patient's open mouth. Often the patients may present with symptoms of non-resolving pneumonia, recurrent pneumonia, lung abscess, focal bronchiectasis or hemoptysis. Findings include abnormal airway sounds, such as wheezing, stridor, or reduced breath sounds. These sounds are often unilateral. If the foreign body

is in the extra thoracic trachea, the foreign sounds are inspiratory while the sounds are expiratory, symmetric but more prominent in the central airway if the foreign body is in the intra thoracic trachea. In case of a bronchial foreign body the breath sounds are usually asymmetric. However a lack of findings on physical examination does not preclude the possibility of an airway foreign body.

Diagnosis

Diagnosis depends upon detailed history of foreign body ingestion, physical examination and radiographs of the neck and chest.

Plain radiographs: Anteroposterior (AP) and lateral neck imaging, inspiratory and expiratory posteroanterior (PA) chest radiographs and lateral chest X-rays. Obtaining two views of the foreign body helps in determining its exact location and excludes the presence of superimposed multiple foreign bodies. In patients who are unable to cooperate for an expiratory film (e.g. children),decubitus Xray -chest or fluoroscopy may show hyperaeration. Most foreign bodies are radiolucent and in the trachea may show a subglottic opacity or swelling from airway inflammation on PA and lateral neck radiographs (Esclamado, 1987). A plain X- ray chest may show an area of focal over inflation or an area of atelectasis, depending on the degree of obstruction. If the material completely occludes the airway (stop valve), the radiograph will show opacification of the distal lung as the residual air in the bronchi is absorbed and no air entry is possible. In cases of partial obstruction, progressive ball valve obstruction is visible, resulting in focal over inflation in the area of the lung directly connected to the affected airway.

CT SCAN chest: May demonstrate the foreign body in the airway, focal airway edema, or focal over inflation not detected in the plain radiographs.

MRI Many authors have reported the use of MRI in identifying aspirated peanuts (Kitanaka, 1992; O'Uchi, 1992; Kimura, 1996; Morijiri, 1994). Using T1-weighted images, these authors demonstrated peanuts with the direct depiction of the high signal intensity emitted by their fat content surrounded by low-intensity lung tissue.

Differential diagnosis

- Asthma
- Bronchitis
- Arteriovenous malformation
- Atelectasis
- Bacterial tracheitis
- Carcinoma
- Croup (laryngotracheobronchitis)
- Epiglottitis
- Esophageal foreign body
- Granuloma
- Papilloma
- Retropharyngeal abscess
- Tracheal mucus
- Pneumonia

Management

Patients with complete airway obstruction are typically aphonic and unable to breathe. In these cases the use of the Heimlich maneuver can help to dislodge the foreign body and prevent hypoxia or death. Patients who are coughing, gagging, and vocalizing have partial obstruction. Most patients who arrive at the hospital are beyond the acute stage and are often not in respiratory distress. In cases with a high index of suspicion, a bronchoscopy is advisable even if the foreign body does not show up on any of the radiographic studies.

Bronchoscopy: Age-appropriate endoscopes, foreign body removal forceps and anesthesia equipment should be selected before the patient enters the operating room. Inhalational anesthetics are used to anesthetize the patients. The patients are kept spontaneously breathing throughout the procedure for control of the airway. In case of laryngeal foreign bodies, an insufflation catheter through the nose with the tip in the hypopharynx can be used to maintain anesthesia and oxygenation. The laryngoscope tip is placed in the vallecula for exposure, and the foreign body is visualized in the larynx and removed with appropriate foreign body forceps. After removal, the larynx is reassessed for other foreign bodies. In tracheobronchial foreign body removal, the bronchoscope is inserted into the airway after visualizing the vocal cords and continuous ventilation of the patient is provided through the ventilating arm of the bronchoscope. In a patient with a bronchial foreign body, the unaffected side is examined first. The bronchoscope is then placed immediately above the foreign body. Secretions are gently suctioned around the object. The patient is oxygenated with 100% oxygen before any attempt at removal. The forceps are placed through the bronchoscope, and the object is grasped after complete visualization of the foreign body. The bronchoscope is advanced to the foreign body while the surgeon continues to grasp the object. The foreign body, foreign body forceps, and bronchoscope are removed as a unit, and the bronchoscope immediately is returned to the airway for ventilation and reassessment for other foreign bodies. Sometimes foreign body may be difficult as large objects are unable to pass through the larynx and have to be broken into pieces and removed. If the object cannot pass through the larynx, a tracheotomy may have to be performed to remove the object through the tracheostoma. At times, the object becomes embedded into the surrounding mucosa because of edema caused by the object or because of multiple failed

attempts at removal. In such situations, it is advisable to wait for 48-72 hours to allow the oedema to subside before attempting again. Occasionally thoracotomy may be necessary when the object stays embedded and endoscopic attempts at removal fail. Foreign bodies in the distal bronchial segments may be removed with the use of a Fogarty endovascular catheter through the suction port of a rigid bronchoscope. The pointed end of sharp foreign bodies tends to engage in the mucosa, causing the object to tumble with the point trailing. In such cases the bronchoscope is placed into the airway, and, using foreign body forceps, the pointed end of the object is disengaged from the mucosa, moved distally, and then removed. Pin-bending forceps may be used in certain situations. Safety pin removal can be performed endoscopically by sheathing the pointed end into the endoscope and locking the keeper outside the endoscope. Postoperatively steroids may be given to reduce aiway oedema Chest physiotherapy is performed after foreign body removal to help remove secretions. Chest radiographs can be performed postoperatively to confirm improvement in the condition or if the patient's signs and symptoms persist or worsen.

Complications

Complications are often due to a delay in diagnosis. Pneumonia and atelectasis are the most common complications secondary to removal of bronchial foreign bodies. Bleeding can occur from granulation tissue surrounding the foreign body or erosion into a major vessel. Pneumothorax and pneumomediastinum can result from an airway tear

References

1. Esclamado RM, Richardson MA: Laryngotracheal foreign bodies in children. A comparison with bronchial foreign bodies. Am J Dis Child 1987 Mar; 141(3): 259-62
2. Kavanagh PV, Mason AC, Muller NL: Thoracic foreign bodies in adults. Clin. Radiol 1999 Jun; 54 (6): 353 -60
3. Kimura H, Aso S, Asai M et al. Magnetic resonance imaging of an inhaled peanut. Ann. Otol. Rhinol. Laryngol. 1996; 195 (7): 574 -6
4. Kitanaka S, Mikami I, Tokumaru A, O'Uchi T: Diagnosis of peanut inhalation by MRI. Pediatric radiol. 1992; 22 (4): 300 -1
5. Morijiri M, Seto H, Kageyama M et al. Assessment of peanut aspiration by MRI and lung perfusion scintigram. J. Comput Assist Tomogr: 1994; 18 (5): 836 -8
6. O'Uchi T, Tokumaru A, Mikami I et al. Value of MR imaging in detecting a peanut causing bronchial obstruction AJR Am J Roentgenol 1992; 159 (3): 481 -2
7. Rothman BF, Boekman CR :1980: Foreign bodies in the larynx and tracheobronchial tree in children. A review of 225 cases. Ann.Otol. Rhinol.Laryngol. 1980; 89 (5): 434-6
8. Tan HK, Brown K, McGill T, et al: Airway foreign bodies (FB): a 10-

Yorick

Yorick is a plastic male skeleton imbedded with electronic and mechanical devices used to replace worn body parts. Yorik was created by Ed Mueller, an engineer in the Division of Mechanical and Material Sciences at the United States Food and Drug Administration (FDA), in Washington, D.C.

Yorik often made appearances at schools, Scout meetings, and hospitals to educate students about bionics and currrent research on implant design development.

Some of the devices implanted in Yorick are: cranial plate, silicone nose, carbon tooth root, interocular lens, cochlear implant, heart valve, artificial heart, cardiac pacemaker, infusion port, vascular grafts, urinary sphincter prosthesis, artificial patella, bone plate, artificial tendons, bone growth stimulator, and artificial hip, knee, elbow, and finger joints.

Hospital Infection Control

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The health care scene is changing in India. Today two thirds of the population seek medical care in the private sector. Corporate hospitals are increasing in number as are those built with NRI funds. Medical tourism is being vigorously pursued in some areas. At the same time foreign insurance companies and Third Party Administrators (TPA's) are entering the arena. In future it is likely that hospitals will only receive reimbursement for DRGs[1] (diagnosis related groups eg. Pneumonia, hernia etc.) and not be payed for disease complications such as hospital acquired infections. This will provide strong motivation for hospital administrators to promote infection control programmes which are already mandatory abroad for hospitals seeking accreditation[2].

Importance of Infection Control Programmes

In the 1970's in the United States the Centres for Disease Control and Prevention (CDC) began a nationwide "Study of the efficacy of nosocomial infection control – the SENIC project". The project involved 638 hospitals nationwide. After a decade the study established that the broad overall activity of infection control programmes predicted infection rates[3]. The most important predictors in decreasing order of importance were intensity of surveillance, intensity of control measures, an infection control practitioner/sister for every 250 beds, presence of a trained infectious disease specialist on the staff and provision of SSI (surgical site infection) rates to surgeons in order to influence their behaviour. Hospitals having such programmes demonstrated a 33% reduction in hospital infections compared to hospitals without any programme[4]. One hospital having an effective programme calculated yearly cost saving in excess of 2 million dollars. Thus substantial gains are to be expected for both doctors and administrators by supporting infection control programmes[5].

The Infection Control Committee

Prevention of hospital infections is essentially a big policing operation. First one has to gather people to perform this function, namely the infection control committee[6]. The core committee consists of a physician, a microbiologist and a surgeon, with representatives from operation theatres, CSSD and ICUs. Inputs are also required at times from others in housekeeping, laundry, food services and engineering, who work as a team to maintain the hygiene and cleanliness of any institution. For committee members the job of infection control isadded on to their other commitments, so that a personworking full time is required to coordinate activities, - this is usually the infection control sister[7]. Finally the committee requires its recommendations to be implemented and so must have access to administrative heads of the institution.

Functions of the Committee

The committee performs three principal functions. The first is to gather data. Each institution needs to know the microflora of its high risk areas such as operating theatres, adult and neonatal ICUs, dialysis units and oncology services. A good microbiology laboratory is essential to isolate organisms, to plot antibiotic resistance patterns and to indicate to clinicians trends and changes in hospital flora[8]. The laboratory is also best suited to identify outbreaks (3 or more cases of infection with the same organism and antibiogram) and to alert clinicians accordingly.

The second function is to carry out surveillance[9]. Whole hospital surveillance is impractical and largely meaningless. Most hospitals target surveillance at infections that (1) are associated with a high level of morbidity (eg ICU related infections and ventilator pneumonia); (2) are costly such as post cardiac surgery wound infections; (3) are difficult to treat such as infections due to antibiotic resistant bacteria; (4) are potentially preventable such as vascular access related infections[10]. Having established the baseline rates of infection for any procedure, surveillance is able to detect sudden increases in these rates so that remedial steps can immediately be taken. The method thus detects breakdowns in aseptic practices or sudden outbreaks of infection[11]. Surveillance is a powerful tool in infection control but is time consuming and expensive. Spot surveillance is sometimes a quicker and cheaper approach; for example how many people in an ICU examine patients without first washing hands or using an alcohol rub. Solution[12, 13].

The third function of the committee is to enforce good infection control practices. For this certain concepts must

be ingrained[14]. Nosocomial pathogens have reservoirs and are transmitted by predictable routes to susceptible hosts. Thus hospital tap water in India may be contaminated with E coli or Legionella and cause infections. Operating theatre air must be kept pathogen free with the aid of 15 air changes per hour and the use of bacterial filters. Sometimes members of the operating team are chronic shedders of staphylococci either from the nose or perineum, who because of their proximity to the surgical site can initiate wound infection. In the wards and ICUs cross infection is a bigger threat. Transfer of organisms on the hands of health care workers from one patient to another makes hand washing the single most important infection control practice[15]. At other times improperly diluted disinfectant solutions can harbour pseudomonas organisms and cause outbreaks of infection.

Hospital infections are increased by invasive devices and there must be a conscious effort to remove these at the earliest opportunity. Bacteraemias, pneumonias, urinary tract infections line infections and surgical site infections are the major causes of morbidity and mortality. In USA 2 million patients suffer from hospital infections each year of whom 88,000 die. The estimated cost is 4.5 billion dollars[16]. In India this cost is more than what the Government spends on total health care. Any hospital can be expected to record a 5-10 per cent incidence of hospital acquired infections even with an active infection control programme because of today's aggressive approach to sick patients.

Hospital Infection Control- the broader view

"The first requirement of a hospital is that it should do the sick no harm" was Florence Nightingale's dictum. Today this has been extended to incorporate the health and safety of hospital employees. Their needs have been highlighted by the HIV and SARS epidemics. The former gave rise to the concept of Universal Precautions (now Standard Precautions) for all diseases that are infectious through blood or body fluids[17]. The latter which affected a disproprotionately large number of health care workers demanded strict isolation of victims in negative air pressure rooms, strict respiratory precautions for attendant health workers, and quarantine for any contact health care worker developing a fever[18]. That level of discipline has yet to be achieved in India.

Hospital waste disposal is also a growing issue[19]. In Mumbai out of 6000 tonnes of waste generated daily, only 40 tonnes comes from hospitals. But the problem is that hospitals are not clearly segregating waste into infectious and non infectious and are therefore contaminating the entire quantum of solid waste. The real risk of infection comes from 'sharps' which transmit HIV, Hepatitis B and C viruses[20] Waste should be handled as little as possible but there is the social problem of rag pickers who remove syringes, needles and the like and recycle these items without sterilization. Hospitals that incinerate waste containing plastics made from organochlorines, release toxic dioxin and furan gases into the environment. Both matters are of concern for public health.

The reuse of expensive 'disposable' items merits consideration in a resource poor country like India. Cardiological societies for instance have made guidelines for the reuse of cardiac catheters after thorough cleaning and sterilization in order to benefit poor patients[21]. The infection risk appears to be minimal if reuse is limited to three occasions.

This brief account outlines the multifaceted nature of Hospital Infection Control. Moreover the reader will appreciate that infection control is a never ending struggle as medicine becomes more invasive and the proportion of ageing and immunocompromised patients in our population continues to increase.

Refrences

1. Wenzel RP. Nosocomial infections, diagnosis related groups and study on the efficacy of nosocomial infection control: economic implications for hospital under the prospective payment system. Am J. Med 1985; 78 : 3 – 7.
2. Haley RW, White JW, Culver DH et al. The financial incentive for hospitals to prevent nosocomial infections under the prospective payment system: an empirical determination from a nationally representative sample. JAMA 1987; 257: 1611 – 14.
3. Haley RW, Culver DH, White JW et al. The efficacy of surveillance and control programs in preventing nosocomial infections in US Hospitals. Am J. Epidemiol 1984; 121 : 282.
4. Joint Commission on Accreditation of Healthcare Organisation, Standards: Infection Control. In JCAHO: Accreditation manual for hospitals. Chicago: Joint Commission Accreditation of Healthcare Organizations 1990.
5. Ingelhart JK. The American health care system expenditure. N. Engl J. Med 1999; 340: 70 – 76.
6. Wiblin RT. Wenzel RP. The infection control committee. Infect Control Hosp. Epidemiol 1996; 17: 44 – 46.
7. O'Boyle C. The expanded role of

the nurse in hospital epidemiology. In Prevention and Control of Nosocomial Infections. Ed. Wenzel RP IVth Edition Lippincott Williams Wilkins 2003; 55 – 65.

8. Emori TG, Gaynes RP. An overview of nosocomial infections, including the role of the microbiology laboratory. Clin Microbiol Rev. 1993; 6: 428 – 442.
9. Vincent JL. Infections in adult intensive care units. Lancet 2003; 361: 2068 – 76.
10. Weinstein RA. Hospital Acquired Infection – In Harrison's Principles of Internal Medicine. Eds Kasper Braunwald Fauci Hause Long Jameson 16th Edition Mc Graw Hill 2003; 775 – 781.
11. Eggleman P, Pittet D. Infection Control in the ICU. Chest 2001; 120: 2059 – 93.
12. Pittet D, Hugonnet S, Harbarth S et al. Effectiveness of a hospital wide programme to improve compliance with hand hygiene. Lancet 2000; 356: 1307 – 12.
13. Farr BM. Reasons for non compliance with infection control guidelines. Infect Control Hosp. Epidemiol 2000; 21: 411 – 16.
14. Burke JP. Infection Control – A problem of patient safety. N Engl J. Med 2003; 348: 651 – 55.
15. Gawande A. On washing hands. N. Engl J. Med 2004; 350: 1283 – 86.
16. Weinstein RA. Hospital Acquired Infection – In Harrison's Principles of Internal Medicine Eds Kasper Braunwald Fauci Hause Long Jameson 16th Edition Mc Graw Hill 2003; 775 – 81.
17. Chamberland ME, Bell DM. Human Immunodeficiency Virus Inf. In Hospital Infections Eds Bennett JV. Bruchman PS. 14th Edition Lippincott – Raven 1998; 665 – 687.
18. Sets WH, Tsang D, Yung RW et all. Effectiveness of precautions against droplets and contact in prevention of nosocomial transmission of severe acute respiratory syndrome (SARS). Lancet 2003; 361: 1519 – 20.
19. Rutala WA, Weber DJ. Infectious waste: mismatch between Science and Policy. N. Engl J. Med 1991; 325: 578 – 82.
20. Kelkar R. Biomedical waste management – a practical approach. Hospital Infection Society India – Mumbai Forum Newsletter – 4th issue Dec 2004.
21. Avitall B, Khan M, Krum D et al. Repeated use of ablation catheters: a prospective study. J. Am. Coll Cardiol 1993; 22: 1367 – 72.

First successful kidney transplant

The idea of transplanting organs is not new & found in myths of the ancient Greeks. Skin and eyes were among the first successful transplants. But the larger, more complex, and imbedded organs posed countless problems. The kidney was the first such organ to be successfully transplanted.

Humans have two kidneys, but can live with just one, the kidney lent itself well to the process. The first attempts in the early 1950s, as in all transplant cases, were made when the only other alternative for the patient was death. These early patients briefly raised hopes by starting a good recovery, but then succumbed. The future of transplant surgery began to look very bleak.

Meanwhile, Peter Medawar in Great Britain had been researching the topic of rejection, which he had observed in skin grafts as a wartime surgeon. He found that graft recipients would form antibodies against the graft, unless they had been exposed to similar foreign tissue early in life. Medawar's work showed that the body's rejection of foreign tissue was indeed an immune response. He and another researcher received the 1960 Nobel Prize for this discovery.

In 1954, Richard and Ronald Herrick were identical twins, but Richard was dying of kidney disease. Ronald donated one of his kidneys. The organ did not appear foreign to Richard's body, which did not reject it.

There were ethical problems in this. To cure one patient, they had to harm another healthy person. But this was the least of their stumbling blocks. How could they trick the body into not rejecting the new, healthy kidney? X-rays were tried, bombarding the patient's entire body. The immune system was indeed knocked out, but in many cases the radiation killed the patient. In 1959, two more doctors in Boston discovered that certain drugs could suppress the immune system as effectively as radiation. One of these drugs was Imuran. In 1960, Peter Medawar introduced a way of typing tissue. By 1962, tissue typing and immune suppression was used for the first time in a human kidney transplant.

An effective immunosuppressant, cyclosporine, has been discovered. Cyclosporine, generally introduced in the 1980s, was a breakthrough in preventing rejection and opened a new era in transplant surgery. In 1986 alone, for example, nearly 9,000 kidney transplants were performed in the United States, with a greater than 85% survival rate for the first year.

Anatomy of the Breast

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Introduction

The breasts are the most prominent superficial structures in the anterior thoracic wall[1]. They form a secondary sexual feature of females and are the source of the nutrition for the neonates and are present in a rudimentary form in the males[2]. In young adult females each breast is rounded in shape and lies within the superficial fascia, anterior to the upper part of the thorax[2]. However, the shape and size of the breast are influenced by a variety of factors such as genetic, racial, dietary, age, parity and menopausal status of the individual[2].

Extent and Relations

The breast extends vertically from the second to the sixth ribs and transversely from the lateral margin of the sternum to the mid axillary line[1]. It lies upon the deep pectoral fascia which in turn overlies pectoralis major, serratus anterior and external oblique muscles. A submammary space containing loose connective tissue separates the breast from the deep fascia. This space imparts some amount of mobility to the breast on the deep pectoral fascia, and this mobility may be restricted in case of advanced mammary carcinoma[2]

'*Axillary Tail of Spencer*' is a prolongation from the outer part of the gland that extends upto the level of the third rib in the axilla where it is in direct contact with the main lymph nodes of the breast (i.e. anterior group). This part of the breast tissue reaches axilla through an opening in the axillary fascia called as '*Foramen of Langer*' and thus lies deep to the deep fascia[3]. Axillary tail of the breast is of great surgical importance. A well developed axillary tail can be mistaken for a mass of enlarged lymph nodes or a lipoma[4].

Architecture

The breast is composed of acini which constitute lobules, aggregations of which form the lobes of the gland. The lobes are arranged in a radiating manner like the spokes of a wheel and converge on the nipple where each lobe is drained by a duct[3]. The lobule is the basic structural unit of mammary gland a´nd their number and size are subject to tremendous variations. There are about 10 – 100 lobules which drain via ductules into a lactiferous duct. There are about 15-20 lactiferous ducts and each duct is lined by a spiral arrangement of contractile, myoepithelial cells[4].

Studies of primary and immortalized myoepithelial cell lines indicate that these cells exhibit a natural tumour suppressor function[5]. Breast cancer and pre cancer cells are influenced by important paracrine regulation from the breast micro environment, which might be a determinant of breast cancer behaviour as the specific oncogenic or tumour suppressive alteration occurring within the malignant breast cells[5]. The knowledge of central and peripheral duct anatomy in human breast is required for developing the intraductal approach to breast cancer[6].

'*Ligaments of Cooper*' are conical projections of fibrous tissue filled with breast tissue, the apices of which are attached firmly to the superficial fascia and thereby to the skin covering the breast[4]. In cancer of the breast, the malignant cells may invade these ligaments and consequent contraction of these strands may result in dimpling of the skin or attachment of the underlying growth to the skin[3]. Further, if cancer cells grow along the ligaments of cooper binding the breast to the pectoral fascia, the breast becomes fixed to the pectoralis major[3].

Nipple

The nipple projects on the centre of the breast anteriorly and its level in the thorax is variable lying at the 4th intercostal space in most young women[3]. The nipple contains smooth muscle fibres arranged concentrically and longitudinally, thus is an erectile structure[4]. Its shape varies from conical to flattened depending on various factors such as nervous, hormonal and developmental. Occasionally the nipple may not evert during pre-natal development and remains permanently retracted, thus causing difficulty in suckling[2].

Areola

Areola is a disc of skin which encircles the base of the nipple and varies in colour from pink to dark brown[2]. It contains involuntary muscles arranged in concentric rings as well as radially in the subcutaneous tissue. The areolar epithelium contains numerous sweat glands and sebaceous glands, the latter of which enlarge during pregnancy and serve to lubricate the nipple during lactation (*Montgomery's tubercles*) [4].

Vasculature

The arterial supply of the breast is derived from

1. Internal thoracic artery through its branches namely- perforating and anterior intercostal branches.
2. Axillary artery through its branches– lateral thoracic and thoraco acromial.
3. Posterior intercostal arteries (2nd, 3rd and 4th intercostal spaces).

The venous drainage of the breast is mainly to the axillary vein but there is some drainage into the internal thoracic vein[1].

The internal thoracic arteries are to be considered the main and constantly reliable source of blood supply to the nipple areola complex (NAC)[7]. Anatomical findings of breast specimens of female corpses have shown a thin horizontal, fibrous septum originating from the pectoral fascia along the level of the 5th rib traversing towards the nipple. This fibrous septum lies in between a cranial and a caudal vascular network and being mesentery like, it is responsible for the supply of NAC. The cranial vascular sheet is supplied by the thoraco acromial artery and a branch from the lateral thoracic artery, whereas the caudal sheet is supplied by perforating branches from anastomoses of intercostal arteries[8].

Innervation

The breast is innervated by anterior and lateral branches of 4th to 6th intercostal nerves[2]. The branches of the intercostal nerves convey sensory fibres to the skin of the breast and sympathetic fibres to the blood vessels in the breast and overlying skin and nipple[1]. The course of the rich neurovascular supply to the nipple runs along a regularly–located, suspensory apparatus and can therefore be predicted exactly[9]. During operations, one should try to avoid damage to the anterior and lateral cutaneous branches of the third, fourth and fifth intercostal nerves, with special attention to the fourth intercostal nerve which is the consistent nerve to the nipple areolar complex[10]. The nerves innervating the nipple and the areola are best protected if resections at the base of the breast and skin incisions at the medial areolar border are avoided[11].

Lymphatic drainage

The lymphatic drainage of the breast is important clinically in view of its role in the metastasis of cancer cells. The lymph passes from the nipple, areola and lobules of the gland to the sub areolar lymphatic plexus[11]. The first attempts to define the lymphatic drainage of the breast were published in the 18th century and summarized later[12]. One hundred years later, Sappey observed the drainage to the sub areolar plexus followed by drainage to the axillary lymph nodes[13]. Although axillary drainage is the principal lymphatic path of the breast, any drainage pattern from any quadrant of the breast can occur[14].

The lymphatics of the breast drain predominantly into the axillary and internal mammary lymph nodes. The axillary lymph nodes receive approximately 85 % of the drainage and are arranged in the following groups[4].

1 Anterior: along the lateral thoracic vessels
2 Posterior: along the subscapular vessels.
3 Lateral: along the axillary vein.
4 Central: embedded in the axillary fat.
5 Interpectoral: lying between pectoral muscles.
6 Apical: lying above the level of pectoralis minor tendon.

The apical group of lymph nodes is in continuity with the lateral group and receives the efferents of all the other groups. The apical group of lymph nodes is also continuous with the supraclavicular nodes and drain into the subclavian lymph trunk.

The axillary lymph nodes are also described in relation to pectoralis minor from a surgical view point[2]

Level 1- lying below pectoralis minor (low nodes).

Level 2- lying behind pectoralis minor (middle group)

Level 3- lying between the upper border of pectoralis minor and the lower border of clavicle (upper group).

The lymphatic mapping with sentinel lymph node biopsy has become an important technique in the staging of patients with breast cancer[2]. Involvement of the sentinel lymph node is a poor prognostic marker and indicates the need for axillary dissection and clearance[2]. The sentinel lymph node biopsy makes it possible to understand the descriptive anatomy as well as to apprehend the lymphonodal metastatic risk in the breast cancer[15].

Clinical Aspects

Developmental anomalies

Supernumerary breasts (polymastia) or nipples (polythelia), absence of breast (amastia), congenital inversion of the nipple may be encountered.

Mode of spread of breast cancer[4]

1 Local spread: The tumour may involve skin, pectoral muscles and even the chest wall.
2 Lymphatic metastasis: It occurs primarily to the axillary lymph nodes and to the internal mammary chain of lymph nodes. The involvement of lymph nodes is not just a

chronological event in the evolution of the carcinoma but it is a marker for the metastatic potential of the tumour

3 Haematogenous route: It may be responsible for skeletal metastases and to distant organs such as liver, lungs, etc.

Investigations

Mammography: In this procedure, soft tissue radiographs are obtained by placing the breast in direct contact with ultrasensitive film and exposing it to X rays.

Ultrasound: It is particularly useful in young women with dense breasts in whom mammograms are difficult to interpret.

MRI: It is very useful for imaging breasts as a screening tool in high risk women.

Fine Needle Aspiration Cytology (FNAC): It is the least invasive technique of obtaining a cell diagnosis and is very accurate if both cytologist and operator are experienced.

Positron Emission Tomography (PET): It is a metabolic radionucleide imaging method in which a tracer labelled with a positron emitter is detected with a dedicated system. 18F-Fluorodeoxy-glucose (FDG) accumulates in tumour cells because of their increased glycolytic activity and is thus widely used as a tracer in oncology. FDG-PET is a very useful tool for detecting and staging cancer[16].

Conclusion

The precise knowledge of anatomy of the breast is of tremendous value in the diagnosis and management of various breast disorders.

References

1. Moore KL & Dalley AF. Clinically Oriented Anatomy. 4th edn, Maryland, Lippincott Williams & Wilkins 1999; pp- 72-79.
2. Standring Susan. Gray's Anatomy. The Anatomical Basis of Clinical Practice. 39th edn, New York, Elsevier Churchill Livingstone 2005; pp- 969-975.
3. Decker CAG & Plessis D J du. Lee McGregor's Synopsis of Surgical Anatomy. Bristol, John Wright and Sons 1999; pp- 161-171.
4. Russel RCG, Williams NS & Bulstrode JKC. Bailey and Love's Short Practice of Surgery. 24th edn, London, Arnold Publications 2004; pp-824-846
5. Barsky SH & Karlin NJ. Mechanisms of disease: breast tumor pathogenesis and the role of myoepithelial cell. Nat Clin Pract Oncol, 2006; 3 (3): 138-51
6. Going JJ & Mohun TJ. Human breast duct anatomy, the 'sick lobe' hypothesis and intraductal approaches to breast cancer Breast Cancer 2006; Res Treat, 97 (3): 285-91.
7. Van Deventer PV. The blood supply to the nipple-areola complex of the human mammary gland. Aesthetic Plast Surg 2004; 28 (6):393-8.
8. Wuringer E, Mader N, Posch E, Holle J. Nerve and vessel supplying ligamentous suspension of the mammary gland. Plast Reconstr Surg 1998; 101(6):1486-93.
9. Wueringer E, Tschabitscher M. New aspects of the topographical anatomy of the mammary gland regarding its neurovascular supply along a regular ligamentous suspension. Eur J Morphol 2002; 40 (3): 181-9.
10. Jaspars JJ, Posma AN, van Immerseel AA, Gittenberger-de Groot AC.The cutaneous innervation of the female breast and nipple-areola complex: implications for surgery. Br J Plast Surg, 1997; 50 (4): 249-59.
11. Schlenz I, Kuzbari R, Gruber H, Holle J. The sensitivity of the nipple-areola complex: an anatomic study. Plast Reconstr Surg, 2000; 105 (3): 905-9.
12. Uren RF. Lymphatic mapping of the breast. In: Uren RF, Thompson JF, Howman-Giles RB, eds. Lymphatic Drainage of the Skin and Breast. Amsterdam; Harwood Academic Publishers, 1999; pp- 125-37.
13. Turner-Warwick RT. The lymphatics of the breast. Br J Surg, 1959; 46: 574-82.
14. Tanis PJ, Nieweg OE, Valdes Olmos RA, Kroon BB). Anatomy and physiology of lymphatic drainage of the breast from the perspective of sentinel node biopsy. J Am Coll Surg, 2001; 192(3): 399-409.
15. Olivier JB, Verhaeghe JL, Butarelli M, Marchal F, Houvenaeghel G. Functional anatomy of the lymphatic drainage of the breast: contribution of sentinel lymph node biopsy. Ann Chir, 2006; Jul 5; [Epub ahead of print].
16. Rouesse J, Alberini JL, Wartski M, Gutman F, Collignon MA, Corone C, Pichon MF, Pecking AP. FDG (18 fluorodeoxyglucose) positron emission tomography and breast cancer. Bull Acad Natl Med, 2005; 189 (5): 963-975.

Physiological Aspects of Breast & Related Recent Advances

Review Article

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The breast or mammary gland is a complex, highly specialized tissue that has evolved to provide nutrition for the young in humans and other mammals. The number of breast pairs varies with the species and is related to the average number of offspring in each litter. Thus the sow has 6-9 pairs, rodents 6 or 7 pairs, while, like man, the anthropoid apes, the lioness and the whale, have but a single pair[1]. The breast is a modified sweat gland. It is found in both sexes. It is well developed in the female after puberty. It forms an important accessory organ of the female reproductive system. In the male, the breast is a rudimentary structure relatively insensitive to endocrine influences and apparently resistant to neoplastic growth. The more complex breast structure, greater breast volume, and the extreme sensitivity to endocrine influences all predispose this organ to a number of pathologic conditions in females. Breasts are the sites of malignant change in as many as 1 in 10 females and the biology of their tissues is at present the focus of much clinical research.

Anatomical Structure- The fully developed breast is a rounded, elevated mass of glandular, fatty, and fibrous tissues positioned in the superficial fascia of the pectoral region and attached to the chest wall by hollow conical projections of fibrous strands called Cooper's ligaments. The axillary tail of Spencer is a small extension that pierces the deep fascia through foramen of Langer and lies in the axilla. The mammary gland consists of skin, parenchyma and stroma. Skin covers the gland and has a central dark pigmented area (areola). Central part of areola is projected above the surface and is called nipple Numerous areolar glands (of Montgomery) become more prominent during pregnancy and function in nipple lubrication. The major lactiferous ducts open onto the skin surface at the nipple.The mammary glands consist of 15-20 lobes and each lobe has a number of lobules. Lobule (milk gland) is the basic structural and functional unit of the mammary parenchyma, which secrete milk. In the human breast, the number and size of the lobules vary exceedingly; they are the largest and most numerous during early womanhood. The glandular tissue mainly consists of alveoli having secretory cells. From 10 to more than a hundred lobules empty by means of epithelium-lined ductules into a lactiferous duct. (Figure 1). Each lactiferous duct is lined by a spiral arrangement of contractile myoepithelial cells and is provided with a terminal ampulla or lactiferous sinus that serves as a little reservoir for milk or abnormal discharges. Secretions from secretory (alveolar) cells are poured by apocrine manner and by exocytosis into the lactiferous ducts.The majority of breast stroma consists of dense fibroconnective tissue admixed with adipose tissue (interlobular stroma) containing elastic fibers supporting the large ducts. Lobules are enclosed by a breast-specific hormonally responsive loose, delicate, myxomatous stroma that contains a scattering of lymphocytes (intralobular stroma). The fatty tissue gives the breast a soft consistency.

Blood supply- The mammary gland is extremely vascular. Branches of internal thoracic, axillary and posterior intercostals arteries supply it. The veins follow the arteries.

Lymphatic drainage- Lymphatic vessels of the breast drain predominantly into the axillary and the internal

mammary lymph nodes[2].

Development of breast

By deliberate analogy with the well-established concept of hematopoiesis, the term "mammopoiesis" is occasionally used to describe the development of the different cellular lineages and functional units in the mammary glands and signifies that it is brought about by the action of somatic stem cells characterized by longevity and multipotency[3,4]. Development of the mammary gland in females is a dynamic, orchestrated process that occurs in a discontinued way during five distinct phases, i.e. fetal, prepubertal, post pubertal, pregnancy, and early lactation periods[5].

Breasts in intrauterine life (embryogenesis)- Development of the mammary glands is initiated in the embryo itself. At 18-19 weeks of gestation mammary glands develop from a thickened mass of epithelium of the epidermis known as mammary bud. From this thickened mass about 16-20 solid outgrowths arise and project into the dermis. Rudimentary duct system is formed by the canalization of these outgrowths as well as the thickened mass. The proximal end of each duct opens into a common pit formed by cavitation of the thickened mass. Nipple is formed by the outward pushing of the wall of the pit due to growth of underlying mesodermal tissue[5,6].

Breasts at birth- At birth the mammary glands are rudimentary consisting of tiny nipple and few ducts radiating from it.

Breasts in prepubertal life- From birth to puberty the mammary glands remain quiescent.

Breasts in pubertal life- With the onset of puberty the breast starts developing (thelarche) and gets enlarged in response to hormonal and local cues to rapidly establish an extensive tree-like network of branched ducts. This process, termed branching morphogenesis, is refined in response to cyclic ovarian stimulation (at menarche) once the margins of the mammary fat pad are met. Thus it is driven by systemic hormonal stimuli that elicit local paracrine interactions between the developing epithelial ducts and their adjacent embryonic mesenchyme or postnatal stroma. This local cellular cross-talk, in turn, orchestrates the tissue remodeling that ultimately produces a mature ductal tree[5,7,8,9].

Breasts in pregnancy- With the onset of pregnancy, massive tissue remodelling within the mammary gland progresses to establish a gland that is densely filled with secretory lobuloalveolar units. During the alveolar morphogenesis phase, rapid and global proliferation of the epithelial cells occurs within the ductal branches and developing alveoli. This increases both epithelial cell number and epithelial surface area, actions essential for sufficient milk production during lactation. Cell differentiation becomes dominant from mid-pregnancy as the gland moves into the secretory initiation phase. The developing alveoli cleave and the alveolar cells become polarised and form a sphere-like single layer of epithelial cells that envelops a circular lumen, connected to the ductal network via a single small duct. Each individual alveolus is surrounded by a basket-like architecture of contractile myo-epithelial cells. The myo-epithelium of the alveoli is discontinuous so that the luminal cells directly contact the underlying basement membrane, which forms part of the extracellular matrix. Some cells of the ductal network also contact the basement membrane[8,9,10,11]. Contact is required for complete lobuloalveolar differentiation, seen morphologically by the appearance of lipid droplets [12] and by the initiation of gene expression in a defined order [13,14]. Nearing parturition, alveolar tight junctions close and milk and colostrum proteins move into the alveolar lumen, in preparation for active milk secretion post-partum, which marks the onset of the secretory activation phase

The epithelial expansion is paralleled by equally dramatic changes in other tissue compartments. Adipocytes lose their lipid content and remain as long projections scattered throughout the alveolar epithelium. A huge expansion of the vasculature also occurs within the stroma, to provide the large quantities of energy, sugars, amino acids and solutes required for milk production[8]. Pigmentation of the areolas usually becomes more intense during the first pregnancy than it does at puberty.

Breasts during lactation- After childbirth the alveolar cells get distended and start forming milk (lactogenesis). Many of the above mechanisms are hijacked, bypassed, or corrupted during the development and progression of cancer.

Control of breast development and growth

Recent evidences indicate that besides interactions of various steroid and polypeptide hormones there is involvement of other factors and substances as well in the process of mammary growth and differentiation. In general, estrogens are primarily responsible for proliferation of the mammary ducts and progesterone for the development of the lobules. During pregnancy, prolactin levels increase steadily until term, and under the influence of this hormone plus the high levels of estrogens and progesterone, full lobuloalveolar development of the breasts takes place[15]. (Figure 2). Estrogens have been called the growth hormones of the breast. They produce ductal growth and branching morphogenesis in the breasts. Breast

Figure 2: Hormonal control of Breast Development

enlargement that occurs when estrogen-containing skin creams are applied locally is due primarily to systemic absorption of the estrogen, although a slight local effect is also produced. Simultaneously, the stroma of the breasts increases in quantity, and large quantities of fat are laid down in the stroma. The central involvement of estrogen in the development of the mammary gland and in the genesis of breast cancer has lent impetus to studies of the links between estrogen action and the cell cycle machinery. Estrogens independently regulate the expression and function of c-Myc and cyclin D1 and the induction of either c-Myc or cyclin D1 are sufficient to recapitulate the effects of estrogen on cell cycle progression. These pathways converge at the activation of cyclin E-Cdk2 complexes. Insulin and estrogen synergistically stimulate cell cycle progression. Antiestrogen treatment of MCF-7 cells leads to an acute decrease of c-Myc expression, a subsequent decline in cyclin D1, and ultimately arrest of cells in a state with features characteristic of quiescence[16]. The initial proliferative phase of alveolar morphogenesis is instigated by an increase in the level of serum prolactin (Prl) and progesterone (Pg). These hormones activate the alveolar switch, a genetic program that coordinates changes in mammary epithelial cell proliferation, migration, differentiation and deletion within the many tissue types of the mammary gland. Pituitary Prl stimulation of ovarian Pg assists in maintaining the required levels of Pg during early pregnancy. In addition, up-regulation of progesterone receptor (Pgr) expression by Prl, and Prl receptor (Prlr) expression by Pg, suggests that these hormones may interact in a synergistic manner to control alveolar development[17, 18].

Members of the Prl-signalling pathway are essential for normal alveolar morphogenesis. Prlr dimerization occurs after Prl binding and leads to the phosphorylation of the associated Janus kinase (Jak2), which in turn phosphorylates specific residues on the Prlr. Stat5 is then recruited to the receptor and is phosphorylated by Jak2. Phosphorylated Stat5 is then translocated to the nucleus where it can activate transcription of multiple genes involved in a variety of processes during alveolar morphogenesis, including establishment of epithelial polarity and cell-cell interactions, stromal epithelial interactions and milk protein expression during lactation[19,20]. Some transcription factors that appear to be involved in alveolar morphogenesis include the homeobox genes, helix-loop-helix genes, Stats, Tcf/Lef family, NF-êB, the Ceb/p family, the nuclear factor family and the Ets transcription factors[21,22].

The maintenance of cellular polarity is regulated by the closure of tight junctions, and the expression of tight junction proteins Claudin-3 and Claudin-7 was reduced in $Prlr^{-/-}$ mammary transplants. The gap junction protein Connexin 26 was also identified and is involved in the exchange of small ions and metabolites. Recently, Connexin-26 was shown to be important in full lobuloalveolar development and in the prevention of alveolar cellular apoptosis[8,

[23]. The effects of Pg on the mammary gland are mediated by two structurally and functionally distinct nuclear receptors Pgr-A and Pgr-B that arise from a single gene. Null mutation of both receptors in Pgr knockout mice has demonstrated a critical role for Pgrs in mediating pregnancy-associated mammary ductal branching and lobuloalveolar differentiation and in initiation of mammary tumors in response to carcinogen. Pg also plays a critical role in the protection against mammary tumorigenesis afforded by early parity[18]. Not all mammary epithelial cells express Pgr and, therefore, are unable to respond to Pg directly. Mammary gland chimeras made from Pgr+/+ and Pgr-/- mammary epithelial cells (MECs) demonstrated that Pgr-/- epithelial cells proliferate in response to Pg, indicating that proliferation is mediated, at least in part, by a paracrine mechanism[9]. Wingless-related MMTV integration site 4 (Wnt4) and receptor activator of nuclear factor (NF)-êB ligand (RankL) are targets of the Pgr signalling pathway and may be the paracrine factors responsible for cellular proliferation in steroid receptor negative cells. The downstream target of Wnt, â-catenin, has specific actions in both the luminal and myoepithelial compartments of the epithelium, and as a component of cell-cell junctions appear to have a role in signalling to luminal epithelial cells. Indeed, activation of â-catenin within the basal epithelial cells results in premature differentiation of the luminal epithelium during pregnancy and persistent proliferation resulting in tumors[24, 25, 26].

The RankL target, NF-êB, is required for cyclin D1 (Ccnd1) activation via the kinase IêB (IKKá) in neighbouring cells resulting in increased alveolar proliferation during pregnancy. RankL also co-localises with Pgrs in response to pregnancy levels of estrogen and Pg, indicating this is an important part of the response. The gene encoding RankL was also identified as potentially regulated by Prl. Interestingly, Prl can induce Ccnd1 expression via induction of insulin growth factor 2, independent of RankL induction. The similarities between Prl- and Pg-mediated effects on both RankL and Wnt signalling is further evidence of the co-operation of these pathways for alveolar cell proliferation during early pregnancy. The cell surface receptor â1 integrin, which is present on luminal epithelial cells, is an essential mediator of extracellular matrix signalling via its ligands collagen and laminin. These play an important part in the epithelial-stromal signalling required for full lobuloalveolar differentiation and gene expression[8, 10, 11]. Activins and inhibins are growth factors involved in cell differentiation and proliferation. Human breast tissues such as normal mammary tissue, fibroadenoma, and breast cancer express inhibin and activin mRNA and proteins. Activin A and its binding protein, follistatin, are also present in human milk during the first week of lactation. The role of activin and inhibin as endocrine and/or paracrine factors in the breast is still uncertain. Activin has complex effects on cell growth during branching morphogenesis, but it is generally considered as an inhibitor of cell proliferation as in vitro studies have shown that activin A treatment of breast cancer cells arrests cell growth. Inhibin is generally considered as a tumor suppressor, but its possible role in the breast is less understood[27]. The neuronal peptide galanin (Gal) has dual actions: firstly, an indirect role by modulating pituitary Prl and phosphorylated Prl release from the pituitary lactotrophs and secondly, a direct cell autonomous role in the formation of lobuloalveoli during pregnancy in the presence of Prl [28] Other hormones can influence alveolar morphogenesis. Growth hormone may act in combination with Prl to mediate alveolar proliferation. Growth hormone treatment restores alveolar morphogenesis but inhibits lactation in $Prlr^{+/-}$ mammary glands. Placental lactogen is released from the placenta during pregnancy and can fully compensate for Prl, allowing alveolar morphogenesis in $Prl^{-/-}$ mice[29].

The receptor tyrosine kinase ErbB (epidermal growth factor) family and their ligands are important mediators of all aspects of mammary development. There are four receptors: epidermal growth factor receptor/ErbB/Her1, ErbB2/Her2/neu, ErbB3/Her3 and ErbB4/Her4, which are activated by a variety of ligands inducing activation via dimerisation and cross phosphorylation[30]. The cytokine Tgf-â1 is an important regulator of mammary cell proliferation during pregnancy. Tgf-â1 is restricted to the luminal epithelial cells and can control cell proliferation via phosphorylation of Smad following Tgf-â receptor activation Tgf-â1 heterozygote mice display accelerated lobulo-alveolar development due to increased proliferation, indicating that the expression of Tgf-â1 restricts alveolar cell proliferation[31]. The ets transcription factor Elf5 is expressed specifically in the luminal cells of mammary tissue, and its expression is increased dramatically during pregnancy, to the levels that far exceed those seen in other tissues. Elf5 is a key mediator of structural and functional development of lobuloalveoli and appears to be a master-regulator of the alveolar switch required for alveolar morphogenesis[8, 21, 32].

Physiology of lactation

There are four phases in physiology of lactation

Mammogenesis- Preparation of breast for milk secretion.

The breasts enlarge during pregnancy in response to high circulating levels of estrogens, progesterone, prolactin, and possibly hCG and is prepared for milk secretion.

Lactogenesis- Synthesis and secretion of milk occurs in two stages.

Stage 1 - Some milk is secreted into the ducts as early as the fifth month, but the amounts are small compared with the surge of milk secretion that follows delivery. The fluid that is secreted in the last few days before and first few days after parturition is called colostrum; it contains essentially the same concentrations of proteins and lactose as milk but almost no fat, and its maximum rate of production is about 1/100 the subsequent rate of milk production. Stage 2- - Initiation of lactation after the birth of the child. In most animals, milk is secreted within an hour after delivery, but in women it takes 1-3 days for the milk to "come in."[5,33]

Although estrogen and progesterone are essential for the physical development of the breasts during pregnancy, a specific effect of both these hormones is to inhibit the actual secretion of milk., never more than a few millilitnes of fluid are secreted each day until after the baby is born. Conversely, the hormone prolactin has exactly the opposite effect on secretion i.e., promotion of milk secretion. This hormone is secreted by the mother's anterior pituitary gland, and its concentration in her blood rises steadily from the fifth week of pregnancy until birth of the baby, at which time it has risen to 10 to 20 times the normal nonpregnant level. After expulsion of the placenta at parturition, there is an abrupt decline in circulating estrogens and progesterone. The sudden loss of both estrogen and progesterone secretion from the placenta allows the lactogenic effect of the prolactin from the mother's pituitary gland to assume its natural milk promoting role. Prolactin causes milk secretion from the breast after estrogen and progesterone priming. Its effect on the breast involves increased action of mRNA and increased production of casein and lactalbumin. However, the action of the hormone is not exerted on the cell nucleus and is prevented by inhibitors of microtubules. Prolactin also inhibits the effects of gonadotropius, possibly by an action at the level of the ovary[34,35].

In addition, the placenta secretes large quantities of human chorionic somatomam- motropin, which probably also has lactogenic properties. This secretion of milk requires an adequate background secretion of most of the mother's other hormones as well, but most important of all are growth hormone, cortisol, parathyroid hormone, and insulin. These hormones are necessary to provide the amino acids, fatty acids, glucose, and calcium that are required for milk formation.

Galactokinesis- Expulsion of milk, Milk is secreted continuously into the alveoli of the breasts, but milk does not flow easily from the alveoli into the ductal system and, therefore, does not continually leak from the breast nipples. Instead, the milk must be ejected from the alveoli into the ducts before the baby can obtain it. A combined neurogenic and hormonal reflex that involves the posterior pituitary hormone oxytocin causes this. Milk Ejection (or "Let-Down") Reflex: It is a neuroendocrinal reflex. When the baby suckles, it receives virtually no milk for the first half minute or so. Sensory impulses generated by stimulation of touch receptors in the skin of nipple and areola by suckling baby are transmitted through somatic nerves to the mother's spinal cord and then to her paraventricular and supraoptic nuclei and thence along the hypothalamo-hypophysial tract to the neurohypophysis causing the release of oxytocin into the bloodstream. The oxytocin is carried in the blood to the breasts, where it causes myoepithelial cells to contract, thereby expressing the milk from the alveoli into the ducts at a pressure of plus 10 to 20 mm Hg. Then the baby's suckling does become effective in removing the milk. Thus, within 30 seconds to 1 minute after a baby begins to suckle, milk begins to flow. This process is called milk ejection or milk let-down reflex. Oxytocin acts via the receptor which is a typical class of I G protein-coupled receptor. Suckling also promotes secretion of prolactin, probably by inhibiting the release of PIF from the hypothalamus. Suckling on one breast causes milk flow not only in that breast but also in the opposite breast. It is especially interesting that fondling of the baby by the mother or hearing the baby crying also often gives enough of an emotional signal to her hypothalamus to cause milk ejection[5,7,33].

Inhibition of milk ejection- Many psychogenic factors or even generalized sympathetic nervous system stimulation throughout the mother's body can inhibit oxytocin secretion and consequently depress milk ejection. Alcohol is also a potent inhibitor of oxytocin[33,36].

Galactopoiesis- Maintenance of milk secretion. Depends on the surge in prolactin secretion. After birth of the baby, the basal level of prolactin secretion returns during the next few weeks to the non-pregnant level. However, each time the mother nurses her baby, nervous signals from the nipples to the hypothalamus cause a 10- to 20- fold surge in prolactin secretion that lasts for about l hour. This prolactin in turn acts on the mother's breasts to keep the mammary glands secreting milk into the

alveoli for the subsequent nursing periods. If this prolactin surge is absent or blocked as a result of hypothalamic or pituitary damage or if nursing does not continue, the breasts lose their ability to produce milk within 1 week or so. However, milk production can continue for several years if the child continues to suckle, although the rate of milk formation normally decreases considerably after 7 to 9 months[34,35].

Importance of lactation- Breastfeeding is the optimal method of infant feeding. Breast milk provides almost all the necessary nutrients, growth factors and immunological components a healthy term infant needs, Other advantages of breastfeeding include reduction of incidences and severity of infections; prevention of allergies; possible enhancement of cognitive development; and prevention of obesity, hypertension and insulin-dependent diabetes mellitus. Health gains for breastfeeding mothers include lactation amenorrhea, early involution of the uterus, enhanced bonding between the mother and the infant, and reduction in incidence of ovarian and breast cancer. From the economic perspective, breastfeeding is less expensive than formula feeding. In most cases, maternal ingestion of medications and maternal infections are not contraindications to breastfeeding. Breastfeeding, however, is contraindicated in infants with galactosemia. Breastfeeding should be initiated as soon after delivery as possible[37]. An important issue for developing countries is prevention of postnatal HIV transmission through breast-feeding. A promising new line of research has recently been broached with the findings from a study in South Africa, which demonstrated that exclusive breast-feeding is associated with a significant reduction in postnatal transmission of HIV[38].

Breast milk

Human milk is often the sole dietary source for the first few months in life. It contains all the nutrients necessary for the infant to thrive, but also ingredients that may provide health benefits beyond those of traditional nutrients. Human milk oligosaccharides (HMO) comprise part of these functional ingredients; 1 L of mature human milk contains approximately 5-10 g unbound oligosaccharides, and >130 different HMO have been identified. Both their high amount and structural diversity are unique to humans. Only trace amounts of these oligosaccharides are present in mature bovine milk and, as a consequence, in bovine milk-based infant formula. The potential health benefits of HMO that were uncovered over the years may affect breast-fed infants both locally and systemically[39].

Composition- The fluid secreted during the first three days after parturition is called colostrum. It is deep yellow in colour, rich in protein and salts. It contains large granular bodies called colostrum corpuscles, which represent either discharged alveolar cells of the gland or else leucocytes loaded with fat. These are abundant in the first few days and disappear at the end of the second week. The milk formed during the first few weeks is called intermediate or transition milk. Mature milk appears at the end of the first month.

Origin of constituents of milk- The specific constituents of milk are elaborated in the gland cells from certain raw materials supplied by the blood. Lactose is derived from plasma glucose.Milk proteins come from plasma amino acids and proteins. Immunoglobulins can pass unchanged from maternal blood to milk. Fat is formed partly from neutral fat of the blood and partly from acetate. The various secretory processes involved in synthesis of milk include; fat synthesis and its secretion; ions and water secretion; transcytosis of immunoglobulins and other substances from interstitial spaces and exocytosis[5,7,33].

Involution of the breast-Programmed cell death during the involution phase of the mammary gland is an essential process that removes all of the development induced by the alveolar switch when they become redundant at weaning. Based on a paradigm developed in the hematopoietic system, it was hypothesised that a primary, persistent self-renewing mammary epithelial stem cell gives rise to a hierarchy of epithelial progenitor cell lineages to ultimately produce the different cells found in the mammary epithelium. The flux of cells through these lineages is likely to be controlled by, and in turn control, the pattern of gene expression that comprise the alveolar switch.

Involution of mammary gland is a two-step process that involves the death of the secretory epithelium and its replacement by adipocytes. During the first phase, remodelling is inhibited and apoptotic cells can be seen in the lumen of the alveoli. In the second phase, apoptosis is accompanied by remodelling of the surrounding stroma and re-differentiation of the adipocytes.

Signalling events in involution- Milk stasis induces the expression of leukaemia inhibitory factor (LIF) and transforming growth factor (TGF)â3 within 12 hours of forced weaning. These, in turn, phosphorylate and activate the transcription factor Stat3. This results in the induction of apoptosis and shedding of dying cells into the alveolar lumen. Neighbouring cells migrate to close the gap and maintain the integrity of the alveolar structure.

Concurrently with these events, members of the death receptor ligand family and their receptors are transcriptionally upregulated and this induces apoptosis through activation of caspase 8. Downstream targets of these pathways are then induced and ensure the transition to the second phase.Following this reversible first phase, matrix metalloproteases (MMP) begin to break down the ECM surrounding each alveolus, resulting in detachment induced apoptosis and collapse of the alveoli. Remodelling is then completed by re-differentiation of the adipoctyes which requires the action of plasmin and MMP3. Full involution returns the gland to a pre-pregnant state.

Gene expression profiling of $Prl^{-/-}$ mice has also identified unique targets of mammary development. Expression of tryptophan hydroxylase, the rate-limiting enzyme in serotonin biosynthesis, is increased by Prl during pregnancy and lactation. Accumulation of serotonin due to milk engorgement experienced during weaning or experimentally via teat sealing inhibits milk gene expression and can induce involution, providing a mechanism that is put in place by Prl to stop lactation at weaning [40,41]

Applied aspects

Breast carcinoma- As medicine enters the 21st century, the field of breast cancer continues to reflect both our greatest successes and our greatest challenges as scientists, epidemiologists, and clinicians. The rising global incidence, morbidity and mortality from breast cancer has led to intensified efforts in the search for etiological factors of the disease. While international variations in the incidence of the disease may implicate a role for environmental factors, available evidence indicates that lifetime estrogen exposure, predominantly 17beta-estradiol, may be a critical factor in breast carcinogenesis. While increasing age and the female sex are well-recognized risk factors, reproductive characteristics such as age at menarche and menopause, menstrual irregularity, age at first and last childbirth, parity and breastfeeding have also been linked to breast carcinogenesis. Early menarche and late menopause are associated with increased lifetime exposure to estrogens. In addition, a long period from Tanner stage-2 breast to onset of ovulatory cycles and a long period of luteal inadequacy and anovulatory cycles characteristic of the perimenopausal years creates long estrogen windows favorable for tumor induction. Recent advances in the understanding of cell-cycle control mechanisms indicate that estrogen exert control over several key G1 phase cell-cycle regulators, namely cyclin D1, Myc, Cdk2, Cdk4, Cdk inhibitors and Cdc25A. Estrogens might regulate several key molecules required for S phase entry, this regulation being independent of cell-cycle transit per se.

The intense differentiation of the terminal duct lobular unit associated with each full term pregnancy and release of various hormones, autocrine and paracrine growth factors during lactation may explain the protective effects of early age at first full term pregnancy, parity and lactation of breast cancer risk. A protective role for xenoestrogens has been postulated and evidence is emerging in support of an increased breast cancer risk with abortion and prolonged use of postmenopausal hormone replacement therapy. The recognition of the importance of the HER-2/neu (c-erbB-2) oncogene, located on chromosome 17, encodes a 185 kD transmembrane glycoprotein with tyrosine kinase activity that functions as a growth factor receptor. Amplification or overexpression of HER-2/neu is seen in approximately 20 to 30% of invasive breast cancers and this has been considered to be an adverse prognostic factor in many studies. However, recent interest in HER-2/neu has largely been focused on its role as a potential target for breast cancer treatment. In particular, recognition of the role of HER-2/neu in breast cancer growth led to the development of a humanized monoclonal antibody directed against the HER-2/neu protein as a therapeutic agent (Herceptin)[42].

Hyperprolactinaemia- Up to 70% of the patients with chromophobe adenomas of the anterior pituitary have elevated plasma prolactin levels. The hyperprolactinemia may cause galactorrhea, but in many individuals there are no demonstrable endocrine abnormalities. Conversely, most women with galactorrhea have normal prolactin levels; definite elevations are found in less than a third of patients with this condition. Another interesting observation is that 15-20% of women with secondary amenorrhea have elevated prolactin levels, and when prolactin secretion is reduced, normal menstrual cycles and fertility return. It appears that the prolactin may produce amenorrhea by blocking the action of gonadotropins on the ovaries, but definitive proof of this hypothesis must await further research. The hypogonadism produced by prolactinomas is associated with osteoporosis due to estrogen deficiency. Hyperprolactinemia in men is associated with impotence and hypogonadism that disappear when prolactin secretion is reduced. The study of the inhibiting dopaminergic system was a landmark in the treatment of hyperprolactinaemia[7,33].

Chiarri Frommel Syndrome- An interesting although rare condition is persistence of lactation (galactorrhea) and amenorrhea in women who do not nurse after delivery. This condition, called the Chiari-Frommel syndrome, may be associated with some genital atrophy and

is due to persistent prolactin secretion without the secretion of the FSH and LH necessary to produce maturation of new follicles and ovulation. A similar pattern of galactorrhea and amenorrhea with high circulating prolactin levels is seen in nonpregnant women with chromophobe pituitary tumors and in women in whom the pituitary stalk has been sectioned in treatment of cancer[7].

Gynaecomastia- Breast development in the male is called gynecomastia. It may be unilateral but is more commonly bilateral. It is common, occurring in about 75% of newborns because of transplacental passage of maternal estrogens. It also occurs in mild, transient form in 70% of normal boys at the time of puberty and in many men over the age of 50. It occurs in androgen resistance. It is a complication of estrogen therapy and is seen in patients with estrogen-secreting tumors. It is found in a wide variety of seemingly unrelated conditions, including eunuchoidism, hyperthyroidism, and cirrhosis of the liver. Digitalis can produce it, apparently because cardiac glycosides are weakly estrogenic. It can also be caused by many other drugs. It has been seen in malnourished prisoners of war, but only after they were liberated and eating an adequate diet. A feature common to many and perhaps all cases of gynecomastia is an increase in the plasma estrogen:androgen ratio due to either increased circulating estrogens or decreased circulating androgens.

Conclusion

The understanding of physiology of breast is undergoing continuous revision as advances in molecular and cell biology result in new paradigms of hormonal action. Increased importance to local cellular environment has emerged. Cell to cell communication (intracrine, autocrine, paracrine) is mediated via local growth factors and their respective receptors. The extracellular matrix (cell-adhesion related proteins) is no longer considered stagnant but alters the architecture of the cells and the expression of multiple genes in their neighbouring cells. A more sophisticated understanding of the mechanism of receptor activation, not only by the classic steroid hormones but also by peptides and growth factors, has replaced older concepts.New knowledge about cellular kinetics and molecular biology makes it increasingly clear that normal physiology of the breast involves a complex interaction of protein kinases, hormones and growth factors that influence the function, proliferation and apoptosis of both epithelial and mesenchymal cells. Discoveries in the areas of breast cancer biology and genetics continue to help us refine our approach to the newly-diagnosed patient as well as guide our development of cancer prevention and early detection strategies.

References

1. Bailey and Love's. The Breast. In Short Practice of Surgery. 21st ed. ELBS Chapman and Hall 1992; 788-821.
2. Bannister LH eds. Breasts (Mammae). In Gray's Anatomy 38th ed. Churchill Livingstone Harcourt Publishers Ltd 2000; 417-424.
3. Shackleton M, F V, Simpson KJ, Stingl J, Smythe GK, Asselin-Labat M-L, Wu L, Lindeman GJ, Visvader JE: Generation of a functional mammary gland from a single stem cell. Nature 2006, 439:84-88.
4. Villadsen R. In search of a stem cell hierarchy in the human breast and its relevance to breast cancer evolution. APMIS. 2005 Nov-Dec; 113(11-12): 903-21
5. Rebar RW, Thomas MA, Myatt L. Fertilisation, Pregnancy and Lactation. In Best and Taylor's Physiological Basis of Medical Practice. 12th ed. Williams and Wilkins Gill GN eds1989; 874-891.
6. Jolicoeur F. Intrauterine breast development and the mammary myoepithelial lineage. J Mammary Gland Biol Neoplasia. 2005 Jul; 10(3): 199-210
7. Ganong WF.The Gonads: Development and Function of the Reproductive System. In Review of Medical Physiology. 22nd ed. McGraw Hill 2005; 411-453.
8. Samantha R Oakes, H.N.Hilton, C.J.ormandy, Key stasges in mammary gland development-the alveolar switch: coordinating the proleferative clues and cell fate decisions that drive the formation of lobuloalveoli from ductal epithelium. Breaset cancer research, 2006, 8: 207
9. Oka T,Yoshimura M. Paracrine regulation of mammary gland growth. Clin Endocrinol Metab. 1986 Feb;15(1):79-97.
10. Brisken C, Park S, Vass T, Lydon JP, O'Malley BW, Weinberg RA: A paracrine role for the epithelial progesterone receptor in mammary gland development. Proc Natl Acad Sci USA 1998, 95:5076-5081.
11. Streuli CH, Edwards GM, Delcommenne M, Whitelaw CB, Burdon TG, Schindler C, Watson CJ: Stat5 as a target for regulation by extracellular matrix.J Biol Chem 1995, 270:21639-21644.
12. Fata JE, Werb Z, Bissell MJ: Regulation of mammary gland branching morphogenesis by the extracellular matrix and its remodeling enzymes. Breast Cancer Res 2004, 6:1-11.
13. Neville MC, McFadden TB, Forsyth I: Hormonal regulation of mammary differentiation and milk secretion.J

Mammary Gland Biol Neoplasia 2002, 7:49-66.

14. Murtagh J, Martin F, Gronostajski RM: The Nuclear Factor I (NFI) gene family in mammary gland development and function.J Mammary Gland Biol Neoplasia 2003, 8:241-254.
15. Rudolph MC, McManaman JL, Hunter L, Phang T, Neville MC: Functional development of the mammary gland: use of expression profiling and trajectory clustering to reveal changes in gene expression during pregnancy, lactation, and involution.J Mammary Gland Biol Neoplasia 2003, 8:287-307.
16. Guyton and Hall. Pregnancy and Lactation. In Textbook of Medical Physiology 11th ed. Elsevier publ 2005; 943-956.
17. Doisneau-Sixou SF, Sergio CM, Carroll JS, Hui R, Musgrove EA, Sutherland RL. Estrogen and antiestrogen regulation of cell cycle progression in breast cancer cells. Endocr Relat Cancer. 2003 Jun; 10(2): 179-86
18. Grimm SL, Seagroves TN, Kabotyanski EB, Hovey RC, Vonder-haar BK, Lydon JP, Miyoshi K, Hennighausen L, Ormandy CJ, Lee AV, et al.: Disruption of steroid and prolactin receptor patterning in the mammary gland correlates with a block in lobulo-alveolar development.Molecular Endocrinology 2002, 16:2675-2691
19. Conneely OM, Jericevic BM, Lydon JP. Progesterone receptors in mammary gland development and tumorigenesis. J Mammary Gland Biol Neoplasia. 2003 Apr;8(2): 205-14
20. Han Y, Watling D, Rogers NC, Stark GR: JAK2 and STAT5, but not JAK1 and STAT1, are required for prolactin-induced beta-lactoglobulin transcription. Mol Endocrinol 1997, 11:1180-1188.
21. Pezet A, Buteau H, Kelly PA, Edery M: The last proline of Box 1 is essential for association with JAK2 and functional activation of the prolactin receptor. Mol Cell Endocrinol 1997, 129:199-208.
22. Oikawa T, Yamada T: Molecular biology of the Ets family of transcription factors.Gene 2003, 303:11-34.
23. Desprez PY, Sumida T, Coppe JP: Helix-loop-helix proteins in mammary gland development and breast cancer.J Mammary Gland Biol Neoplasia 2003, 8:225-239.
24. Bry C, Maass K, Miyoshi K, Willecke K, Ott T, Robinson GW, Hennighausen L: Loss of connexin 26 in mammary epithelium during early but not during late pregnancy results in unscheduled apoptosis and impaired development. Dev Biol 2004, 267:418-429.
25. Brisken C, Heineman A, Chavarria T, Elenbaas B, Tan J, Dey SK, McMahon JA, McMahon AP, Weinberg RA: Essential function of Wnt-4 in mammary gland development downstream of progesterone signaling.Genes Dev 2000, 14:650-654.
26. Srivastava S, Matsuda M, Hou Z, Bailey JP, Kitazawa R, Herbst MP, Horseman ND: Receptor activator of NF-kappaB ligand induction via Jak2 and Stat5a in mammary epithelial cells.J Biol Chem 2003, 278:46171-46178.
27. Teuliere J, Faraldo MM, Deugnier MA, Shtutman M, Ben-Ze'ev A, Thiery JP, Glukhova MA: Targeted activation of beta-catenin signaling in basal mammary epithelial cells affects mammary development and leads to hyperplasia. Development 2005, 132:267-277.
28. Reis FM, Luisi S, Carneiro MM, Cobellis L, Federico M, Camargos AF, Petraglia F. Activin, inhibin and the human breast. Mol Cell Endocrinol. 2004 Oct 15;225(1-2):77-82
29. Naylor MJ, Ginsburg E, Iismaa TP, Vonderhaar BK, Wynick D, Ormandy CJ: The neuropeptide galanin augments lobuloalve-olar development.J Biol Chem 2003, 278:29145-29152.
30. Allan GJ, Tonner E, Barber MC, Travers MT, Shand JH, Vernon RG, Kelly PA, Binart N, Flint DJ: Growth hormone, acting in part through the insulin-like growth factor axis, rescues developmental, but not metabolic, activity in the mammary gland of mice expressing a single allele of the prolactin receptor. Endocrinology 2002, 143:4310-4319.
31. Jones FE, Stern DF: Expression of dominant-negative ErbB2 in the mammary gland of transgenic mice reveals a role in lobuloalveolar development and lactation.Oncogene 1999, 18:3481-3490.
32. Ewan KB, Shyamala G, Ravani SA, Tang Y, Akhurst R, Wakefield L, Barcellos-Hoff MH: Latent transforming growth factor-beta activation in mammary gland: regulation by ovarian hormones affects ductal and alveolar proliferation.Am J Pathol 2002, 160:2081-2093.
33. Zhou J, Chehab R, Tkalcevic J, Naylor MJ, Harris J, Wilson TJ, Tsao S, Tellis I, Zavarsek S, Xu D, et al.: Elf5 is essential for early embryogenesis and mammary gland development during pregnancy and lactation. EMBO J 2005, 24:635-644.
34. Keele CA, Neil E, Joels N.

Physiology of Reproduction. In Samson Wright's Applied Physiology 13th ed. Oxford Medical Publ 1982; 563-599.

35. Ben-Jonathan N, Hugo ER, Brandebourg TD, LaPensee CR. Focus on prolactin as a metabolic hormone. Trends Endocrinol Metab. 2006 Apr;17(3):110-6. Epub 2006 Mar.
36. Horseman ND: Prolactin and mammary gland development. J Mammary Gland Biol Neoplasia 1999, 4:79-88.
37. Heil SH, Subramanian MG. Alcohol and the hormonal control of lactation. Alcohol Health Res World. 1998;22(3):178-84.
38. Jackson KM, Nazar AM. Breastfeeding, the immune response, and long-term health. J Am Osteopath Assoc. 2006 Apr;106(4):203-7
39. Kuhn L, Peterson I. Options for prevention of HIV transmission from mother to child, with a focus on developing countries. Paediatr Drugs. 2002;4(3):191-203.
40. Bode L. Recent advances on structure, metabolism, and function of human milk oligosaccharides. : J Nutr. 2006 Aug;136(8):2127-30.
41. Watson CJ. Involution: apoptosis and tissue remodelling that convert the mammary gland from milk factory to a quiescent organ. Breast Cancer Res. 2006;8(2):203. Epub 2006 Apr 10
42. Barcellos-Hoff MH, Ewan KB: Transforming growth factor-beta and breast cancer: Mammary gland development.Breast Cancer Res 2000, 2:92-99.
43. Schnitt SJ. Breast cancer in the 21st century: neu opportunities and neu challenges. Mod Pathol. 2001 Mar;14(3):213-8

Bloodletting

Bloodletting represents the folly of the past, the sorcery and the misguided physiology that we now proudly say marked the dark ages of medicine - or did it ? In fact, bloodletting has a place in medicine today and a history that is worthy of review.

The four humors

The traditionally held "Father of Medicine" was the Greek physician Hippocrates (460-370 BC), who taught medicine on the island of Cos. One of his major precepts was the rule of harmony, the theory that all body systems were in balance and that disease resulted from an imbalance. Galen (130-201 AD) was the physician to Marcus Aurelius and became the heir to Hippocrates and one of the most influential physicians of all times. He taught the importance of maintaining balance between the four bodily fluids, or "humors" : blood, phlegm, yellow bile, and black bile. Each fluid was associated with a specific personality characteristic. **Blood** was associated with a sanguine personality, that is laughter, music, and a passionate disposition. Someone with a **phlegmatic** personality was sluggish and dull, while **yellow bile** represented an individual quick to anger or choleric (cholera meaning yellow as in yellow fever). Lastly, **black bile** represented a melancholic or depressed personality, melan meaning black. It was the job of the physician to restore harmony in those four humors by the use of emetics, cathartics, purgatives, and by bloodletting. Bleeding was used to reduce excess circulation, to slow the pulse, and to "reduce irritation", all felt to be the cause of inflammation. Dr. Benjamin Rush, a signer of the Declaration of Independence, was a major figure in colonial American medicine and was an important proponent of bleeding, though unfortunately he mistakenly thought that the body held 12 instead of 6 quarts. Shortly before his death, George Washington was bled 4 ‡ quarts in 24 hours for an infected throat and died not long after.

Early transfusion was based on the notion that giving blood would help balance the humors. On June 15, 1667, Jean Davis replaced part of a patient's blood with sheep's blood though the patient died and Dr. Davis was subsequently accused of murder. Transfusion was set back until the 19th century, well before blood typing was understood.

The First Bloodletting Technique

Leeches were used for bleeding by Syrian physicians as early as 100 BC. Hirudo Medicinalis were imported to the United States from Europe and have suction cups at both ends. On the "business end" are 3 sharp teeth and hirudin, which is an anticoagulant that is now being investigated for use in some medical procedures. The leeches were placed on the patient and drank their fill, to be used again several days later after being stored in glass or very fancy porcelain jars . Leeches could be directed to small areas such as the mouth, ear, or vagina, by placing them in a small receptacle called a "leech tube". Toward the end of the 19th century, technology began to take over and artificial leeches were manufactured which drew blood essentially the same way.

8

Pharmacological Aspects of Drugs for Breast Disorder

Review Article

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Right from the stage of development, the breasts are prone to a variety of disorders. Many of these disorders are benign, requiring either no treatment or mild surgical treatment. However, breast cancer has become an important cause of morbidity and mortality in the recent past. Early diagnosis and treatment are the mainstay of management of this condition.

Breast disorders

Breast pain

Breast pain can be cyclic or non cyclic. Cyclic breast pain can occur during the late luteal phase of the menstrual cycle, in association with premenstrual syndrome or independently and resolve at the onset of menses. Non-cyclic breast pain is unrelated to the menstrual cycle. Identifiable triggers include tender cyst, rupture through the wall of an ecstatic duct or a particularly tender area of breast nodularity.

Treatment- In the absence of a mass or discharge, mild symptoms of cyclic pain warrant reassuring the patient regarding the absence of serious disease. Controlling the cyclic breast pain may require the use of oral contraceptives to modulate the hormonal changes during the menstrual cycle. In addition, the drugs tamoxifen and danazol can be very effective in reducing breast pain. For mild cases, evening primrose oil, a fatty acid supplement, can provide relief of symptoms if taken regularly over a period of several weeks. Precise fitting brassiere to provide support for pendulous breast may provide pain relief.

Danazol is an isoxazole derivative of ethisterone with weak progestational, androgenic and glucocorticoid activities. It inhibits the mid-cycle surge of LH and FSH. The major adverse effects are weight gain, edema, decreased breast size, acne and oily skin, increased hair growth, deepening of voice, headache, hot flushes, changes in libido and muscle cramps.

Postmenopausal women on estrogen supplements may find relief by lowering the dose of the supplemental estrogen or by discontinuing it entirely or by the addition of an androgen to estrogen replacement therapy. Oral contraceptive preparations containing low dose estrogen (20 mg of ethinyl estradiol) and 19-nor progestins may be beneficial.

For women not on supplemental estrogen, anti-inflammatory medications etc. may be utilized to manage the pain. No standard regimen has been recommended for management of moderate to severe breast pain. Initial treatment may include the use of mild analgesic agents such as acetaminophen, non-steroidal anti-inflammatory drugs (NSAIDs) as aspirin.

Other approaches, as mentioned above, include tamoxifen, at a dose of 10 mg daily for three to six months. If there is no response, a change to danazol, 200 mg daily (or only during the luteal phase of the menstrual cycle) can be made. Evening primrose oil, 1-3 g daily orally has been tried. Gonadotrophin releasing hormone (GnRH) agonists have also been tried in severe pain.

For non-cyclic pain truly arising from breast, the patient is treated as for cyclic pain. Diffuse chest wall pain may require oral or topical NSAIDs. Some patients get temporary or permanent relief from the use of combination of anesthetic and steroidal drugs injected into the tender site.

Nipple discharge

Nipple discharge is a common breast symptom. Although, this symptom is particularly alarming, only 5% of these patients are found to have various underlying disease. Nipple discharge is considered to be pathologic if it is spontaneous, arises from a single duct, is persistent and contains gross or occult blood. Age is an important risk factor for development into cancer. Fig 2 gives the algorithm for the evaluation and treatment of breast discharge.

Fibrocystic change

Fibrocystic changes present in an otherwise normal breast do not require treatment per se. Excessive caffeine consumption can cause the development of fibrocystic changes. Women with symptomatic fibrocystic changes particularly with complaints of breast pain may be counselled to limit their caffeine intake or to undergo drainage of large cyst if they are present.

Breast infection

Breast infections are classified as breast abscesses or as mastitis.

Abscesses

Abscesses are well-defined collections of infected material or pus that generally require some form of drainage for management. Symptoms include redness or warmth in the area of the abscess and breast pain. Infections including fever or

chills may be present.

Breast abscesses that occur directly behind the nipple are often caused by a condition known as periductal mastitis or duct ectasia. These types of breast abscesses tend to recur even after satisfactory drainage and antibiotic therapy. Multiple recurrences of abscesses behind the nipple may eventually lead to the recommendation to have the diseased ducts surgically removed.

Abscesses that occur further away from the nipple in other quadrants of the breast can be seen in the immediate post-partum period. These abscesses may respond to drainage using a needle-guided approach but occasionally will require surgical drainage in addition to antibiotic therapy.

Breast abscesses in post-menopausal women that occur outside of the nipple area require special consideration. Without an underlying cause such as lactation or periductal mastitis, it is uncommon for post-menopausal women to develop abscesses. It is important to perform a thorough imaging evaluation including mammogram and ultrasound to exclude an underlying breast cancer. Drainage of an abscess in this age group always requires close follow up to make sure there is not an underlying breast tumor.

Mastitis

Mastitis refers to an infection in the soft tissue of the breast, but no well-defined collection that requires drainage. This is most commonly seen in women who are lactating and breastfeeding. Most cases of mastitis will respond to antibiotic therapy. Severe cases may require intravenous antibiotics and when symptoms begin to improve, oral antibiotics can be utilized. Women who are beyond childbearing age who develop symptoms of diffuse redness in one breast should be evaluated for inflammatory carcinoma.

Phyllodes tumor

Phyllodes tumors are rare solid lumps that usually present as a mass found during a woman's breast self-examination or on a routine physical examination. Phyllodes tumors appear very similar to a benign lump known as a fibroadenoma. These lumps are usually well circumscribed and painless. Imaging evaluation including a mammogram and ultrasound is usually performed and when a solid lump is identified a biopsy is important to obtain tissue for accurate diagnosis. Risk factors for phyllodes tumor are rapid growth and size greater than 2 cm at the time of the evaluation. Phyllodes tumors are not all cancerous. Many will be benign and will not require further evaluation. Malignant phyllodes tumors are best managed with a wide excision of normal breast tissue around the tumor to obtain clean margins. Very large malignant phyllodes tumors may require complete removal of the breast for management.

Paget's disease

Paget's disease is the identification of breast cancer cells within the skin around the nipple. Symptoms include the development of redness, itching or peeling of the skin on the nipple of their breast. Nipple discharge may be absent. The diagnosis of Paget's disease can be made by performing a biopsy of the nipple skin. In the vast majority of cases Paget's disease of the nipple is associated with an underlying breast cancer. Women identified with Paget's disease and an underlying breast cancer are most often managed with a total mastectomy, however, there are exceptions to this rule.

Focal lesions

Careful examination is required to distinguish solitary, discrete, dominant, persistent masses and vague nodularity and thickening. Small focal lesions require mammography and referral to a surgeon.

The triple test (palpation, mammography, often is conjunction with ultrasonography, biopsy) is usually required for women more than 35 years of age with dominant masses. Among carrier of the BRCA mutation, fibroadenomas require diagnostic core needle biopsy or fine needle aspiration, as medullary cancer may be found in such patients.

Breast cancer

Next to skin cancer, breast cancer is the most common type of cancer in women, only to lung cancer as a cause of death. Endogenous estrogen levels influence breast cancer. Higher level of estrone, total estradiol and free estradiol and lower level of estradiol bound to sex hormone binding globulin was found in women who developed breast cancer than in women who remained free of breast cancer. Early menarche and late menopause are positive risk factors. Oophrectomy resulting in early menopause is a negative factor. Postmenopausal estrogen replacement therapy increases the risk of breast cancer. Breast cancer gives BRAC1 and BRAC2 are implicated to 3 to 5 % of breast cancers. Ataxia telangiectasia gene also predispose to cancer.

Prevention of breast cancer

Both tamoxifen and raloxifene have been used for prevention of breast cancer. Their use however, have been offset because of complication due to increased blood coagulability and endometrial cancer in case of tamoxifen and low maturation of cataract. Both these drug if used at all, should be used cautiously for breast cancer prevention since both decrease but do not eliminate breast cancer risk and both are associated with significant complications.

Intensive and frequent screening with

use of multimodality imaging may be required for high-risk patients.

Chemotherapy for breast cancer

The need for chemotherapy depends on how much the cancer has spread. In some, chemotherapy will be recommended before surgery to shrink a large tumor so that it can be removed more easily. In others, chemotherapy is given as an adjuvant therapy following surgery and radiation therapy to eliminate the occult metastases responsible for late recurrences. Chemotherapy is usually given in cycles: a treatment period followed by a recovery period, then another treatment period and so on.

The presence or absence of estrogen, progesterone and HER-2/ neu receptors in the cytoplasm of tumor cells is of paramount importance in the management of breast cancer. Patients whose primary tumors are receptor positive have more favorable courses than those whose tumors are receptor negative.

Adjuvant systemic therapy

Adjuvant cyclophosphamide, methotrexate and fluorouracil (CMF) given on days 1 and 8 of each month for 12 months showed significant improvement in survival for premenopausal women with node positive diseases.

The anthracycline antibiotics, doxorubicin and epirubicin have been studied and compared with CMF.

The use of six cycles of fluorouracil plus adriamycin and cyclophosphamide (FAC) or fluorouracil plus epirubicin and cyclophosphamide (FEC) has shown improved survival compared to CMF alone. For node negative patients, most oncologists offer 4 cycles of AC or 9 cycles of CMF in the adjuvant setting.

For node-positive patients, taxanes are now frequently combined with anthracycline-based regimens, as considerable reductions in recurrence and improvement in disease free survival was seen with the use of paclitaxel. Paclitaxel is now approved for use as adjuvant therapy in node positive breast cancer. The current recommendation for adjuvant therapy is for 3-6 months of commonly used regimens. The addition of taxanes requires an additional duration of therapy of upto 6 months. Increasing the frequency of chemotherapy administration (dose dense chemotherapy) has been shown to be superior to standard dosing in recent trials.

Adjuvant hormonal therapy with tamoxifen or anastrozole, the aromatase inhibitor is effective in decreasing recurrence and mortality in women with ER-positive tumors.

Use of high dose chemotherapy with autologous bone marrow or stem cell transplantation showed inconsistent results in different trials and recommendations are not available.

Palliative treatment

This is done for disseminated disease incurable by surgery.

Hormone therapy

The choice of endocrine therapy depends on menopausal status of the patient. Within one year of their last menstrual period, women are considered to be premenopausal and women whose menstruation ceased more than a year ago are postmenopausal. The term primary hormonal manipulation is used if endocrine therapy is the initial choice and subsequent endocrine treatments are called secondary or tertiary hormonal manipulations.

Premenopausal patient

Tamoxifen is the endocrine treatment of choice for primary hormonal therapy. It is usually given orally in a dose of 20 mg daily. Toremifene, a tamoxifen analogue has side effects similar to tamoxifen but it is less likely to cause uterine cancer. Chemical ovarian ablation using a GnRH analog can be utilized.

For secondary or tertiary hormonal therapy on patients who do not respond to tamoxifen or oophrectomy, cytotoxic drugs or another form of endocrine therapy can be tried. Patients who relapse often showing some improvement after oophrectomy should receive tamoxifen or an aromatase inhibitor. Megestrol acetate, a progestational agent may be tried. These drugs cause less morbidity and mortality than surgical adrenalectomy and can be discontinued once the patient improves.

Postmenopausal women

For primary hormonal therapy, tamoxifen 20 mg daily or anastrozole, 1 mg daily is the initial therapy of choice. Anastrozole, an aromatase inhibitor has fewer side effects than tamoxifen and has been found to be at least equally as effective.

Patients not responding to tamoxifen or anastrozole should be given cytotoxic drugs such as CMF or AC as secondary or tertiary hormonal therapy.

Trastuzumab, a monoclonal antibody that binds to HER-2/neu receptors on the cancer cell has been shown to increase survival when combined with AC or paclitaxel in patients with metastatic disease having HER-2/neu oncogene over expression.

Medications used to treat breast cancer

Selective estrogen receptor modulators (SERMs)

These drugs have a chemical resemblance to the hormone estrogen. Breast cancers that are estrogen dependent depend on estrogen in order to survive and reproduce. SERMs bind to estrogen receptors (ER) in the breast cancer cells

and block estrogen from breast cancer cells thereby starving the cancer cells.

Tamoxifen, a competitive partial agonist inhibitor of estradiol at the estrogen receptor is extensively used in the palliative treatment of advanced breast cancer in postmenopausal women. It has been approved by US FDA to help treat both early and advanced stages of breast cancer and also for use in post-menopausal women at high risk of breast cancer. It is a non-steroidal agent given orally in doses of 10-20 mg twice daily. Hot flushes, nausea, vomiting are the common side effects. Increased risk of endometrial cancer is a major limiting side effect. Other side effects include menstrual irregularities, vaginal bleeding, increased risk of thromboembolic events.

Toremifene is a structurally similar compound with similar properties and indications as tamoxifen.

Raloxifene is another partial estrogen agonist antagonist at some but not all target tissues. It does not stimulate the endometrium or breast. Though raloxifene has been FDA approved for the prevention of postmenopausal osteoporosis, a large clinical trial (study of tamoxifen and raloxifene, STAR) is currently underway to investigate whether it is as effective as tamoxifen in preventing breast cancer. Side effects include hot flushes, leg cramps, a threefold increase in deep vein thrombosis and pulmonary embolism.

Other SERMs under trail for treatment of breast cancer include arzoxifene and is in phase III clinical trials. Arzoxifene is described to be a next generation SERM.

Aromatase inhibitors

These drugs work by binding to the body's aromatase enzyme, an enzyme required for estrogen synthesis. This binding prevents production of estrogen resulting in starvation of estrogen dependent cancer cells.

Anastrozole, a selective non - steroidal inhibitor of aromatase is approved for first line treatment of post menopausal women with metastatic breast cancer that is ER-positive, and has progressed while on tamoxifen therapy and as adjuvant therapy of postmenopausal women with hormone-positive, early stage breast cancer. It is given in a dose of 1 mg orally daily. Side effects include mild nausea, headache, fatigue, hot flushes, anthralgias.

Letrozole, a non-steroidal competitive inhibitor of aromatase acts in the same way as anastrozole. It is also indicated for first line treatment of postmenopausal women with hormone receptor positive metastatic breast cancer and for second line treatment of postmenopausal women with advanced breast cancer after progression on tamoxifen therapy. It is given in a dose of 2.5 mg orally daily.

Exemestane, a steroid molecule is an irreversible inhibitor of aromatase and is referred to as 'suicide substrate'. It has been approved for use in advanced breast cancer in postmenopausal women whose disease has progressed on tamoxifen therapy. It is given in an oral dose of 25 mg daily. They have similar side effect profile as anastrozole.

Biologic response of modifiers

These drugs bind to certain proteins on breast cancer cells, thereby preventing their growth.

Trastuzumab (Herceptin) is a monoclonal antibody that attaches to the HER2/neu protein found on breast cancer cells, thus preventing them from growing and dividing. It is given as IV loading dose of 4 mg/kg and then 2 mg/kg/week as maintenance dose. Side effects include nausea, vomiting, infusion related hypersensitivity reaction. Cardiomyopathy, myelosuppression and pulmonary toxicity are delayed effects. Trastuzumab is only indicated for breast cancer patients who over express the HER2/neu protein. Patients should be tested for HER2/neu expression to determine whether trastuzumab is a viable treatment option.

Other hormonal therapies

Selective Estrogen Receptor Downregulators (SERDs)

SERDs are also termed as "pure antiestrogens" and include fulvestrant, RU5866, SR16234, etc. SERDs are devoid of any estrogen agonist activity.

Fulvestrant is the first FDA approved SERD for postmenopausal women with hormone receptor positive metastatic breast cancer that has progressed despite antiestrogen therapy. It is hypothesized to have an improved safety profile, faster onset and longer duration of action than SERMs due to their pure ER antagonist activity. This steroidal antiestrogen binds to the ER with an affinity more than 100 times that of tamoxifen and inhibits its dimerization and increases its degradation. As a consequence of ER down regulation ER mediated transcription is abolished, completely suppressing the expression of estrogen dependent genes. This may partially explain why fulvestrant demonstrates efficacy against tamoxifen resistant breast cancer. Maximum plasma concentrations are reached about 7 days after intramuscular administration and are maintained over a period of 1 month. It is administered as a 250 mg intramuscular injection at monthly intervals. Side effects include gastrointestinal upset, headache, back pain, hot flushes, pharyngitis, asthenia, etc.

GnRH analogs

GnRH and its analogs (leuprolide, goserelin, nafarelin, buserelin, etc.) block the release of estrogen in breast cancer patients, thereby preventing breast cancer

cells from growing. Side effects include transient flare of tumor symptoms, pain at injection site, hot flushes, impotence and gynecomastia.

Cytotoxic agents

5-Flurouracil (5-FU)

5-FU is a prodrug, which undergoes biotransformation reaction to ribosyl and deoxy ribosyl nucleotide metabolites. One of the metabolites, 5-fluoro-2'-deoxyuridine-5'monophosphate (fdUMP) forms a covalently bound ternary complex with thymidylate synthase enzyme and the reduced folate $N^{5,10}$-methylenetetrahydrofolate, a reaction critical for the synthesis of thymidylate; resulting in inhibition of DNA synthesis through "thymineless death". It also interferes with RNA processing and mRNA translation.

Fluorouracil is one of the drugs used in CMF regimen for premenopausal women with node-positive disease. It is given in a dose of 15 mg/kg/day intravenously for 5 days by 24-hour infusion and 15 mg/kg weekly intravenously. Nausea, mucositis, diarrhoea, myelosuppression, hand and foot syndrome and neurotoxicity are the observed side effects with this drug.

Capecitabine

Capecitabine is a pyrimidine antimetabolite, which is converted to 5'-deoxy-5-flurocytidine by carboxylesterase activity in liver and other normal and malignant tissues. It is then converted to 5'deoxy-flurodeoxy uridine by cytidine deaminase. Finally, thymidine phosphorylase cleaves off the 5'-deoxy sugar, leaving intracellular 5-flourouracil (5-FU).

Capecitabine is approved by the FDA for the treatment of metastatic breast cancer in patients who have not responded to a regimen of paclitaxel and an anthracycline antibiotic and also in metastatic breast cancer when used in combination with docetaxel in patients who have had a prior anthracycline-containing regimen. The recommended dose is 2500 mg/m^2 daily, orally in two divided doses with food for 2 weeks followed by a rest period of 1 week. The cycle is then repeated two more times. Diarrhea, hand and foot syndrome, myelosuppression, nausea and vomiting are the delayed side effects of this drug.

Cyclophosphamide

Cyclophosphamide is an alkylating agent, which must be activated by liver microsomal cytochromeP450 mixed function oxidase system to 4-hydroxy-cyclophosphamide and aldophosphamide. These metabolites are delivered by the blood stream to both tumor and normal tissue where non-enzymatic cleavage of aldophosphamide to the cytotoxic drugs phosphoramide mustard and acrolein occurs.

As a single agent, a daily oral dose of 100 mg/m^2 for 14 days has been recommended as adjuvant therapy for breast cancer. A higher dosage of 500 mg/m^2 intravenously every 2 to 4 weeks in combination with other drugs often is employed in the treatment of breast cancer. Gastrointestinal ulceration, cystitis, nausea, vomiting, myelosuppression, may occur as side effects.

Taxanes

Paclitaxel and docetaxel function as mitotic spindle poison through high affinity binding to microtubules with enhancement of tubulin polymerization. This promotion of microtubule assembly occurs in the absence of microtubule-associated proteins and guanosine triphosphate and results in inhibition of mitosis and cell division.

Paclitaxel is administered as a 3 hour infusion of 135 to 175 mg/m^2 every 3 weeks or as a weekly 1 hour infusion of 80 to 100 mg/m^2 intravenously over 1 hour every 3 weeks. Paclitaxel exerts its primary toxic effects on the bone marrow. Neutropenia occurs in 8 to 11 days after a dose which reverses by days 15 to 21. Doses as high as 250 mg/m^2 over 24 hours can be tolerated if used with filgrastim (granulocyte colony stimulating factor; G-CSF). Peripheral neuropathy can occur with high doses. Hypersensitivity reaction can occur with the drug.

Docetaxel causes more severe but short-lived neutropenia than paclitaxel. Fluid retention leading to peripheral edema, pleural and peritoneal fluid and pulmonary edema can occur with docetaxel. Oral dexamethasone, 8 mg/day, given 1 day prior to drug infusion and continued for 3 days ameliorates fluid retention.

Paclitaxel is now approved for and increasingly employed as adjuvant therapy in node positive breast cancer.

Anthracycline antibiotics

Anthracyclines exert their cytotoxic action through inhibition of topoisomerase II, binding to DNA through intercalation with consequent blockade of the synthesis of DNA and RNA and DNA strand scission, binding to cellular membranes to alter fluidity and ion transport and generation of free radicals.

Doxorubicin (adriamycin) is given in a dose of 50 to 75 mg/m^2, by rapid IV infusion. The dose is repeated after 21 days. It is a valuable component of various regimens of chemotherapy for adjuvant and metastatic carcinoma of breast.

Epirubicin, a doxorubicin analogue, was approved for use as a component of adjuvant therapy of early stage, node-positive breast cancer but is now also used for the treatment of metastatic breast cancer.

Myelosuppression is a major dose limiting complication with leucopenia appearing first followed by thrombocytopenia and anemia. Stomatitis, gastrointestinal disturbances and alopecia can occur. Acute and chronic forms of cardiotoxicity can occur. They can produce "radiation recall" reaction with erythema and desquamation of the skin observed at sites of prior radiation therapy.

Monoclonal antibodies

Trastuzumab is a humanized monoclonal antibody against the HER2/neu (Erb B-2) member of the epidermal growth factor family of cellular receptors. This HER2/neu glycoprotein encodes a tyrosine kinase that activates downstream signals and enchances metastatic potential and inhibits apoptosis. HER2/neu has been shown to be overexpressed in upto 30% of breast cancers and has also been shown to be associated with clinical resistance to cytotoxic and hormone therapy. Trastuzumab is approved for HER2/neu overexpressing metastatic breast cancer in combination with paclitaxel as initial treatment or as monotherapy following chemotherapy relapse. Trastuzumab is also synergistic with other cytotoxic agents in HER2/neu over expressing cancers. It is given as intravenous loading dose 4 mg/kg and then maintained at 2 mg/kg/week. Side effects include fever, chills, nausea, dyspnea and rashes and infusion related hypersensitivity reactions. Cardiomyopathy, myelosuppression and pulmonary toxicity have been reported as delayed effects.

Bevacizumab is a monoclonal antibody active against vascular endothelial growth factor (VEGF) and inhibits its interaction with the VEGFR1 andVEGFR2 receptors. VEGF expression is increased in a variety of tumor types including breast, ovarian, non-small cell lung and colorectal cancer. Its expression correlates with neovascularization within tumor masses. Though bevacizumab has been tried in breast cancer in combination with chemotherapy, its status for this condition is not yet clear.

Recent advances

Omega-3-fatty acids, docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA) combined with propofol have been studied on breast cancer cell lines in vitro. The results showed that propofol and DHA or EPA have been much more significant effect on cancer cells when used in combination as conjugates than when used alone. The conjugates inhibited cancer cell adhesion, reduced cell migration and increased apoptosis.

Metronomic antiangiogenic chemotherapy refers to the prolonged administration of relatively low drug doses at close regular intervals with no significant breaks. This has been studied at preclinical level using single chemotherapeutic drugs, frequently in combination with a targeted antangiogenic drugs. A doublet combination metronomic chemotherapy treatment using two oral drugs, UFT, a 5-flourouracil (5-FU) prodrug administered by gavage and cyclophosphamide in mouse model of advanced, terminal metastatic human breast cancer was found to be superior to monotherapy and seemed to be a safe and highly effective experimental antimetastatic therapy.

S1 is a newly developed fluorinated pyrimidine, containing 1M tegafur (FT) and two classes of modulator, 5-cholro-2,4-dihydroxypyrimidine (CDHP) and potassium oxonate (oxo) at a molar ratio of FT:CDHP:oxo=1:0.4:1. S1 is administered orally and may be a promising agent as third line chemotherapy for the heavily treated breast cancer patients. Side effects include neutropenia, diarrhoea and stomatitis

Cyclooxygenase enzyme has recently been identified as a potential target for breast cancer. Aromatase transcript expression and enzyme activity in breast tissue has been shown to be greater than that in the normal breast tissue and prostaglandins has been shown to increase CYP19 expression and aromatase activity in breast cancer cells. Higher levels of COX-2 isoform have been observed in breast cancer tissue compared to normal breast tissue. A strong association between CYP19 gene expression and the expression of COX genes has been found. Both NSAIDS and COX selective inhibitors have been shown to suppress aromatase in RNA expression and enzyme activity in breast cancer cells. Thus drugs targeting COX enzyme may serve as potential targets for treatment of breast cancer.

Phosphorylated Akt (P-Akt) is an attractive molecular target as it contributes to the development of breast cancer and confers resistance to conventional therapies. Akt also serves as a signaling intermediate for receptors such as human epidermal growth factor receptor (HER)-2, which is overexpressed in 30% of breast cancers. Celecoxib analogues have been found to be potent inhibitors of P-Akt signaling and also to kill breast cancer cells that overexpress HER-2. An association between HER-2 and P-Akt also been shown in primary breast tissue, suggesting that these inhibitors may benefit patients requiring new therapeutic options.

Pharmacogenomic markers and use of nanoparticles will allow simultaneous tumor targeting and drug delivery is a unique manner. Application of pharmacogenomics may be applied for prediction of response, resistance and toxicity of both new and existing anticancer agents. Moreover, individualized selection of the most

effective adjuvant chemotherapy for breast cancer based on the molecular characteristics of the tumor could improve the risk: benefit ratio of current therapies and could also streamline the development of new regimens for patients who have not responded to the existing regimens.

Other agents like prebiotics and resveratrol have also been tried in breast cancer. Dietary treatment with inulin or oligofructose incorporated in the basal diet for experimental animals have been shown to reduce the incidence of mammary tumors induced in Sprague-Dawley rats by methylnitrosourea. Moreover, dietary treatment with these agents has been shown to potentiate the effects of sub therapeutic doses of some cytotoxic drugs. Such dietary treatment may thus be introduced into classic protocols of human cancer treatment as a new, non-toxic and easily applicable adjuvant cancer therapy.

Resveratrol, a polyphenolic compound found in plants has been shown to afford protection against several types of cancer. Its antioxidant, anti-inflammatory and apoptotic properties may modulate cell cycle and estrogen receptor functions in breast cancer lines. This has shown a remarkable promise as a potent chemotherapeutic agent in breast cancer.

Anticancer agents from natural products

Several Chinese investigators have shown a potential of natural products for use in breast cancer.

Chimmitecan is a novel amphoteric 9-substituted camptothecin, a natural alkaloid isolated from Camptotheca acuminata. Chimmitecan has been shown to confer improved anticancer pharmacological profiles both in vitro and in vivo.

Salvicin, a natural product derivative from Salvia prionitis, is a new topoisomerase II inhibitor. It showed prominent anti-multidrug resistance effects and transcription factor c-Jun was shown to play a principal role in exerting this effect.

Pseudolarix acid B, from Chinese plant Pseudolarix kaempferi has been shown to cause depolymerization of tubulin by binding to a novel site and abrogated secretion of VEGF. All these compounds are in the early experimental stages and need further evaluation.

References

1. Saten RJ, Mansel R. Benign breast disorders. N Engl J Med 2005; 353: 275-285.
2. Giuliano AE. Breast. In: Tierney LM Jr, Mcphee SJ, Papadakis MA, editors. Current Medical Diagnosis and Treatment. 45th edition. Lange Medical Books/Mc Graw-Hill New York 2006: 702-727.
3. Chabner BA, Amrein PC, Druker BJ, Michaelson MD, Mitsiades CS, Goss PE, et al. Antineoplastic agents. In: Brunton LL, editors. Goodman and Gilman's The Pharmacological Basis of Therapeutics.11th edition. McGraw –Hill, New York 2006: 1315-1403.
4. Munoz R, Man S, Shaked Y, Lee CR, Wong J, Francia G, et al. Highly efficacious non toxic preclinical treatment for advanced metastatic breast cancer using combination oral UFT-cyclophophamide metronomic chemotherapy. Cancer Res 2006; 66: 3386-3391.
5. Anonymous. Trastuzumab: new indication. Metastatic breast cancer, in combination with docetaxel: promising, but more evaluation is needed. Prescrire Int 2006; 15: 3-5.
6. Brueggemier RW, Diaz-Cruz ES. Relationship between aromatase and cyclooxygenases in breast cancer: potential for new therapeutic approaches. Minerva Endocrinol 2006; 31:13-26.
7. Kucab JE, Lee CS, Chen CS, Zhu J, Gilks CB, Cheang M, et al. Celecoxib analogues disrupt Akt signaling, which is commonly activated in primary breast tumors. Breast Cancer Res 2005; 7: R796-807.
8. Yezhelvev MV, Gao X, Xing Y, Al-Hajj A, Nie SO, Regan RM. Emerging use of nanoparticles in diagnosis and treatment of breast cancer. Lancet Oncol 2006; 7: 657-67.
9. Pusztai L, Symmans FW, Hortobagyi GN. Development of pharmacogenomic markers to select preoperative chemotherapy for breast cancer. Breast Cancer 2005; 12: 73-85.
10. Taper HS, Roberfroid MB. Possible adjuvant cancer therapy by two prebiotics - inulin or oligofructose. In vivo 2005; 19: 201-204.
11. Lecorre L, Chalabi N, Delort L, Bignan YJ, Bernard-Gallon DJ. Resveratrol and breast cancer chemoprevention: molecular mechanisms. Mol Nutr Food Res 2005; 9: 462-71

Breast problems in Infancy and Childhood

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Breast development

The mammary gland begins development early in embryological life and only culminates in the postpartum lactation of the adult female. During the fourth week of gestation, paired ectodermal thickenings termed mammary ridges or milk lines develop on the ventral surface of the embryo and extend in a curvilinear fashion towards the midline from the axillae to the medial thigh, Normally these ridges disappear except at the level of the fourth inter-costal space on the anterior thorax, where the mammary gland subsequently develops. In the fifth week of gestation, the remnant of the mammary ridge ectoderm begins to proliferate and is termed as the primary mammary bud, by the 10th week, the primary bud begins to branch, yielding secondary buds and by the 12th week, and these buds continue lengthening and branching. During the 20th week, small lumina develop within the buds that coalesce and elongate to form the lactiferous ducts. The mesoderm surrounding the area proliferates, creating the nipple. The surrounding areola is formed by the ectoderm during the fifth month of gestation. The areola also contains other epidermal glands, including glands of Montgomery. At term, approximately 15-20 lobes of glandular tissue have formed, each containing a lactiferous duct, which eventually develop into the mammary lobules of the adult breast. At birth, the breast is composed of radially arranged mammary lobes draining via lactiferous ducts into ampullae that empty onto the nipple. These rudimentary mammary glands are identical in males and females. Shortly after birth, the nipples become everted and the areolae develop a slight increase in pigmentation.

Several factors including hormones like progesterone, growth hormone, insulin like growth factor, estrogen, prolactin, adrenal corticoids, and triiodothyronine regulate growth of the developing mammary gland

Congenital malformations

Congenital breast malformations range from 2-6 percent. Minor malformations may not even be recognized, while major deformities may cause significant functional, psychological, and aesthetic concerns. These malformations may be in the form of supernumerary breast tissue or the absence or underdevelopment of breast tissue.

Supernumerary breast- The presence of supernumerary breast tissue indicates incomplete involution of the milk line, resulting in the formation of accessory mammary tissue from the redundant clusters of ectopic primordial breast cells. Approximately one third of affected individuals have more than one site of supernumerary breast tissue development. Most of this accessory breast tissue has no physiologic significance, but some may enlarge with the onset of puberty, pregnancy, or lactation, and can be the site of breast carcinoma. The accessory breast tissue commonly occurs in the thoracic or abdominal portions of the milk line(67%), often just below the inframammary crease and more often on the left side of the body followed by axilla (20%). The remaining locations include buttock, back, face, and neck. Supernumerary tissue present in any location other than along the milk line represents a migratory arrest of breast primordium during chest wall development.

Kajava's classification for supernumerary breast tissue is as follows.

Class I : complete breast with nipple, areola, and glandular tissue.

Class II : nipple and glandular tissue but no areola.

Class III : areola and glandular tissue but no nipple.

Class IV : glandular tissue only.

Class V: nipple and areola but no glandular tissue (pseudomamma).

Class VI: nipple only (polythelia).

Class VII : an areola only (polythelia areolaris).

Class VIII : Consists a patch of hair only (polythelia pilosa).

Polythelia- The most common form of supernumerary breast tissue is polythelia.Males and females have an overall equal incidence. Most cases are sporadic, however 6% are familial, Polythelia is often associated with Nephrologic abnormalities such as cysts, duplications, or unilateral renal agenesis, renal adenocarcinoma and even end-stage renal disease.

Polymastia- The second most common form of supernumerary breast tissue, occurring in 1-2% of the female population, most common being Kajava

Classes I. The most common location is in the axilla followed by the inframammary region, Most cases are sporadic,also has been observed as a heritable trait. The presence of supernumerary tissue can be psychologically disturbing to adolescents. Excision is recommended prior to puberty or at any age when the condition is recognized and becomes of concern to the individual.

The absence or underdevelopment of breast- The underdevelopment or absence of breast tissue is less common than the supernumerary tissue. These conditions may result from partial or complete underdevelopment of the mammary bud, it can be unilateral or bilateral.

Amastia- The complete absence of glandular tissue, nipple, and areola is very rare. Amastia can be iatrogenic due to unnecessary surgical removal of mammary bud. Amastia may be associated with scalp defects, ear abnormalities, renal hypoplasia, and cataracts it may also be associated with autosomal dominant Finlay-Marks syndrome.

Hypoplasia- The presence of very small rudimentary breasts, is the most common form. This may be associated with scalp defects, ear and renal anomalies. Hypoplasia also may occur in patients with Turner syndrome, congenital adrenal hyperplasia

Aplasia- The absence of glandular tissue in the presence of a nipple and areola, is most commonly encountered in Poland syndrome, This is often accompanied by musculoskeletal deformities of the chest wall and ipsilateral upper extremity.

Asymmetry- Asymmetry of breast development is not rare, it may be insignificant or may be associated with chest wall anomalies. Asymmetry mostly needs reassurance, however if it is significant may require cosmetic repair. The surgical therapy to achieve breast symmetry may best be performed in late adolescence when the contralateral breast has reached its mature size and shape. However, earlier intervention may be indicated in the patient with a significant sense of deformity that is adversely affecting body image. Techniques to achieve symmetry may include prosthetic devices such as implants or expanders, autologous tissue such as the latissimus dorsi or rectus abdominis muscles, or both

Athelia - The absence of the nipple and areola in the presence of glandular tissue, is rare. It is infrequently seen as an isolated defect except in ectodermal dysplasia syndromes.

Inverted nipples- The Failure of the nipples to evert is common, usually caused by fibrous bands and a hypoplastic ductal system tethering the nipple in the inverted position. This condition is familial in 50% of patients. Patients with breast anomalies should be aware of the need for regular physical examination and urinalysis. Any abnormality noted should alert the physician to the need for a renal ultrasound

Acquired breast abnormalities

Neonatal breast enlargement- The enlargement of neonatal breast is a common phenomenon.it is obseved in over 70% of neonates, it can be unilateral or bilateral breast enlargement may bee seen in as many as 70% of neonates, this is mainly due to the levels of maternal estrogen in the neonate. Often accompanied by the secretion of witch's milk, consisting of water, fat, and cellular debris. These changes occur equally among male and female neonates within several weeks as neonatal prolactin production declines Rarely becomes infected. Regresses spontaneously. May persist for up to six months

Neonatal mastitis/breast abscess- Mastitis or breast abscesses are seen equally in males and females, except after 2 weeks of age when they occur principally in females. The most common causative agents are S. aureus, Group B streptococci, Gram-negative coliforms and Salmonella. May be associated with overlying skin lesions and trauma

Most of the babies are asymptomatic and afebrile. May present with unexplained excessive cry. Occasionally the blood culture is positive.

Treatment usually consists of antibiotic therapy and drainage of the abscess, when necessary.

Nipple discharge- Children may present with milky, serous or sero-sangineous or rarely bloody discharges. A milky discharge from the nipple is often seen in mature infants, it is self-limited condition that should be managed conservatively. Rarely Galactorrhea may be seen in prolactin producing pituitary lesion or hypothyroidism. Bloody nipple discharge is rare, Surgical procedures should be avoided, because injury to the breast bud may cause permanent damage.

Atrophy-the atrophy of the breast may be seen in adolescents secondary to severe malnutrition

Mastodynia- painful breast engorgement is seen in late adolescents due to the ovulatory cycles, Can be managed by analgesics

Gynecomastia

Galen introduced the term gynecomastia, derived from the Greek words gyne and mastos, ie female like breasts. The basic mechanisms of gynecomastia are a decrease in androgen production, an

absolute increase in estrogen production, and an increased availability of estrogen precursors for peripheral conversion to estradiol during puberty, is thought to cause gynecomastia. It is a benign condition that accounts for more than 65% of male breast abnormalities. Occurs in any age, but 40% of cases occur in adolescent boys aged 14-15 years.

Pseudogynecomastia- Adolescents who are overweight may have an enlarged breasts because of increased fat and not true breast tissue.

Classification of gynecomastia- The are several classification for the gynecomastia depending upon the etiology, the glandular components or according to the size of the gynecomastia

Etiological classification

- Idiopathic gynecomastia (75%)
- Physiologic gynecomastia-newborns, adolescents.
- Pathologic gynecomastia
- Due to testosterone deficiency, increased estrogen production, or increased conversion of androgens to estrogens.
- Associate conditions eg. Congenital anorchia, Klinefelter syndrome, testicular feminization, hermaphroditism, adrenal carcinoma, liver disorders, and malnutrition.
- Drug Induced gynecomastia.
- Drugs that act exactly like estrogens, such as diethylstilbestrol, birth control pills, digitalis, and estrogen-containing cosmetics.
- Drugs that enhance endogenous estrogen formation, such as gonadotropins and clomiphene.
- Drugs that inhibit testosterone synthesis and action, such as ketoconazole, metronidazole, and cimetidine.
- Drugs that act by unknown mechanisms, such as isoniazid, methyldopa, captopril, tricyclic antidepressants, diazepam, and heroin.

Webster classification of gynecomastia according to glandular components.

The glandular : Patients with a glandular component require surgical removal of the gland.

The fatty glandular. With the fatty glandular form, surgery combined with liposuction allows good contouring.

The simple fatty. In the cases that are primarily fatty in nature, liposuction alone provides good results.

Simon classification according to the size of the gynecomastia.

Group 1: minor but visible breast enlargement without skin redundancy.

Group 2A: moderate breast enlargement without skin redundancy.

Group 2B: moderate breast enlargement with minor skin redundancy.

Group 3: gross breast enlargement with skin redundancy that simulates a pendulous female breast.

Pseudogynecomastia: an accumulation of excess fat in a male breast.

Diagnosis: The diagnosis of gynecomastia is usually made based on a detailed physical examination including a testicular examination. A review of any medications that your child is taking will also be done. Most boys with gynecomastia will notice a small, firm, tender mass under one or both nipples. Enlargement is usually central and symmetric, although occasionally it is eccentric. They may continue to grow a little at first, but they will then eventually flatten out again, often within a few months or years. The tenderness is also usually temporary. Idiopathic and drug-induced gynecomastia is usually unilateral; however, in pubertal and hormonal cases, the changes are often bilateral.

Investigations

Blood examination for liver function tests

Hormonal assays for FSH, LH, HCG, TSH, thyroxin, estrogen, estradiol, and testosterone levels . 17-ketosteroid levels in urine.

A sex chromatin study should be performed to exclude Klinefelter syndrome

Imaging studies

Ultrasound examination of the testes and breasts, Computed tomography scan of adrenal glands, Magnetic resonance imaging of sella turcica, and mammography.

Excisional biopsy or fine-needle aspiration of breast tissue should be performed if suspicion of a breast tumor exists.

Treatment

Generally, gynecomastia is a benign condition although distressing to many teen boys who think that they are developing breasts, they should be reassured that the condition is benign and common, and usually doesn't progress and in most cases goes away without any treatment

Medical therapy

Should observe for 9 period of time to make sure that spontaneous regression does occur. Over 90% of gynecomastia disappear with in 2-3 years. Medical management is most successful when the gynecomastia is of recent onset and is caused by testosterone deficiency. Testosterone administration has inconsistent effects in persons with

Klinefelter syndrome, but it can cause dramatic improvement in those with other forms of testicular failure (eg, anorchia, viral orchitis). Various drug regimens have been tried. These drugs include the anti-estrogens tamoxifen and clomiphene, the aromatase inhibitor testolactone, and danazol. Treatment with dihydrotestosterone, which cannot be aromatized to estrogen, has also been reported to cause significant symptomatic improvement in persons with gynecomastia

Surgical therapy

Although not usually necessary, if a teen boy has very large breasts or his gynecomastia isn't going away, then surgical treatment can be an option. Most experts recommend waiting for at least two years before considering surgical intervention. Man have surgery because of psychological problems.The objectives of surgical management for breast gynecomastia are (1) to restore the normal male breast contour and (2) to correct deformity of the breast, nipple, or areola. Mastectomy or Liposuction-assisted mastectomy may be considered.

Prognosis

Regardless of the etiology of gynecomastia, the prognosis is excellent. Studies have shown that 90% of physiological gynecomastia involutes spontaneously within 2 years. In pathological-induced gynecomastia, medical or surgical treatment of the cause regresses gynecomastia, in most cases. In drug-induced gynecomastia, withdrawal of the medication leads to regression in 60% of patients. If the gynecomastia is of long duration, it is unlikely to spontaneously regress. Patients who have gynecomastia and Klinefelter syndrome are at about 50% increased risk of male breast cancer.

Premature thelarche- isolated breast development without signs and symptoms of other secondary sexual traits. Common between the ages of 2-5 and usually not progressive. No further evaluation necessary other than observation and if secondary sexual traits develop, ultrasound and endocrine evaluation may be necessary.

Breast masses

Breast cancer is rare in children. Presence of breast masses usually produce anxiety in the patient and families. Benign proliferative changes and benign masses such as fibroadenomas are the most common entities encountered in the adolescent patient may present as multiple, mobile, firm lesions. rarely fibrocystic disease may present as diffuse bilateral breast thickening. Bilateral enlargement of breast is also seen in virginal hypertrophy (macromastia). Evaluation of breast complaints includes a careful history and physical examination. Ultrasonography is the best modality to assess the adolescent breast. Surgical intervention usually is contraindicated in pre-pubertal patients. In the post-pubertal patient, discrete breast masses, which are not suspicious on clinical examination, may be observed. Additionally, FNA(Fine Needle Aspiration) and surgical removal are also safe diagnostic and therapeutic alternatives in this patient population.

Trauma

Trauma to breast is more common now with the increased participation of females in sports

References

1. Arca MJ, Caniano DA. Breast disorders in the adolescent patient. Adolesc Med Clin. 2004 Oct; 15(3):473-85.
2. Brown L, Hicks M. Subclinical mastitis presenting as acute, unexplained, excessive crying in an afebrile baby. Pediatr Emerg Care.2001 Jun;17(3): 189-90
3. Carlson BM: Integumentary, skeletal, and muscular systems. In: Human Embryology and Developmental Biology. 1st ed. 1994; 153-181.
4. Casey HD, Chasan PE, Chick LR: Familial polythelia without associated abnormalities. Ann Plast Surg 1996; 36: 101-104
5. Denk MJ: Topics in pediatric plastic surgery. Pediatr Clin North Am 1998; 45(6): 1479-1506
6. Dudgeon, David. Pediatric breast lesions: Take the conservative approach. Contemporary Pediatrics. January 1985.
7. Forsyth IA: The mammary gland. Baillieres Clin Endocrinol Metab 1991; 5(4): 809- 832
8. Gershin T, Mogilner JG. Bloody nipple discharge in an infant Harefuah. 15;122(8):505-6, 551. 1992 Apr
9. Gilbert SF: Cell interactions at a distance: hormones as mediators of development. In: Developmental Biology. 5th ed. 1997; 733-772.
10. Kajava Y: The proportions of supernumerary nipples in the Finnish population. Duodecim 1915; 31: 143-170.
11. Kamalati T, Niranjan B, Yant J, Buluwela L: HGF/SF in mammary epithelial growth and morphogenesis: in vitro and in vivo models. J Mammary Gland Biol Neoplasia 1999 Jan; 4(1): 69-77.
12. Karl SR, Ballantine TV, Zaino R. Juvenile secretory carcinoma of the breast. J Pediatr Surg. 20(4):368-71 1985 Aug;
13. Kelly V. et al. Bloody Nipple Discharge in an Infant and a Proposed Diagnostic Approach.

Pediatrics April 2006

14. McCarty KS Jr, Carpenter SA, Georgiade GS: The breast: embryology, anatomy, and physiology. In: N Georgiade, G Georgiade, R Riefkohl, eds. Aesthetic Surgery of the Breast.1st ed. 1990; 3-18.
15. Medina D: The mammary gland: a unique organ for the study of development and tumorigenesis. J Mammary Gland Biol Neoplasia 1996 Jan; 1(1): 5-19
16. Moore, KL, Persuad, TVN: The integumentary system. In: Before We Are Born: Essentials of Embryology and Birth Defects. 5th ed. 1998; 481-496.
17. Plessis G, Le Treust M, Le Merrer M: Scalp defect, absence of nipples, ear anomalies, renal hypoplasia: case of Finlay-Marks syndrome. Clin Genet 1997; 52: 231-234
18. Robinson GW, Karpf AB, Kratochwil K: Regulation of mammary gland development by tissue interaction. J Mammary Gland Biol Neoplasia 1999; 4(1): 9-19.
19. Santen R, Mansel R. Benign Breast Disorders. NEJM 2005; 21,
20. Urbani CE, Betti R: Sporadic unilateral intra-areolar polythelia. Report of an additional case and review of the literature. Acta Derm Venereol 1996.

Greek and Roman surgical instruments

Scalpels: Scalpels could be made of either steel, bronze, or a combination of the two metals (such as a steel blade and a bronze handle). Ancient scalpels had almost the same form and function as their modern counterparts do today. The two long steel scalpels that make up the first and third columns of the accompanying image are examples of the most ordinary type of scalpel from antiquity. These long scalpels could be used to make a variety of incisions, but they seem to be particularly suited to making either deep or long cuts. The four bronze scalpels which make up columns two and four are generally referred to as "bellied scalpels." This variety of scalpel was another favorite of physicians in antiquity since the shape of its handle allowed more delicate and precise cuts to be made (such as incisions between ribs).

Hooks: Hooks were another common instrument used regularly by Greek and Roman doctors. The hooks the ancient doctors used came in two basic varieties: sharp and blunt. Both of these types of hooks are still used by modern surgeons' for many of the same purposes for which the ancient doctors first used them. For instance, blunt hooks were primarily used as probes for dissection and for raising blood vessels. Sharp hooks, like those pictured in the accompanying image, were used to hold and lift small pieces of tissue so that they could be extracted and to retract the edges of wounds.

Bone drills: Bone drills were generally driven in their rotary motion by means of a thong in various configurations. Greek and Roman physicians used bone drills in order to excise diseased bone tissue from the skull and to remove foreign objects of considerable thickness (such as a weapon) from a bone.

Catheters and bladder sounds: Physicians in the Classical World employed catheters in order to open up a blocked urinary tract which allowed urine to pass freely from the body. These early catheters were essentially hollow tubes made of steel or bronze and had two basic designs: one with a slight S curve for male patients (figure 1) and another straighter one for females (figure 2). The same doctors also used simular shaped devices which were solid, as opposed to hollow, in order to probe the bladder in search of calcifications (figure 3).

Vaginal speculum: Vagina specula are among the most complex instruments employed by Greek and Roman physicians. Several examples of such specula have survived and they generally demonstrate the high degree engineering skill available to the ancient doctors. Most of the vaginal specula consist of screw device which when turned forces a cross-bar to push the blades outwards.

Evaluation and Management of Nipple Discharge

Review Article

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Thanks to increasing awareness of cancer breast, more and more women with nipple discharge are seeking medical attention. Spontaneous nipple discharge in non lactating women is reported to occur in 10% of women who undergo routine health examinations. It is third most common symptom after breast lump and pain.

Female breast has some degree of fluid secretion throughout post pubertal life. In a non lactating woman small plugs of tissue block the nipple ducts and keep the nipple away from discharging fluid. Difference between lactating and non lactating breast is in the volume of secretion and in the chemical composition of fluid.

Causes of nipple discharge

Discharge from the surface

Pagets disease
Skin disease (Psoriasis, Eczema)
Rare causes(Chancre)

Discharge from single duct

Blood Stained
Intraductal carcinoma
Intraductal papilloma
Duct ectasia

Serous (any color)

Fibrocystic disease
Duct ectasia
Carcinoma

Discharge from multiple ducts
Blood stained

Carcinoma
Ectasia (Dilatation and hardening of ducts due to age or damage)
Fibrocystic disease

Purulent

Infection

Milk

Lactation
Hypothyroidism
Pituitary tumour

Intraduct papilloma and papillomatosis are the commonest causes of pathological nipple discharge which is bloody or serous (90%).A papilloma is a wart like benign tumour with branching or stalk that has grown inside the breast duct. Papilloma frequently involves large milk ducts near the nipple. Multiple papillomas may also be found in the small breast ducts further from the nipple. Papillomas usually cause discharge from single duct.

Bloody discharge during pregnancy or lactation is fairly common. It is caused by duct irritation due to rapid growth of breast tissue. This should not interfere with breast feeding. If it is persistent after lactation has stopped it should be evaluated further.

Galactorrhoea is milky discharge (cloudy, whitish or almost clear, thin, non sticky) from both the breasts. Mostly it is caused by lactation or increased stimulation of nipple due to fondling or suckling. True galactorrhoea is discharge which contains fat, lactose, milk specific proteins. Drugs or hormones which stimulate prolactin secretion can cause galactorrhoea. Serum prolactin radioimmunoassay is diagnostic. Pituitary tumours, hormonal imbalance,certain drugs such as sedatives, tranquillisers, hormone replacement, birth control pills can cause hyperprolactinemia.

To distinguish physiological nipple

discharge from pathological nipple discharge it should be further classified

- Spontaneous (without squeezing the nipple) or provoked
- Unilateral or bilateral
- Persistent or intermittent
- Single duct or multiple duct
- Bloody or blood mixed or milky or serous

Nipple discharge is of concern if it is

- Spontaneous
- Persistent
- Unilateral
- Bloody or clear serous
- Single duct

Both male and female adolescents may experience milky discharge during puberty. Nipple discharge in adult male is more often associated with a malignant change. Mammography should be performed and if a mass or mammographic abnormality is found, biopsy should be performed.

Evaluation for nipple discharge

- Clinical breast examination to identify and classify the nipple discharge
- Nipple aspiration fluid cytology to look for blood cells, malignant cells, pus cells
- Associated mass evaluated with mammography and biopsy
- Ductography may aid in diagnosis of intraduct papilloma seen as filling defect
- Recently fibreoptic ductoscopy and ductal lavage are new modalities for evaluation of nipple discharge. But cost of equipment, availability and learning curve still remains the areas of concern.

Treatment of nipple discharge

Medical treatment in the form of antibiotics and anti-inflammatory drugs is given to all patients with multi duct discharge, purulent discharge.

Spontaneous, persistent discharge coming from a single duct orifice needs duct excision or microdochectomy. It is a day care procedure usually done under conscious sedation and pain relief.

- Patient is strictly instructed not to express any discharge preoperatively.
- Position the patient supine with arm raised to flatten the breast.
- Discharge is evoked from the nipple by manual compression.
- Discharging duct is identified and cannulated with number one monofilament suture without using any force.
- An elliptical incision starting from the centre of nipple extending out to areolar edge in the direction of suture is given.
- Clamp the suture with a small hemostat or apply silk ligature to secure it.
- Grasp the tissue with an Aliss forceps and carry the dissection into breast tissue to the deepest extent of suture.
- Excised tissue is cut open to identify the discharging duct mucosa and any gross intraductal pathology.
- Electrocautery and layered closure allows hemostasis.
- Nipple and areola skin is carefully reapproximated with a subcuticular incision.

Advantages of the technique

- Resolves the nipple discharge by removing the pathological duct completely.
- Preserves the responsiveness of myoepithelial elements of nipple to stimulation by maintaining the innervation between areolar skin and underlying tissue.
- Avoids nipple necrosis because radial incision parallels the blood supply and does not cross it as circumareolar incision does.
- Uses the excellent healing property of areolar skin to minimize scarring.
- Leaves most of the uninvolved ducts intact preserving future lactation.

Refrences

1. Falkenberry SS. Nipple discharge. Obstet gynecol clin North Amer 2002;29: 21-29.
2. King TA, Carter KM, Bolton JS, Fuhrman GM. A simple approach to nipple discharge. Am Surg 2000; 66; 960-966
3. Lois F,O Grady M D et al. A Practical approach to breast diseases, Boston: Little, Brown and company, 1995 pp 131-139
4. Shau ZM, Hu Y, Nguyen M. The role of breast ductal system in the the diagnosis of cancer. Oncology reports 2001; 8: 153-156 Shen KW, Wu J, Lu JS et al. Fibroptic ducto-scopy for patients with nipple discharge. Cancer 2000,89 :1512-1519.

Breast Cancer in Pregnancy

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Pregnancy and cancer evoke two diametrically opposing emotions. One leads to joyous elation and the other one, to the depth of despair. When they occur together the patient is terrified and the obstetrician is faced with a therapeutic dilemma. Breast cancer occurring during pregnancy or within a year after delivery is referred as Pregnancy Associated Breast Cancer (PABC). This is the most common cancer in pregnant and post partum women. Average age is 32 – 38 years. It accounts for 15 % cancer deaths in female[1]. Incidence is 1 in 3000 pregnancy. At Pondicherry Institute of Medical Science it is one in 7500. It is more common in women who delay the pregnancy until 35 years.

Anatomy of breast

The paired hemispheres of breast tissue are attached on their planoconcave surface against the fascia of the ventral chest wall from the parasternal to the anterior axillary line covering the second through the seventh ribs. The adult female breast has two components. These are the epithelial elements responsible for milk formation and transport, namely the acini and ducts, and the supporting tissues, muscle, fascia and fat. The epithelial elements consist of twenty or more lobes. Each lobe drains into a mammary duct, each of which ends separately at the nipple. The lobe consists of lobules, the number of which is very variable. Each lobule is a collection of between ten and hundred acini grouped around, and converting on a collecting duct.

Fig 1

The Various Anatomic Sites where Breast Lesions can occur are the Terminal duct, Acini, Segmental duct, Lactiferous duct, Lobule and Ductules

Fig 2

Pathology

Pathology of the lesions are similar whether the patient is pregnant or non pregnant.

They are Spheroidal Cell, Pagets disease & Adeno carcinoma

The various other lumps that can occur in the breast are Fibroadenoma, Fibrocystic disease, Sarcoma, Fat necrosis, Galactocoel, Sebaceous cyst, Histiocytoma & Lipoma

Fig 3

PABC(Pregnancy Associated Breast Carcinoma) – is unique because there is delay in diagnosis, delay in investigations & delay in treatment

This Delay influences the outcome adversely

Causes for delay in diagnosis

There is increase in size and weight (double, due to proliferation) and increase

in vascularity. It increase by 180 % during pregnancy. This increase in size, weight, vascularity and density makes detection of mass lesions difficult both clinically and mammographically. Mass may become buried in the breast tissue. Breast may be swollen, painful, with red hot oedematous skin and can be mistaken for mastitis. The differentiation is by clinical test, using antibiotics. This 5-7 months delay in diagnosis along with increase in vascularity and lactation promotes metastatic spread. 75 % of pregnant women with cancer breast have nodal metastasis.

Causes for delay in investigation

Mammography has limited value as increase in density reduces sensitivity of mammography of pregnant Breast. Cyto-pathologist may be confused with proliferation of normal pregnant and lactating breast tissue and there is always the reluctance to perform biopsy during pregnancy and lactation

Causes for delay in treatment

Perhaps no aspect of breast cancer case is more challenging than the treatment of pregnant patient. In addition to the usual complexities of treatment decisions, one is faced with calculable factors related to the importance of child bearing and potential side effects on the child or the foetus through exposure to chemotherapy or radiotherapy. Hence the management is complex and needs multi disciplinary approach. Radiotherapy is not feasible during pregnancy and for chemo therapy one should wait for at least until 14 weeks.

Effect of cancer on pregnancy

Biopsy of the lesion during pregnancy and lactation may lead to milk fistula. The necessity to use various treatment modalities like chemotherapy, Radiotherapy may result in MTP(Medical Termination of Pregnancy). Other than this cancer as such has no effect on pregnancy.

Life style modification- Weight control; stop smoking, decrease alcohol, exercise – decrease fat, avoid non diagnostic ionizing radiation.

High risk factors

Hormonal factors: Situations which increases the duration of endogenous, estrogen such as early menarche, late age at pregnancy, nulliparity is associated with increased risk and parity reduces the risk[3] & late menopause how ever the influence of hormonal factors in pregnancy is uncertain[4]

Age: Is the most significant risk factor. Cancer breast is there in a women who are younger then 25 years. However having a baby at younger age is not a protection against cancer breast

Non lactating: Lactation is of some protection against cancer breast. Each year of Breast feeding decreases the occurrence of Cancer breast by 4%.

Genetic: The risk is more for carriers of $BRCA_1$ & $BRCA_2$ Mutations[5]. If mother and sister have cancer breast the risk is 4 times higher.

5. Environmental: People living in North America & North Europe, have more risk than the people living in London, Japan, Hawaii. However when these people from Japan and Hawaii migrate, they face higher risk of cancer breast.

Obesity: Increases risk of cancer breast because of extra glandular conversion of fat into estrogen.

Food habits: Alcohol increases the risk. Probably through increasing the estrogen level.

Smoking: Increases peri-ductal fibrosis and increases the risk.

Hormone replacement therapy: Increases the risk (1.35 times for 10 years use). The use of oral contraceptive pills increases the risk (1.24 times for 10 years use, normalizing 10 years from discontinuing). The progesterone-only pill is not associated with increased risk. The use of diethylstilbesterol increases risk

Evaluation

Our aim is to achieve most appropriate form of therapy. And this is done by triple assessment clinical, imaging – mammography, ultra sonogram & fine needle biopsy

Clinical

Majority of early cancer breast are asymptomatic.

However, the lump– whether it is hard, irregular focal nodularity, asymmetry with other breast

Change in size

- Skin dimpling due to fixation
- Nipple inversion (Recent.)
- Single duct discharge (Blood stained)
- Auxiliary lump
- Ulceration
- Peau d'orange

Should alert one to the presence of cancer breast

Among imaging

Mammography has limited value because of increased density of breast tissue and decrease sensitivity. The other modalities are Ultra sound of Breast and Doppler. (MRI, Scinti mammography, Positron Emission Tomography are not used during pregnancy)

Biopsy

FNAC – Fine-needle aspiration cytology is useful in distinguishing benign breast

masses of pregnancy from those with marked cytologic atypia requiring surgical biopsy and minimizes the delay in diagnosis of carcinoma associated with pregnancy.[6]

Breast biopsy may be performed under local or general anaesthesia. Procedures using local anaesthesia are usually without risk to the fetus. The nursing mother should be advised to stop breast-feeding and allow milk production to cease prior to biopsy, to avoid the occurrence of milk fistula.

Inflammatory abscess that are drained during pregnancy and lactation should have biopsy of the wall

Management depends upon staging & period of pregnancy

Staging is done so as to have the best choice of first line treatment (TNM classification)

Tumor

- Stage TX – Tumour not assessable
- Stage T0 – No primary tumor
- Stage Tis – Carcinoma in situ
- Stage T1a – Tumour 0.5 cm
- Stage T1b – Tumour larger than 0.5 – 1 cm
- Stage T1c – Tumour larger than 1 - 2 cm
- Stage T2 – Tumour larger than 2-5 cm
- Stage T3 – Tumour larger than 5 cm
- Stage T4a – Involvement of chest wall
- Stage T4b – Involvement of skin
- Stage T4c – Stages T4a and T4b
- Stage T4d – Inflammatory cancer

Node

- Stage NX – Node not assessable
- Stage N0 – No regional
- Stage N1 – Palpable ipsi-lateral axillary lymph nodes
- Stage N2 – Fixed ipsi-lateral axillary lymph nodes
- Stage N3 – Ipsi-lateral internal mammary nodes

Metastasis

- Stage – Metastasis not assessable
- Stage M0 – No evidence of metastasis
- Stage M1 – Distant metastasis, including ipsi-lateral supra-clavicular nodes.

Management

Management also needs a team approach consisting of breast surgeon, Oncologist, Obstetrician. It is very difficult to make general comment. Each case has to be individualize depending on

- Stage of the disease
- Period of pregnancy
- HR Status
- Lymph node involvement

In early stage + late pregnancy (3rd trimester onwards)

Surgery is the first line of treatment modified radical mastectomy is done where; pectoralis major, minor muscles are preserved for better arm motion and thoracic outline. Post operative lymph oedema will be less. Termination of pregnancy is advised once foetal maturity is achieved. Radiotherapy and chemotherapy can be advocated after prevention of lactation.

In early stage +early pregnancy 1st Trimester & 2nd Trimester

MRM – Modified Radical Mastectomy is done followed by Chemotherapy which is delayed until 14 weeks

Late stage irrespective of period of pregnancy 5 years survival rate is only 10 %. The motto is termination of pregnancy. When the foetus is border line i.e. 28 – 34 weeks there is dilemma. Before 28 weeks we can do therapeutic abortion

Beyond 34 weeks foetus is salvageable. The psychological dilemma is termination of pregnancy for a woman who may live for a year or two with all the treatment. This requires active involvement and participation of the patient and the relatives in decision making.

Role of chemotherapy

Chemotherapeutic agents are usually teratogenic especially from 5-10 weeks of gestation (Organogenesis is complete by 13th week). They cause spontaneous abortion, congenital malformation (10-20% as oppose to 3% in general population) IUGR and IUD. Chemotherapy can be given in the form of cyclophosp-hamide, Methotrexate and 5-flourouracil safely during 2nd & 3rd semester[7]. Role of Tamoxifen is not established since 80 % tumors are ERPR negative

Role of surgery

Radical Mastectomy – Where pectovalis major, pectovalis minor are removed

MRM Mastectomy – Where pectovalis major, pectovalis minor are conserved with nodal clearance or sampling

Breast conversion surgery (Quadrantectomy Major Lumpectomy) is most suitable when PABC is diagnosed during late 3rd trimester[7] since it can safely be followed with radiotherapy. Toilet Mastectomy is done for advance cases.

PABC & breast feeding

If treatment is completed, breast feeding can be allowed. If the patient is on chemo or radio therapy breast feeding should not be allowed. Biopsy should not be done during lactation.

Fertility after PABC

PABC has no direct effect on fertility. But the therapy, chemo or Radio may lead to Premature Ovarian Failure. Ovarian ablation is not followed now-a days. Ovarian stimulation is not advisable for fear of oestrogen sensitive tumors. An interval of two years is necessary after completion of treatment before pregnancy is attempted. Past PABC increases the chances of spontaneous abortion but no effect on fetus or neonate. Role of cryo preservation of healthy ovarian tissue in egg is not well established.

Follow up palliative care

These patients should be followed once in 3 months for 1 year, with Mammography of the other breast. Once in 6 months for 4 years, MRI can be done on the operated scarred breast. Followed by annual visits for 5 years.

Follow up is done to manage adverse effects of treatment, to monitor the response of metastatic disease to treatment, to offer psychological support and to detect and treat recurrences

Role of MTP in PABC

In 1960 MTP was a must when PABC was diagnosed. However ER & PR –ve tumors in PABC excluded the necessity of MTP. The medical recommendation to terminate a pregnancy should be based on whether the pregnancy will present a significant obstacle to effective therapy and whether the fetus will sustain harm as a result of therapy. As chemotherapy can not be given before 14-15 weeks of pregnancy, therapeutic abortions may be considered in the first or second trimester so that metastatic disease can be treated promptly, particularly if the patient is ER-positive[8].

Prognosis

Breast cancer is generally believed to carry a worse prognosis during pregnancy because of the potential adverse effects of anticancer treatment on the fetus and of pregnancy related hormonal and immunological modifications on the disease[9]. Also, most studies indicate that PABC tends to be more advanced at initial presentation because pregnancy-related changes in the breasts obscure clinical and radiological manifestations. Actually, breast cancer has equivalent prognosis in pregnant and non pregnant women when matched by age and stage at diagnosis at the same institution during the same time period.[10,11,12,13.] One of the most successful indices of prognosis in breast cancer is the Nottingham prognostic NPI Index (NPI) which can be used to select patients for adjuvant treatment and which makes use of the following proven prognostic indicators.[14]

Prophylaxis

Clinical Breast examination – Every three years between 20 to 40 years.

Breast self examination – Monthly, Screening Mammography – Annual after 40 years. Breast self examination should be done once every month. In the shower look for lumps, thickening; in front of mirror arms by the sides- look for lumps, dimpling, swelling, and puckering of nipple or breast skin, look for these with arms raised, hands on hips and press down; Lying down with pillow under shoulder, hand under head.

References

1. Breast Breast cancer evaluation 2004 august 12 –Hemant singhal Sr. Lecturer Department of Surgery Imperial College of School of Medicine London – England (Internet)
2. R, Greenberg ER etal Age at any full term pregnancy and breast cancer risk. Chie WC Hsich C, Newcomb PA Longnecker MP, Mittendorf Am.J Epideniology 2000 151:715-22
3. RCOG guidelines No.12 revised January 2004
4. Lipworth L, Heish CC, Wide L, Ekbon A, YuSZ, YuGP etal Maternal pregnancy hormone levels in an area with a high incidence (Boston USA) and in an area with a low incidence (Shangai, China) of breast cancer Br.J. cancer 1999, 79, 7-12.

Nobel prize winners for 2006

Nobel Prize for Peace-Muhammad Yunus and Grameen Bank "for their efforts to create economic & social development from below"

Nobel Prize for literature -Orhan Pamuk "who in the quest for the melancholic soul of his native city has discovered new symbols for the clash and interlacing of cultures"

Nobel Prize for Economics - Edmund S. Phelps "for his analysis of intertemporal tradeoffs in macroeconomic policy".

Nobel Prize for Chemistry-Roger D. Kornberg "for his studies of the molecular basis of eukaryotic transcription".

Nobel Prize for Physics-John C. Mather and George F. Smoot"for their discovery of the blackbody form and anisotropy of the cosmic microwave background radiation".

Nobel Prize for Physiology or Medicine-Andrew Z. Fire and Craig C. Mello "for their discovery of RNA interference - gene silencing by double-stranded RNA".

History and Clinical Diagnosis of Common Breast Diseases

Review Article

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"Diagnosis precedes treatment",
(Russell John Howard, 1875-1942)

The most common breast problems for which women consult a physician are breast pain, nipple discharge and a palpable mass. Most women with these complaints have benign breast disease. Regardless of the type of breast problem, the goal of the evaluation is to rule out cancer and address the patient's symptoms.

History

The diagnosis of breast diseases starts with a thorough history. It is important to remember that diagnosis of breast cancer cannot be excluded by any single finding in the patient's history. For example factors such as patient's young age, race or ethnicity, her lack of risk factors for breast cancer and benign appearing symptoms associated with a breast mass cannot be used to exclude the diagnosis of breast cancer. History by itself is not sensitive enough to exclude carcinoma.

History assumes much greater importance in the diagnosis and treatment of benign conditions of the breast, including mastalgia and nipple discharge. Most patients seen in breast clinics are subsequently found to have normal or benign conditions of the breast.

Components of the medical history of a breast problem

All women

- Age at menarche
- Number of pregnancies
- Number of live child births
- Age at first birth
- Family history of breast cancer, including affected relative, age of onset and presence of bilateral disease
- History of breast biopsies (& Histologic diagnosis if available).

Premenopausal women

- Date of last menstrual period
- Length and regularity of cycles
- Use of oral contraceptives

Postmenopausal women

- Date of menopause
- Use of HRT

History pertaining to symptom (Pain, nipple discharge, lump)

Clinical examination

Examination of the breast is inherently subject to interobserver variation and interpretation. However, certain elements in the examination should be noted.

- It should be conducted unhurriedly in a setting that allows for minimal distraction and adequate patient privacy. Examination gowns should be adjusted to minimize unnecessary or unintended exposure of patient.
- Patient should be examined in both the upright and supine position.
- The approximate size (measurement with ruler), location, mobility and consistency of any mass should be recorded. Any associated skin changes such as dimpling, retraction, erythema or nipple scaling should be noted.
- If patient reports nipple discharge, each nipple should be gently squeezed to examine discharge.
- The nodes in axilla and supraclavicular area should be examined. Examination should state whether nodes are clinically negative (normal size, soft, mobile). If nodes are suspicious, assessment should indicate their consistency, number and mobility.
- Breast examination should be completely documented even if it is normal. A diagram showing any abnormal finding is valuable as a part of documentation.

Mastalgia

Breast pain is the most common breast complaint in women and it is often a concern for patients because of their fear of cancer. The diagnosis of carcinoma must be ruled out in all women with this complaint. There are no pathognomonic adjectives that describe pain associated with carcinoma. Ten percent of breast cancer patients have pain on first presentation. Persistent, unilateral, localized pain may necessitate biopsy even in the absence of other evidence of malignancy.

Breast pain can be classified as

- Cyclic (associated with menses)
- Noncyclic
- Non breast

A careful history consisting of pain charts documenting when pain occurs

during the month, as well as physical examination and radiological procedures when appropriate, can differentiate the three groups. Mastalgia is more common in premenopausal women than in postmenopausal women, and it is rarely a presenting symptom of breast cancer. Its relationship to the menstrual cycle and its more frequent occurrence in premenopausal women suggest a hormonal etiology, but no reproducible alterations in estrogen, progesterone or prolactin levels have been identified in women with mastalgia. Special attention should be given to the type of pain, its location and its relationship to the menstrual cycle (cyclical mastalgia). It is most severe before the menses. However breast pain can also be unrelated to the menstrual cycle or can occur postmenopausally (noncyclical mastalgia). Cyclical pain is usually bilateral and poorly localized. It is generally localized as a heaviness or soreness that often radiates to the axilla and arm. The pain has a variable duration and is often relieved after the menses. Mostly cyclic pain resolves spontaneously.

Noncyclical mastalgia is most common in women 40 to 50 yrs of age. It is often unilateral and is described as a sharp, burning pain that appears to be localized in the breast Noncyclic mastalgia is occasionally secondary to the presence of a fibroadenoma or cyst and the pain may be relieved by treatment of the underlying breast lesions.

Menstrual irregularity and emotional stress have been shown to exacerbate mastalgia. In obtaining history, questions should be directed at identifying problems in these areas. Although breast examination should be performed to exclude the presence of a breast mass. In the absence of a mass, women 35 yrs of age and older should undergo mammography. When the physical examination is normal, imaging is not indicated in women younger than 35 yrs of age. In vast majority of mastalgia patients, physical examination and mammography reveal no evidence of breast pathology. In these situations, it is usually sufficient to reassure the patient that cancer is not the cause of mastalgia.

Nipple discharge

Nipple discharge is not a common presenting symptom of carcinoma. Only 3-5% of breast cancer patients present with nipple discharge. Often, patients with carcinoma breast presenting with nipple discharge don't have isolated physical findings.

A bilateral nipple discharge usually has a systemic cause, rather than a local one. All nipple discharges are not associated with pathology and galactorrhoea can be distinguished from physiologic and pathologic causes of nipple discharge by a careful history, a physical examination and the appropriate use of laboratory data. Galactorrhea is not a symptom of breast cancer or primary breast pathology. Galactorrhoea is usually bilateral, milky and from multiple ducts. Common causes of galactorrhoea include hypothalamic lesions or dysfunctions, chest lesions (chest trauma, burns, herpes zoster, lung cancer), renal disease and non pituitary prolactin producing tumor (eg. lung, kidney). The work up should include tests to exclude these causes. Physiologic discharge is serous, unilateral or bilateral, nonspontaneous and from multiple ducts. Physiologic causes include excessive breast manipulation by the patient and her partner during sex or by a poorly fitted bra during exercise. Blood stained discharge can arise during pregnancy from leakage of weak, newly formed capillaries into the ducts. With no other findings, only observation is needed, because this resolves in the postpartum period.

Pathologic discharge could be due to benign lesions like intraductal papilloma, ducts ectasia and cancer. Nipple discharge that is nonlactational, spontaneous, unilateral, serous or bloody (or both), and single duct in origin is more likely to have pathologic significance, and histologic diagnosis is necessary. The incidence of breast cancer presenting with nipple discharge varies widely in literature but is usually around 5 to 10%. The incidence of malignancy in patients with nipple discharge increases with age and the presence of a mass.

Guidelines for management of patients with Breast pain

Skin changes

Suspicious lesions of the breast especially when involving nipple or areola, must be evaluated by biopsy. Benign conditions of the nipple, including psoariasis and herpes, can thus be differentiated from malignant Paget's disease or other rare malignancies of the breast such as basal cell carcinoma, melanoma and squamous cell carcinoma. Paget's disease which can present with symptoms of nipple itching or discomfort, is a red, scaly, eczematous lesions of the nipple or areola that is associated with underlying in situ ductal carcinoma. Diagnosis of Paget's disease is made by incisional biopsy, which reveals large cells with clear cytoplasm.

Mastitis

Mastitis or cellulitis of the breast, can be puerperal (lactational) or nonpuerperal. Puerperal mastitis can present in either of two settings, epidemic or endemic. Epidemic mastitis is related to a hospital carrier in a maternity ward, occurs within a day of delivery, is most commonly caused by S. aureus and involves the lactiferous glands and ducts. Patients present with fever and chills, as well as breast erythema, warmth and tenderness. The infant carries the organism as well,

so treatment includes discontinuation of breast feeding (but continued breast pumping to prevent engorgement), penicillinase – resistant penicillin, ice packs and analgesics.

Puerperal endemic mastitis is a periductal infection and is polymicrobial in origin. Signs and symptoms are similar to those of epidemic mastitis except that they occur weeks, not days after delivery. Because the infant is not commonly the source of the infection, breast feeding is continued to prevent engorgement and possible abscess formation.

Guidelines for the management of patients and nipple discharge

Breast masses

Determining what constitutes a dominant mass is often difficult, particularly in premenopausal women. The normal glandular tissue of the breast is nodular, and this nodularity is usually most pronounced in the upper outer quadrant of the breast and the area of inframammary ridge. Nodularity particularly when it waxes and wanes during the menstrual cycle, is a physiologic process and is not an indication of breast pathology.

Dominant masses are characterized by persistence throughout the menstrual cycle. These masses may be discrete or poorly defined, but they differ in character from the surrounding breast tissue and the corresponding area in the contralateral breast. The differential diagnosis of a dominant mass includes macrocyst (clinically evident cyst), fibroadenoma, prominent areas of fibrocystic change, fat necrosis and cancer. If patient or examiner is uncertain about the nature of a vague mass, then FNAC, mammogram/or USG should be considered. Imaging should be performed before aspiration as FNAC may produce bleeding that can cause difficulty in interpreting the mammogram or USG.

Cystic breast masses

Cysts are a common cause of dominant breast masses in premenopausal women more than 40 yrs of age but are infrequent cause of such masses in younger women. Although cyst may occur at any age, they are relatively uncommon in postmenopausal women who are not taking hormones.

Cysts often fluctuate with the menstrual cycles and are particularly common during periods of hormonal irregularity. Clinically, cysts are usually well demarcated from the surrounding breast tissue. They are characteristically firm and mobile. Cyst that have filled rapidly may be tender. On physical examination, it is often difficult to distinguish a cyst from a solid mass. Ultrasonography or aspiration must be used to establish a definitive diagnosis. The most common cause of painful mass is a cyst.

Solid breast masses

In premenopausal women are clearly different from the surrounding breast tissue and require histologic sampling by fine needle aspiration cytology or trucut biopsy.

Solid masses in women < 40 yrs age – If the physical examination reveals no evidence of a dominant breast mass, the patient should be reassured and instructed about self breast examination. If the clinical significance of physical finding is uncertain, a directed ultrasound examination is performed. In women 35-40 yrs of age who have normal or equivocal ultrasound exam; a mammogram may also be obtained. In younger women, mammography is rarely useful.

In a patient with a dominant mass, the approach varies with the degree of clinical suspicion. A suspicious mass is solitary, discrete, hard and often adherent to adjacent tissues. If such a mass is present, mammography is performed before an attempt is made to obtain a pathologic diagnosis.If clinically benign mass is present, the options of excision or follow up are discussed with the patient. If the patient desires surgical excision, no additional testing is done. If patient opts for further work up, an ultrasound examination and FNAC are performed to confirm that mass is benign. This approach is often referred to as "Triple Test" (Clinical exam, USG or Mammography and FNAC). If dominant mass is kept under observation, examine patient every 2â3 monthly to ensure stability of mass.

Solid mass in women > 40 years age – As patient's age increase, clinically evident benign breast problems become less frequent. Therefore, abnormality detected on physical examination in older women should be regarded as possible cancers until they are documented to be benign. Women after 40 yrs age should have Mammography as standard part of evaluation of solid breast masses.

Clinically suspicious mass is discrete, firm and may or may not be fixed to adjacent tissues. It is unilateral and nontender. However, breast cancers are known to present clinically in a highly variable manner.

Regardless of the age of a woman, a clinically suspicious lesion should be evaluated completely. All palpable, discrete, solitary, noncystic masses without a definitive diagnosis, should be excised.

Guidelines for the management of patients with breast lumps

High risk patients

Patients with a history of breast cancer should have oncologic follow up with regularly scheduled clinical and imaging

examination. Patients at high risk of developing breast cancer as indicated by a family history of breast cancer among premenopausal first degree relations, diagnosis of atypia on breast biopsy, or multiple previous biopsies, may require different screening regimens.

Breast examination that are difficult

Breast examinations are difficult

- when she has had reduction mammoplasty or augmentation implantation
- has extremely large or dense multinodular breasts
- has had multiple biopsies with multiple scars
- is pregnant or lactating

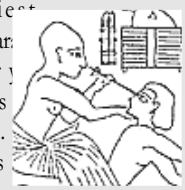
Physical diagnosis of breast cancer in pregnant or lactating women may be extremely difficult. Approximately 1 in 2000 pregnant or lactating women has breast cancer and about 1% to 2% of breast cancers are diagnosed in pregnant women.

References

1. Austoker J. Mansel R eds. Guidelines for referral of patients with breast problems. 2nd Ed. Cancer screening Programmes NHS Cancer Research UK. pp 11-20
2. Morrow M. The evaluation of common breast problems. Am Fam Physician 2000; 61 : 2371-8, 2385
3. Minnesota Breast & Cervical Cancer Control programme. Evaluation of common breast problems. pp 7-11.
4. Bland KI, Copeland EM. eds. The Breast. Comprehensive Management of Benign & Malignant Diseases, 2nd ed. WB Saunders Company. pp 233-260.
5. Harris JR etal eds. Diseases of Breast 3rd ed. Philadelphia : Lippincot.

Cataract Surgery in Antiquity

Sanskrit manuscripts from the 5th century B.C. describe the earliest type of cataract surgery known as couching. In this procedure,



the cataractous lens was displaced away from the pupil to lie in the vitreous cavity in the back of the eye. The displacement of the lens enabled the patient to see better. Vision, however, was still blurred due to the unavailability of corrective lenses. Recent excavations in Iraq, Greece and Egypt have uncovered bronze instruments that would have been used for cataract surgery. In 29 A.D., the practice of needling or discission was noted in De Medicinae. This technique breaks up the cataract into smaller particles, thereby facilitating their absorption.

Cataract Surgery in the Modern Era

In 1748, Jacques Daviel of Paris introduced a type of cataract surgery where the cataract is actually extracted from the eye. This was a form of extracapsular surgery in which the inner lens contents were removed, but a portion of the lens capsule or outer covering and the zonules that attached it, were left in place. Five years later, Samuel Sharp of London introduced the concept of cataract surgery by using pressure with his thumb to remove the entire lens intact through an incision. By 1902 small suction cups and other various capsular forceps were invented to grasp the lens for removal.

It was not until the late 1840s that general anesthesia was introduced for surgical procedures. By 1884, anesthesia in the form of eye drops (cocaine) was developed. Previously, the services of a strong assistant were required to hold the patient's head still while surgery was performed.

Anaesthesia for Breast surgery - a Review

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Over the last 30 years, there has been an advancement and evolution in breast surgery techniques affecting the anesthetic concerns in a breast cancer patient undergoing surgery. An anaesthesiologist has a vital role to play in providing perioperative care to these patients who may undergo varying surgical procedures like breast biopsy, lymph node biopsy, axillary dissection, lumpectomy, simple/ radical/modified radical mastectomy and breast or chest wall reconstruction. The anaesthetic concerns differ amongst these patients, depending on many factors including primarily: type of surgical procedure and perioperative chemotherapy, radiotherapy and therefore, these patients must be individualized.

Anaesthetic concerns for breast biopsy and sentinel lymph node biopsy

Breast masses may vary in size and depth, which partially determines the most suitable anaesthetic technique for the particular procedure in these otherwise healthy patients. Typically, these excisional biopsies can be accomplished with monitored anesthesia care (MAC) with or without sedation under local anaesthesia. The suitability of local versus general anaesthesia (GA) may be decided by preoperative discussion with surgical team; however, patient's wishes must be considered in anaesthetic plan.

These patients are likely to be very anxious perioperatively concerning the possibility of breast malignancy, and should therefore, be reassured and premedicated adequately with anxiolytics. An oral dose of benzodiazepine like 0.1 to 0.2 mg/kg of diazepam during night and in the morning 1 hour before may be given to relieve anxiety. Day care patients may be given shorter acting agents like midazolam 1-2 mg with or without fentanyl 25-50 mg intravenously prior to induction, in patient holding area or operating room as an alternative. Standard fasting guidelines are adhered to as usual. Patients may be taken up for surgery after obtaining haemogram and other laboratory tests, as indicated by other co-morbid conditions of the patient.

GA or local anaesthesia with or without sedation are both appropriate techniques depending on patient's requirement. Propofol infusion at 25- 100 mg/kg/ min, combined with analgesics such as fentanyl, remifentanil or sufentanil with anxiolytics like midazolam, titrated, are the most commonly used regimens during MAC. Bupivacaine (0.25 to 0.5 %) or lignocaine (1 to 2%) remain standard drugs used as local anaesthetics, though newer agents like ropivacaine are also promising. Anaesthesiologist may need to supplement surgical field block with local anaesthetic or occasionally convert to GA. GA may be chosen as the first choice if the size of the swelling is large or if the patients refuses for local anaesthesia. Standard anaesthetic techniques for induction and maintenance may be used for GA. Maintenance of airway with a facemask or laryngeal mask airway (LMA) may be appropriate. Muscle relaxants are not required and best avoided for this short surgical procedure.

A balanced salt solution like ringer lactate infused at rate of 3 – 5 ml/kg/hour through an 20 – 22 gauge intravenous canula is used for perioperative fluid management. Minimum monitoring standards are adopted for these procedure. Additionally, it is important to maintain verbal contact with patient during 'conscious sedation' in MAC [1].

Sentinel lymh node identification may involve use of either isosulfan blue vital dye (lymphozurin 1%) or 99^m technetium – labeled sulfur colloid (TSC). Surgeons should inform the anaesthesiologist when injecting the dye because of a transient drop by 2-5 % in pulse oximetry readings[2]. Also, patient may retain a bluish hue for few hours and may pass blue coloured urine, stool or emesis for 24-48 hours. Allergic reactions varying from mild pruritis with discolouration of local skin to life threatening anaphylactic reactions have been known as a complication to dye[2-4]. An antihistaminic like pheniramine and an anti-inflammatory agent like hydrocortisone may be used for milder forms of allergic reaction. However, an allergic reaction with hypotension may require epinephrine boluses and or infusion. Radiation exposure associated with TSC technique is considered negligible. The tracer has very low radioactivity and it is considered safe to handle specimens, which require no special protection.

Anaesthetic concerns for breast conserving surgery and mastectomy

Treatment of invasive breast cancer has evolved tremendously during recent years. Radical Mastectomy, which

removes breast, underlying pectoral muscles and the axillary lymph nodes, has been replaced by modified radical mastectomy or lumpectomy (partial mastectomy) with axillary dissection. Modified radical mastectomy (MRM) entails removal of breast and axillary lymph nodes. Lumpectomy and axillary dissection are normally done through separate incisions. Post operative adjuvant radiation therapy is routinely recommended in breast conserving surgery and is administered following the completion of adjuvant chemotherapy. A simple/total mastectomy removes only breast tissue without any axillary dissection. It is done mainly for extensive duct carcinoma in situ.

Anaesthetic implications for these procedures vary depending upon the possible metastatic spread through systemic circulation to various organs, and systemic effects of chemotherapy and radiotherapy in breast cancer patients. Chemo-therapy (eg. Adriamycin or Doxorubicin > 550 mg/m^2 as cumulative dose) increases the risk of cardiac dysfunction including arrythmias and congestive cardiac failure (CCF) unresponsive to digitalis with mortality of > 50%[5]. An acute form of toxicity characterized by ST and T wave alterations with reversible reduction in ejection fraction due to impaired impulse conduction may sometimes be seen within 24 hours of single use, though is brief and rarely a serious problem. Rarely, an exaggerated manifestation of acute myocardial damage may present as frank CCF with pericardial effusion. A detailed cardiac evaluation by cardiologist employing ECG, ECHO or MUGA is must in the patients being treated with such cardiotoxic drugs. Cineangiography is considered as most promising technique for early detection of CCF. Risk of CCF is aggravated with concomitant radiotherapy and administration of cyclophophamide.

Chemotherapeutic agents like Bleomycin, Cyclophosphamide and Melphalan are associated with progressive pulmonary fibrosis. Bleomycin carries the greatest risk of pulmonary toxicity (5-10%) with mortality of 1%. Bleomycin increases secretion of cytokines (tumor growth factor B and tumor necrosis factor) from macrophages, initiating pulmonary fibrosis. It presents as dry cough, fine rales and diffuse basilar infiltrates on X-ray and may progress to irreversible pulmonary fibrosis. Radiological changes may present as interstitial fibrosis, cavitations, atelectasis, lobar collapse or even consolidation. Carbon Monoxide diffusion capacity is reduced at doses above cumulative dose of 250 U, though single dose of > 30 U / m2 is also associated with pulmonary toxicity[5]. Administration of high FiO2 during anaesthesia / respiratory therapy may aggravate or precipitate Bleomycin induced pulmonary toxicity and thus it is advisable to avoid FiO_2 > 30% in such patients[5]. The risk is also increased in patients above 70 years and with pre-existing pulmonary pathology. Preoperatively, a chest X ray is required to rule out pleural effusion, rib or vertebral metastatic lesion. A room air ABG may be required in any patient showing clinically respiratory compromise, particularly those receiving chest radiotherapy. Pulmonary function tests may be indicated to find pulmonary reserve, risk assessment and identifying patients in need of post operative ventilatory care, if CXR or ABG suggest abnormal findings.

Breast cancer patients can present with focal neurological deficits or altered mental status, following metastasis to CNS. Additionally, headache and vomiting because of intracranial hypertension may be found. Neurologist should be consulted in such cases and a thorough but prompt work up with CT scan / MRI is recommended before taking up for surgery. Anemia is common in such patients because of chronic disease, malnutrition or secondary to chemotherapeutic agents induced bone marrow depression. A complete hemogram including differential and platelet count with peripheral smear examination might help in finding possible cause of anemia. Renal or hepatic dysfunction may be present because of metastatic involvement or toxicity of chemotherapeutic agents. Bone metastasis may be suggested from increased alkaline phosphates. Chemo-therapy induced immunosuppression increases likelihood of infection peri-operatively in these patients. As such, strict asepsis should be practiced and adequate antibiotic prophylaxis should be provided.

Preoperative reassurance, counseling and thorough premedication have a crucial role in preparation of patient for surgery. General anaesthesia with entotracheal intubation or LMA remains the standard approach in these patients. Standard techniques for induction, and maintenance of anaesthesia, monitoring are practiced as with patients for biopsies. However, regional anaesthesia in breast surgery is associated with less PONV(Post-Op. Nausea, Vomiting), decreased postoperative pain and earlier discharge from the hospital[6-8].

Although controversial, the use of muscle relaxants during axillary dissection may be avoided to permit surgical identification of nerves by nerve stimulator or if electrocautery is used. Longer acting muscle relaxants like pancuronium are best avoided for same reason. Longer duration (typically few hours) requires appropriate eye care (padding / taping) and padding pressure

points. BP cuff and intravenous line, when both are applied on the same arm may pose problem of blood rushing up intravenous tubing, every time BP cuff is inflated. A simple method to avoid this complication is to route the infusion set tubing through the BP cuff[9]. Alternatively, BP cuff may be applied to legs.

Typically, these surgeries are associated with mild to moderate blood loss. A 16 G or 18 G intravenous canula is appropriate to infuse balanced salt solution like Ringer Lactate for perioperative fluid management. Blood transfusion is avoided usually but may sometimes be needed, especially in anaemic patients, if blood loss exceeds maximal allowable limits. Prophylactic antiemetics are required in these patients because of high risk of PONV(Post-Op. Nausea, Vomiting) in breast surgeries.[10]. Metoclopramide 0.2 mg/kg iv, Ondensteron 0.1 mg/kg iv or Granisteron 40 ug/kg iv 30 minutes before end of case are commonly used effective prophylactic antiemetic regimens in these patients [11,12].

Unilateral multiple level paravertebral block typically blocking C_7-T_6 levels, provides satisfactory anaesthesia for modified radical mastectomy and lumpectomy with axillary lymph node dissection [6,7,13]. Bupivacaine 0.5% or ropivacaine 0.5% with or without 1: 3,00,000 epinephrine are suitable local anaesthetics (4-5 ml/level). Sedation is useful during block placement and is continued intraoperatively. Patient's refusal, infection at site, previous history of allergy to LA or anatomic distortion because of pathology or previous surgery may not allow performance of block. Paravertebral block may also be complicated because of inadequate block, Horner's syndrome, inadvertent epidural and sometimes pleural puncture and pneumothorax.

Intercostal block has been used successfully as an alternative to paravertebral block especially for minor breast surgeries [14]. Both paravertebral [15] and intercostal block [16] have been performed successfully as a suitable alternative to GA in patients with advanced breast malignancy or with comorbidities. Thoracic epidural combined with Interscalene Brachial Plexus Block provides not only effective anaesthesia but also better postoperative pain relief, faster anaesthetic recovery and great patient satisfaction as compared to GA[8]. Recently, cervical epidural has also been used as a cheap alternative to GA, however, is generally avoided because of risk of associated complications [17].

Post operative pain may be controlled by systemic analgesics administered (orally), intramuscular diclofenac/ ketorolac or intravenous fentanyl, pethidine, morphine ketorolac by bolus/ infusion /PCA (patient controlled analgesia). Alternatively, a catheter placed in paravertebral or thoracic epidural space might be used to provide regional analgesia (bolus /infusion or PCA). Local anaesthetics in lower concentration (like 0.0625-0.25% bupivacaine) and/or opioids (such as fentany l 2-10 ug /ml) infused at 5-8 ml/hour might be appropriate for pain control.

Anaesthetic concerns in patients for breast and chest wall reconstruction

The goal of breast reconstruction is to create an aesthetic breast whereas that of chest wall reconstruction is to provide a stable chest wall for respiration and obtain a clean healed wound. In patients undergoing mastectomy, reconstruction may be performed immediately after the mastectomy or it may be delayed and performed at a later date. Postoperative chest radiation may be a relative but not absolute contraindication to immediate reconstruction.

Two approaches are commonly used 1) Prosthetic Reconstruction with a temporary tissue expander or saline filled implant placed behind the pectoral muscles and 2) Autologous Myocutaneous flaps (Latissimus dorsi and transverse rectus abdominis or TRAM flaps) for breast reconstruction. Latissimus dorsi myocutaneous flap consists of muscle with overlying skin rotated from back to anterior chest for creation of a breast. Usually a breast implant is placed between latissimus dorsi and pectoralis major to increase volume of breast. On the other hand, TRAM flap replaces breast with an ellipse of abdominal skin and subcutaneous tissue without need of implant and also giving a cosmetic advantage of 'tummy tucked in' appearance. Tumor resection or removal of osteoradionecrosis of the chest wall, which often involves full thickness removal of skin, muscle and underlying rib cage may be required in few cases. The rib cage may be reconstructed with prosthetic material or bone grafts followed by covering with pectoralis major, latissimus dorsi or rectus abdominis myocutaneous flaps.

These patients coming for reconstruction, particularly chest wall reconstructions are at high risk for anaesthetic and surgical problems because of the associated co-morbidities.

There is a increased likelihood of cardiorespiratory problems in patients receiving radiotherapy or chemotherapy, as discussed earlier. Additionally, patients with prior sternotomy or rib resection may have decreased respiratory reserve and may require assessment with chest X-ray, ABG or PFT's. Patients with respiratory compromise and deranged PFT, CXR or ABG may be at increased risk of peri-operative respiratory complications and need post operative ventilatory care. It is important to

perform a detailed musculoskeletal examination and document, if any, peripheral nerve involvement such as long thoracic nerve presenting as winged scapula. Additionally, these patients being at increased risk of perioperative nausea & vomiting because of chemotherapy as well as nature of surgery, and may require anti-emetic prophylaxis.

Preoperative reassurance and premedication with anxiolytics is crucial for patient's preparation for surgery. General anaesthesia with endotracheal intubation is the standard technique. Induction and maintenance are achieved with standard protocols as in patients for breast malignancies. The position during surgery is usually supine or lateral depending on surgical approach. Good muscle relaxation is an important requirement in such patients, which may be guided by neuromuscular monitoring. It may be useful to monitor temperature, urine output and sometimes CVP (in patients with cardiac dysfunction) for these prolonged major surgeries (average duration of 3-6 hours), which may sometimes involve extensive blood loss, as during sternal debridement. It is important to secure at least one intravenous broad gauge (16 G or larger) canula before surgery starts.

There may be certain concerns related to specific surgical procedure in these patients. Patient warming measures like warming blanket, warm fluids, warm humidified gases should be used so as to minimize hypothermia induced peripheral vasoconstriction, which might impair graft perfusion. Patient needs to be kept well hydrated, as guided by hemodynamics, blood loss, urine output & CVP, if used. Blood loss should be measured frequently and replaced, as and when indicated. Standard care as regard to patient positioning, eye care, padding pressure points is provided. An arterial line can be helpful in real time monitoring of blood pressure as well as a source for arterial blood for repeated analyses in prolonged major surgeries in which extensive blood loss is anticipated. A close watch on airway pressures, SpO_2 and BP may help in earlier detection of pneumothorax.

Often the patient needs to be placed in seated or semi-fowler position for skin closure in flap surgeries. This may sometimes provoke bucking on endotracheal tube, which can be reduced by bolus of lignocaine or opioids such as fentanyl. Flexion of OT table may be required by as much as $45\text{-}60^0$ during closure and dressing in TRAM flap surgery Additionally, it is prudent to discontinue N_2O before closure in these patients as it may cause abdominal distension and interfere with abdominal closure.

Reconstruction surgeries are likely to be very painful (Visual Analogue pain score of about 5) and require systemic opioids by boluses or infusion or PCA for pain relief. Metoclopramide 0.2 mg/kg iv, ondansetron 0.1 mg/kg iv or granisetron 40 ug/kg iv are commonly used effective prophylactic antiemetic regimens in such patients. Furthermore, these patients may require close observation for few hours in a Post Anaesthesia Care Unit (PACU) or high dependency unit (HDU) before they can be safely shifted to ward.

References

1. Sa Rego M M, White P. Monitored Anesthesia Care. In: Ronald D. Miller ed. Anesthesia, 5th ed .Philadelphia, Pennsylvania: Churchill Livingstone, 2000: 1452-1469.
2. Sandhu S, Farag E ,Argalious M . Anaphylaxis to isosulfan blue dye during sentinel lymph node biopsy. J Clin. Anesth 2005 Dec; 17 (8): 633-5.
3. Sprung J, Tully M J , Ziser A. Anaphylactic reactions to isosulfan blue dye during sentinel node lymphadenectomy for breast cancer. Anesth Analg 2003 Apr; 96 (4): 1051-3.
4. Scherer K, Studer W, Figueiredo V, Bircher A J. Anaphylaxis to isosulfan blue and cross reactivity to patent blue V: Case report and review of the nomenclature of vital blue dyes. Ann Allergy Asthma Immunol 2006 Mar; 96 (3): 497-500.
5. Chabner B A, Ryan D P, Paz-Ares L etal. Antineoplastic agents.In: Gilman AG, Hardman J G, Limbird L E eds. The pharmacological basis of therapeutics. 10th Ed. McGraw Hill publications, United States of America. 2001: 1389-1460.
6. Coveney E, Weltz C R, Greenglass R etal. Use of paravertebral block anaesthesia in the surgical management of breast cancer: experience in 156 cases. Ann Surg. 1998 Apr; 227(4): 496-501.
7. Weltz C R, Greengrass R A, Lyerly H K. Ambulatory surgical management of breast carcinoma using paravertebral block. Ann Surg. 1995 Jul; 222 (1): 19-26.
8. Sundarathiti P, Pasutharnchat K, Kongdan Y etal. Thoracic epidural anaesthesia with 0.2% ropivacaine in combination with ipsilateral brachial plexus block for modified radical mastectomy. J Med Assoc Thai. 2005 Apr; 88 (4): 513-20.
9. Dorsch J A, Dorsch S E. Automatic noninvasive blood pressure monitors. In Zinner S ed. Understanding Anesthesia Equipment, 4th ed. 1999: 905-918.
10. Layeeque R, Siegel E, Kass R etal. Prevention of nausea and vomiting

following breast surgery. Am J Surg 2006 Jun; 191 (6): 767-72

11. Fujii Y, Tanaka H, Kawasaki T. A comparison of granisetron, droperidol, and metoclopramide in the treatment of established nausea and vomiting after breast surgery: a double blind, randomized, controlled trial. Clin. Ther. 2003 Apr; 25 (4) 1142-9.

12. Sadhasivam S, Saxena A, Kathirvel S etal. The safety of prophylactic ondansetron in patients undergoing modified radical mastectomy. Anesth Analg 1999 Dec; 89 (6): 1340 –5.

13. Terheggen M A, Borel Rinkes I H, Lonescu T I et al. Paravertebral blockade for minor breast surgery. Anesth Analg 2002 Feb; 94 (2): 355-9.

14. Atanassoff P G, Alon E, Pasch T etal. Intercostal nerve block for minor breast surgery. Reg Anesth 1991 Jan-Feb; 16 (1) :23-7.

15. Najarian M M, Johnson J M, Landercasper J etal. Paravertebral block: an alternative to general anaesthesia in breast cancer surgery. Am Surg 2003 Mar; 69 (3): 213-8.

16. Kolawole I K ,Adesina M D, Olaoye I O. Intercostal nerves block for mastectomy in two patients with advanced breast malignancy. J Natl Med Assoc. 2006 Mar; 98 (3): 450-3.

17. Singh A P, Tewari M, Singh D K etal. Cervical epidural anaesthesia: a safe alternative to general anaesthesia for patients undergoing cancer breast surgery. World J Surg. 2006 Aug 16; [Epub ahead of print]

Fleming discovers penicillin
1928 – 1945

Photo of the dish with bacteria and Penicillin mold

Alexander Fleming re turned to his research lab at St. Mary's Hospital in London after World War I. His battlefront experience had shown him how serious a killer bacteria could be, much worse than enemy artillery. He wanted to find a chemical that could stop bacterial infection.

He discovered lysozyme, an enzyme occurring in many body fluids, such as tears. It had a natural antibacterial effect, but not against the strongest infectious agents. In 1928, he was straightening up a pile of Petri dishes where he had been growing bacteria, but which had been piled in the sink. He opened each one and examined it before tossing it into the cleaning solution. One made him stop and say, "That's funny."

Some mold was growing on one of the dishes... not too unusual, but all around the mold, the staph bacteria had been killed... very unusual. He took a sample of the mold. He found that it was from the penicillium family, later specified as *Penicillium notatum*. Fleming presented his findings in 1929, but little interest was raised. He published a report on penicillin and its potential uses in the *British Journal of Experimental Pathology*.

In 1935, Australian Howard Florey was appointed professor of pathology at Oxford University heading a lab. One researcher he hired soon after his arrival was Ernst Chain. Chain was paid to do cancer research, and work that spilled over into Florey's own interest and work on lysozyme.

The Oxford team began experimenting with the penicillin mold. They took it one step further than Fleming did: they did not just try it topically or in a petri dish, but injected it in live mice. With controlled experimentation, they found it cured mice with bacterial infections. They tried it on a few human subjects and saw amazing results. As Fleming first foresaw, the wartime need for an antibacterial was great, but resources were tight and penicillin still very experimental. Florey had connections at the Rockefeller Foundation in the United States who funded further research.

The biggest problem was producing enough penicillin, hard and expensive. Florey and another researcher found this chemical manufacturers in Peoria, Illinois. The nutrient base for the penicillin grown there was corn (maize), which was not commonly grown in Britain. The penicillin loved it, and yielded almost 500 times as much as it had before. More vigorous and productive strains of the mold were sought, and one of the best came from a rotting canteloupe from a Peoria market!

By this point, the United States had entered World War II as well. Penicillin's benefits was now known, and the government pushed industry into producing penicillin, recruiting more than 21 chemical companies into production.

Recent Advances in Orthopaedic Surgery

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Orthopaedic Surgery has made paradigm shift in its scope in the past few decades. The future years promise even greater advances, particularly in the areas of materials sciences, computer aided manufacturing technology, molecular biology, implant and prosthetic design. Better understanding of biomechanics and improved imaging methods and surgical techniques have also contributed greatly to this progress. Among the most important changes is the increase in evidence based practice, which uses studies of patients outcomes.

Implants and inter fixation techniques

Interlocking intramedullary nails which permit locking of the nail to the bone proximally and distally by screws have largely replaced conventional intramedullary nailing. This permits early weight bearing in the lower limb fractures. Unlike the conventional Dynamic Comoression Plates (DCP), Limited Contact-Dynamic Compression Plates (LC-DCPs) allow circulation under the plate and a narrow area of circumferential callus to regenerate at the fracture site. Currently most Orthopaedic implants are constructed of stainless steel. However newer plates made of commercially pure titanium or Titanium-aluminum-Vanadium alloys are being developed to reduce the metal corrosion Biodegradable implants made from adsorbable polyesters, such as Polygylocolic acid are currently under investigation and have been used in limited clinical applications.

External fixation of fractures

New techniques in treating fractures or osteotomies with adjustable external fixators are found at the interface between trauma and elective orthopaedic surgery. A fundamental principle of fracture treatment used to be that fractured bones should never be held apart if healing was to take place. Techniques pioneered by Ilizarov have turned this concept on its head and led to a proliferation of techniques for dealing with the complications of fractures and short limbs. It depends on the principles of Distraction Osteogenesis. This technique can be used to lengthen both limbs by several centimeters in some forms of dwarfism, as well as to correct the length of a limb when a part of the bone has been lost as a result of trauma or exised to eradicate bone infection. The problem is that the technique is immensely time consuming: the lengthening process often takes more than a year to perform and the new bone needs to be any time. In which case the limb may have to be amputated. Clearly, the technique should be used only with extreme caution when used only for cosmesis.

Flexible nailing of long bone fractures

Femoral fractures in children have traditionally been treated with traction and hospital stays of 4-12 weeks depending on the child's age. Earlier hospital discharge is possible if a plaster spica is used, but these are uncomfortable and difficult for children and parents to manage. Flexible nailing of the femur allows early mobilization. Flexible nails produced from new metal alloys are small enough to fit the intramedullary cananl in children but are also able to maintain their shape after contouring and are strong enough to provide stable fixation. The length of time spent in hospital was reduce3d significantly. The indications for flexible nailing have now been extended to include fractures of the tibia and forearm.

Trauma life support

Advanced trauma life support advocated in U.S. has transformed the management of severely injured patients.

Joint replacement surgery

Total joint replacement of the hip and knees are among the most successful group of surgical procedures in Orthopaedics. Total hip or total knee replacements can restore near normal function to patients with severe pain or markedly limited function. Although joint replacements using bone cement have an established success rate over decades, the problem of aseptic loosening remains, requiring a revision arthoplasty. Uncemented total hip replacement in selected patient has potential to avoid aseptic loosening, this can be done in young patients the longevity required is more. Total elbow and total shoulder replacements are being increasingly done and their success rates have been good.

Metal on metal prostheses for hip replacement

Total hip replacement is the treatment of choice for arthritis in elderly people. The most commonly used prostheses are metal femoral components with plastic acetabular cups. The greatest long term problem after hip replacement is loosening of the components which

results in bone loss and pain. This often requires complex revision surgery. This is one of the most important factors that restricts the use of total hip replacement among middle aged patients. The problems are caused by small plastic particles produced by the wearing of the cup. Activated macrophages attempt to clear the particles. And this results in an inflammatory reaction that produces foreign body giant cells; chemical mediators then activate osteoclasts which resorb bone from around the prosthesis producing bone cysts and loosening. An understanding of the mechanism behind this type of loosening has stimulated research into the potential use of other materials, such as ceramics and metal on metal hips. To avoid unnecessary excision of neck for arthritic hip, resulted into the development of surface replacement which is more physiological.

Custom prosthesis in bone tumours

The most recent advance in the surgical approach to skeletal defects after tumour resection involves the use of custom-made prosthetic joints for the replacement of defects near the hip, knee and shoulder. The development of metallurgy and bone cement and their successful use in joint replacement surgery gave way to the use of endoprosthesis is bridging defects in the long bones and joints An individually designs, custom made bone and joint replacement prosthesis is the optimum method of obtaining the best possible results for the patient. These custom made prostheses are made of either titanium or stainless steel alloy.

Autologous chondrocyte transplantation

Articular cartilage is vulnerable in injury and has poor potential for repair so damage can lead to arthritis many years after injury. In elderly people, joint replacements surgery has revolutionized the treatment of arthritis, but the management of damage to articular cartilage in young patients remains a problem. The ideal treatment would replace damaged articular cartilage, restore joint function, and prevent the development of arthritis. Fibrocartilage is unable to withstand the high mechanical loads within a joint and only hyaline cartilage, which has predominantly type II cantilage, has the potential for good, long term results. Transplantation of hyaline cartilage has been used for a number of years,but there are few sites where donor articular cartilage can be harvested without damaging the joint. Thus, only small articular defects can be treated with this method. However, a newer technique allows small amounts of hyaline cartilage to be harvested, the chondrocytes extracted, and the cell population increased in tissue culture. The number of cells increases by about 15 times over four weeks. These cells can then be reimplanted beneath a periosteal patch which is sutured over the articular defect.

Gene therapy in fracture healing

The fracture of a bone initiates a complex healing cascade similar to that in other tissues : haemostatis, inflammation, and infiltration of granulation tissue, followed by callus formation and remodeling. The process may be influenced by systemic factors, such as nutrition and calcium balance, and local factors, such as blood supply and the mechanical stability of the fracture. Advances in molecular biology have improved our understanding of the complex chemical mediators responsible for the healing cascade. Manipulation of these mediators has the potential to enhance fracture healing and accelerate recovery.

Bone morphogenic proteins and transforming growth factor 3 enhance fracture healing. Other factors, such as insulin-like growth factor II and platelet derived growth factor, are also important. Bone morphoginic proteins regulate chemotaxis, mitosis, and differentiation, and are fundamental in initiating fracture repair. Transforming growth factor 3 is 100 times more concentrated in bone than in other tissues, and osteoblasts have a high concentration of receptors of it. The activity of transforming growth factor 3 is not fully understood but the net effect is an increase in bone matrix. The use of these growth factors may stimulate fracture repair and minimize the rate of non-union. TheyT could be delivered to the fracture site by direct injection, and bone defects could be filled with a collagen or hydroxyapatite matrix containing these factors to stimulate new bone formation. Unfortunately these proteins have short biological half lives and must be maintained at therapeutic concentrations at the fracture site to be effective.

Investigation of joints

The vogue for investigating all young patients with knee pain by arthroscopy is now being replaced with a much more selective policy since magnetic resonance imaging was shown to be at least as reliable as arthropscopy in diagnosing torn menisci. It is also cheaper and less invasive. Luckily the fashion for replacing torn anterior cruciate ligaments, which has dominated orthopaedic practice. However, not all patients with torn anterior cruciate ligaments seem to need an operation. This is firstly because some may obtain reasonable function without surgery and secondly, because in the long term most of the substitutes for the anterior cruciate ligament seem to become stretched or to fail. The diagnosis of congential dislocation of the hip is becoming easier with the use of ultrasonography. In the right hands, a dynamic examination of the hip by ultrasonography seems to provide far

more information than x-ray films ever could and it is without any radiation risk.

Prophylactic anticoagulant treatment

The role of Prophylactic anticoagulants therapy is widely accepted in major elective surgery for prevention of pulmonary embolus which is one of the most important cause of death.

Percutaneous osteosynthesis of the upper limb

Many minimally invasive surgical techniques are performed on upper extremity. The advantages of external fixation as a Minimally Invasive Surgery are mostly the absence of material at the fracture site, the easy care of associated injuries and the possible adaptation of the frame configuration to the actual mechanical characteristics of the callus.

Arthroscopy

The Arthroscope has dramatically changed the approach to a variety of joint ailments. Arthroscopy is not only diagnostic but can also have therapeutic applications. Internal derangements of the knee and shoulder are largely operated by arthroscopic techniques. Arthroscopy assisted anterior cruciate ligament reconstruction permits earlier return to work or professional sports. The rotator cuff injuries are treated more by arthroscopic procedures, than by open surgery. Arthroscopic arthrolysis of the elbow is also a newer technique. Wrist arthroscopy allows excellent visualiszation of ligament tears, Endoscopic technique for neurolysis of carpal tunnel (elbow cubital tunnel), lateral epicondylagia or of retroolecranon bursitis is also a newer invention.

Spinal surgery

Inter vertebral disc prolaps is a common clinical problem in orthopaedic practice. Open disc surgery is being gradually superseded by microdiscectomy which requires a smaller opening and an operating microscope. The other options in treatment of disc prolaps include Automated percutaneous lumbar discectomy and endoscopic disc excision. These minimally invasive techniques allow rapid rehabilitation and reduce spinal instability resulting from extensive laminectomy. Better understanding of the biomechanics of the spine has resulted in the design of newer implant system for use in spinal surgery. Use of these systems both anteriorly and or posteriorly in spinal injury along with decompression permits earlier patient mobilization. With the advent of modular segmental spinal instrumentation systems and intra-operative spinal cord monitoring by somatosensory evoked potentials, it is possible to correct fully spinal deformities such as scoliosis. Kyphoplasty is an innovative technique that combines vertebroplasty with balloon catheter technology developed for angioplasty. The procedure shows great promise in the treatment of painful, progressive osteoporotic or osteolytic vertebral compression fractures.

Still with these advances, like other clinical specialty, Orthopaedics desperately lacks the tools, the will, and the resources to assess whether each change is an advance or merely another passing fashion.

Computed tomography

CT (computed tomography), sometimes called CAT (computer-assisted tomography) scanning, uses x-ray equipment to obtain image data from different angles around the body, and then computers to process that information and show a cross-section of body tissues and organs. The advantage of CT imaging is that in addition to bone, it can show soft tissue such as lung and blood vessels with great clarity.

The 0100 ACTA Scanner (which stands for automated, computerized, transverse axial scanner) is the world's first whole-body scanner. Earlier machines scanned only the head, and needed a water bath. The ACTA scanner was invented by dentist and biophysicist Robert S. Ledley and put into clinical operation in 1973 at the Georgetown University Medical Center in Washington, D.C. NMAH acquired it in 1984.

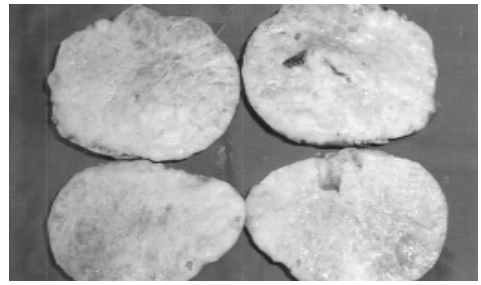
The ACTA scanner joins other new imaging modalities being collected at the Museum, such as ultrasound and MRI, to document the major advances in body imaging since the discovery of x-rays in 1895.

Unusual case of Non-Hodgkins lymphoma involving intestine & bilateral ovaries in an 18 year old girl

Involvement of the female genital tract by Non Hodgkins lymphoma is extremely rare. The most common sites of involvement of lymphoma are gastrointestinal tract, skin, bone, upper respiratory tract.

An 18 year old unmarried girl was admitted as an emergency case with history of fever, pain abdomen for 15days, severe pain on the admission day and amenorrhoea for 1½ months. She was referred to Basappa Memorial Hospital for pain and mass per abdomen by a local doctor. She was taking treatment for dry cough for 4 months. Examination revealed mild anemia, temperature 100^0 F, pulse 120/min, BP: 120/80mmHg. No lymphadenopathy, abdominal examination revealed a mass in the lower abdomen of 24weeks, irregular and tender, no free fluid in the abdomen. Liver and spleen were not palpable. Patient was subjected for investigation such as chest X Ray, ESR, complete hemogram, Ultrasound of the abdomen/pelvis. There was mild anemia. Abdominal scan showed bilateral hydronephrosis with a large mixed echogenic mass measuring 12cms. Impression was probably ovarian dermoid and both ovaries were not seen separately from the mass. Uterus was normal.

Keeping in mind the possibility of torsion of ovarian tumour and malignancy of the ovaries and after arranging 3 bottles of compatible blood, patient was taken up for laparotomy under general anaesthesia. Abdomen was opened in layers. There was no free fluid in the abdomen, liver and spleen appeared normal. There were bilateral lobular, fleshy haemorrhagic masses replacing the ovaries. Uterus was normal. On further exploration, there was huge retroperiotoneal mass adherent to terminal part of the ileum, caecum and ascending colon. Then bilateral ovariotomy was done and radical hemicolectomy was done by anastomosing terminal part of ileum to the transverse colon. Post operative period was uneventful and the patient was discharged on 20^{th} post operative day without any complications. Patient was referred to cancer institute for further treatment. Histopathology and immunochemistry confirmed, the diagnosis of non hodgkins lymphoma.



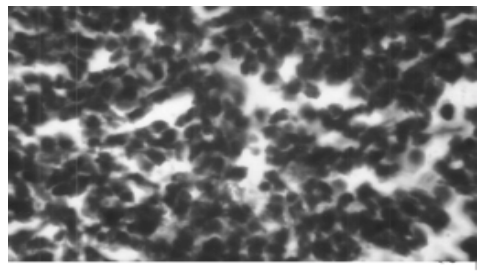


Plate I - High power view of diffuse nonhodgkin's lymphoma with predominant lymphocytes.

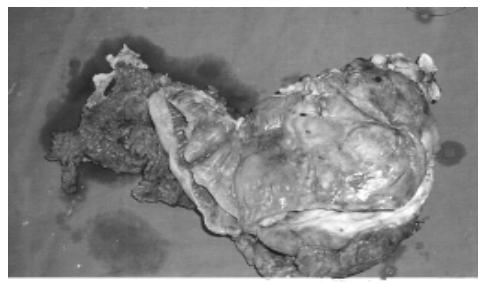


Plate III – Gross photo of primary nonhodgkin's lymphoma intestines.

Discussion

Johnson and Soule reviewed 1269 cases and there was only one case of ovarian lymphoma. Nelson et al described 6 cases of ovarian lymphomas but questioned the existence of a primary lesion in the ovary, because lymphocytic aggregation are never present in the ovary. Study by Rotmenseh et al reported 20 cases of ovarian lymphoma and reviewed 35 previous cases reported by Woodruff. Lymphoid tissue may be present in hilum and medulla of the ovary, thus primary ovarian lymphoma is

possible. Spread is multifocal. Susceptibility theory says malignant cells circulate in the body freely and they grow in preferential sites. The management is essentially surgical resection followed by radiotherapy or chemotherapy. Disease free 2 year survival rate is expected to be 50%. And follow them for 2years after which recurrence of the disease involving gastrointestinal tract occur with decreasing frequency.

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Secondary Chondrosarcoma in a solitary Osteochondroma of the Pubis – A Case Report

Solitary osteochondroma or osseocartilaginous exostosis is a relatively frequent lesion that arises in bones developing through endochondral ossification. It can be associated with several complications. The most serious and most dreaded complication is the malignant transformation in to chondrosarcoma, the risk of which is approximately one percent [1].

Case report

A young female of 17 years of age presents with dull aching pain the right pubic region since 2-3 three months. On palpation there is no obvious abnormality except for mild tenderness. Routine laboratory investigations and the past history were unremarkable.

The patient then underwent a radiographic examination, which revealed a large osseous protuberance arising from the right pubic bone (figure 1). The lesion revealed an irregularly calcified matrix and a thick soft tissue rim displacing the fat planes. The skeletal survey of the patient did not reveal any other similar lesion. Based on these findings, the diagnosis of the solitary osteochondroma arising from the right pubic bone is made. The patient then underwent US for evaluation of the cartilaginous cap of the lesion. US revealed an irregularly calcified mass with areas of hypoechogenicity and a hypoechoic rim, which exceeded 1 cm at several places. The maximum thickness of the cartilage cap appeared to be 1.6 cm in the anteroinferior part of the lesion. Corroborating the findings of the US with that of the radiograph and clinical features, the possibility of the malignant transformation of the solitary osteochondroma was suggested.

The patient was then taken up for CT examination of the pelvic bone, which revealed a large, sessile osseocartilaginous excrescence arising from the anterior and the inferior cortex of the right pubic bone. The matrix of the lesion was irregularly calcified. There were multiple areas of low attenuation within the lesion. The margins of the lesion appear irregular at multiple areas (figure 2 a, b, c, d). The soft tissue rim exceeded 1 cm at several places and the maximum thickness was noted to be 1.8 cm in the anteroinferior part of the lesion. There was associated bony sclerosis in the adjacent pubic bone. Based on the findings in the radiological investigations and clinical features the high probability of the secondary chondrosarcoma was suggested.The patient then underwent guided biopsy, which confirmed the above diagnosis.

Discussion

Solitary osteochondroma or osseocartilaginous exostosis is a relatively frequent lesion regarded as a true neoplasm by some and developmental physeal growth defect by others. These lesions arise from bones, which develop through a process of endochondral ossification and are related to the physis. The lesions can rarely arise from the diaphysis or epiphysis (Trevor's disease or dysplasia epiphysealis hemimelica). Multiple osteochondroma are associated with diaphyseal aclasia [2,3,4].

These lesions are primarily encountered in children and adolescents incidentally as a slow growing firm mass. They are usually painless and nontender. Larger lesions may however be related with symptoms related to fracture, irritation or compression of the adjacent important anatomic structure. The common sites of occurrence include long tubular bones especially femur, humerus and tibia. In the innominate bone, these lesions are usually large and lead to a soft tissue mass and displacement of the adjacent structures and the patterns of calcification are variable and irregular. Potential complications of these lesions include fracture, osseous deformity, vascular injury, neurological compromise, bursal formation and malignant transformation. The risk of malignant transformation of a solitary osteochondroma[1, 2, 3] is about 1% and in case of multiple lesions [2], the risk approaches 25%. Commonest malignancy occurring in such lesions is chondrosarcoma. Features suggesting malignant transformation include clinical features (pain, sudden swelling or soft tissue mass) and radiological features (recent enlargement of the lesion, bone erosion, irregular or scattered calcification, cartilage cap thicker than 1 cm[2,3].

Radiologically, this lesion is characterised by a osseous protuberance arising from the external surface of the bone and containing spongiosa and cortex that is continuous with those of the parent bone. The lesion may be that may be sessile

(broad, flat base) or pedunculated (narrow stalk with a bulbous tip). A cartilage rim caps the lesion. The lesions are typically directed towards the diaphysis in the tubular bones. Ultrasound examination can be used to analyze the cartilaginous cap, which appears as a hypoechoic rim. Lesions situated deep or oriented inwards are suboptimally evaluated by US. Computed tomography can be used to demonstrate the typical cortical and medullary continuity of the lesion in regions of complex anatomy and can also demonstrate the internal matrix, thickness of the cartilaginous cap and associated complications. Magnetic resonance imaging of these lesions is more sensitive and specific in evaluation of the above features than CT. A normal bone scan virtually excludes the diagnosis of the malignant transformation of the exostosis[2,5].

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References

1. Satish K Bhargava, Textbook of Radiology and Imaging, 1st edition, CBS
2. Donald Resnick, Mark J. Kransdorf, Bone and Joint Imaging, 3rd edition, Elsevier Saunders
3. David Sutton, Textbook of Radiology and Imaging, 7th edition, Churchill Livingstone
4. Schajowicz F, Tumors and Tumorlike Lesions of Bones and Joints. New York, Springer-Verlag, 1981

Hudson TM, Chew FS, Manaster BJ, Scintigraphy of benign exostosis and exostotic chondrosarcoma. AJR 1983; 140: 581

FIGURE 1: Anteroposterior radiograph of the pelvis shows a large osseous protuberance arising from the right pubic bone

FIGURE 2: CT sections in the axial (a, c) and coronal MPR (b, d) in the soft tissue (a, b) and bone (c, d) window settings showing the secondary chondrosarcoma in a case of solitary osteochondroma

Organ Preservation and Minimal Trauma in Ovarian Cysts

Adnexal masses are common among women of all ages. Most tend to be benign, but malignancy can be excluded only by histopathologic examination. A preoperative test which can give a tentative diagnosis can prevent unnecessary surgery for benign functional cysts, use of minimally invasive surgery in persistent benign lesions and appropriate preoperative, perioperative and postoperative management in malignant ovarian tumours.

In premenopausal women physiological ovarian cysts are common and can be managed expectantly. Persistent cysts in these women commonly are endometriomas and dermoid cysts,[1] which account for over two-thirds of cases. Majority of them can be diagnosed by its morphological features with transvaginal sonography.

Simple ovarian cysts are also common in Postmenopausal women. Risk of malignancy in cysts measuring < 5 cm is extremely small. Majority of them are benign cystadenomas.

Jacobs et al combined CA 125 values with ultrasound morphologic findings and menopausal status of the patient to calculate their risk of Malignancy index. Poor sensitivity and specificity of CA-125 limit its use as a sole screening test for early ovarian cancer. Likelihood of malignancy in a simple ovarian cyst with no solid papillary projections is low. Granberg et al[2] noted that the risk of malignancy in a cyst containing solid projection is high as 50%.

Use of Colour-Doppler information can be misleading, because of false positive results from corpora lutea and dominant follicles especially in premenopausal

women. Furthermore, there is a real overlap in colour Doppler findings between benign and malignant ovarian masses.

Using logistic regression model Timmerman et al[3] demonstrated that a mathematical approach can improve the diagnosis. Initially 22 different criteria were taken into consideration for performing extensive gray-scale morphologic examination including colour Doppler and hence compared with histopathologic analysis and staging. This approach should enable operators with different levels of experience to more easily achieve consistent results.

Anil Tailor et al[4] used more sophisticated model using neural networks. They have shown that predictions based on a combination of two indices such as the time averaged maximum velocity and the probability index allow a better discrimination between benign and malignant tumours than when the prediction is based on either of the single indices alone. However, none of these approaches can improve on the subjective impression of a mass by an experienced observer.

Majority of ovarian pathology can be accurately characterized in this way. However certain lesions like cystadenofibromas, with ovarian pathology and borderline tumours can cause difficulty in diagnosis and needs second stage tests to evaluate further.

In this way appropriate patients can be treated either expectantly, with minimal invasive surgery or referred to oncology units for further management.

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References

1. Mais V, Guerriero S, Ajossa S, Angiolucci M, Paoletti AM, Melis GB. Transvaginal sonography in the diagnosis of cystic teratoma. Obstet Gynaecol 1995, 85:48-52.
2. Granberg S, Wukland M, Jansson I. Macroscopic characterization of ovarian tumours and the relation to the histological diagnosis; criteria to be used for ultrasound evaluation. Gynecol Oncol 1969, 35:139-144.
3. Dirk Timmerman, Thomas. H. Bourne, Anil Tailor, William P. Collins, Herman Verrelst, Kaniel. Vandenberghe and Lgnace Vergote. Comparison of methods of preoperative discrimination between malignant and benign adnexal masses; The development of a new logistic regression model Am J Obstet Gynaecol 1999; 181: 57-65.
4. Anil Tailor, Davas Jurkovie, Thomas H. Bourne, William P. Collins, Stuart Campbell. Sonographic prediction of malignancy in adnexal masses using an artificial neutral network. Br. J Obstet Gynaecol 1999, 106; 21-30.

First Heart Implant

Dr. Christiaan Barnardin, became the first surgeon to perform a heart transplant on a human being in December of 1967.

Barnard, the son of a poor Afrikaner preacher belonged to Beaufort West, a town on South Africa's semi-arid Great Karroo plateau. He studied medicine at the University of Cape Town and the University of Minnesota. In Minneapolis he began helping researchers who were working on a heart-lung machine, and soon switched his specialty from general surgery to cardiology and cardiothoracic (heart-lung) surgery.

By 1967, Barnard was senior cardiothoracic surgeon at the Groote Schuur Hospital in Cape Town, where he had introduced open heart surgery and other pioneering surgical procedures. The first successful kidney transplant had been done in 1954, opening this exciting surgical frontier. Barnard had a patient, 55-year-old Louis Washkansky, who had diabetes and incurable heart disease. Washkansky could either wait for certain death or risk transplant surgery with an 80 percent chance of surviving. He chose the surgery.

In December of 1967, Denise Darvall, a woman was fatally injured in an accident. She had had the same blood type as Washkansky. She died shortly after arriving at the hospital, but her heart was still healthy. Barnard successfully replaced Washkansky's diseased heart with the healthy heart. It was a surgical success.

Barnard had been bothered by rheumatoid arthritis since he was young, and advancing stiffness in his hands forced his retirement from surgery in 1983. He took up writing, however, and wrote a cardiology text, an autobiography, and several novels, including a thriller about organ transplants. He has just two regrets in his long and eventful career. First, he endorsed an "anti-ageing" skin cream in 1986, which turned out to be of dubious effectiveness and was withdrawn from the U.S. market in 1987. Although his endorsement made him a great deal of money, it tarnished his medical reputation. His only other regret was not fighting harder against South Africa's policy of apartheid.

DNB- "Rural Surgery"

Medical education in our country needs a change in direction. Bureaucracy and political patronage has put postgraduate medical education in shackles and has not allowed it to grow in the right direction. In the seventies the world witnessed a spurt in the growth of medical (including surgical) technology. Improved and sophisticated intensive care facility, improved and sophisticated investigation tools, minimal access surgery, organ transplantation and artificial implants. All these were industry based and carried a price tag with it. This price tag led to a revolt by the payers and the societies of the western world. Cost effectiveness and cost benefit analyses were introduced in a bigger way in these countries. Then came the concepts of "prioritisation", technology assessment, quality assurance and medical decision making. Greater importance was given to patient compliance and quality of life. Came the ideas of Evidence based medicine, patient oriented evidence and finally "outcome analysis"[2] to assess the necessity of these inputs on the health of the individual and of the society. The industry had to be harnessed from being profit oriented to being service oriented at the taxpayers cost.

In many universities round the world, medical education also moved in this direction. Problem based learning was introduced in Mc Master University in Canada and in Maastricht in Holland. The Royal Colleges of the UK changed its postgraduate examination and training pattern to adjust to the increased technological input and its societal needs. And in India, I venture to say, the postgraduate course in rural surgery is a great step in the same direction. However, the concept of "rural surgery" has to be clear for the society to benefit from the introduction of the course.

Concept of rural surgery[1]- Way back in 1986, a symposium on "surgery in rural areas" was held in the Association of Surgeons of India`s annual conference. Following this a rural healthcare committee was formed by the Association to look into the working constraints and CME needs of surgeons working with limited resources in small towns and in rural areas of the country. A survey was conducted by Dr. R.D.Prabhu in which 140 surgeons responded. This showed that most of these surgeons were performing multidisciplinary surgery including obstetric and genealogical surgery to meet the needs of the community. Many of them did not have the facilities of para-surgical disciplines. And they out of necessity, trained village boys and girls to meet their hospital needs which was in fact a human resource development activity[5]. Improvisation and innovation was being done to meet these deficiencies. Many of them were also small institution builders. And these institutions survived with contributions from both the surgeon and the community.

The per capita GNP of India is around 400US Dollars. While those of the developed countries varies from 20,000US Dollars to 45,000US Dollars(UNICEF). In a study by the Late Prof.Krishnan of the centre of developmental economics, Thiruvananthapuram, it came to light that while 80% of our population live in rural and periurbanslums, 80% of hospital beds are in large cities. And 80% of these beds are occupied by people coming from rural areas![3] Again, according to the voluntary health assoc. of India, 400 million have NO ACCESS to modern health care. Either it is not accessible or affordable to them. With the increasing cost of care and impact of opening up and privatisation, therefore, a sustainable model of accessible and affordable health and medical care had to be evolved which could be used both in the government and voluntary(private) sectors with equal efficiency. The concept of "rural surgery" aspires to meet this need of the country. Although it is named "surgery" it transcends the barriers of only surgical care as has been put by the western norms requiring a high cost infrastructure institution for its practice. And cold tertiary care surgery remains outside the ambit of this speciality. What does it include. It includes what the WHO defines as "essential surgical care" and "essential trauma care". A rural surgeon performs all types of basic surgery across different specialities, that is routine open surgeries, obstetric and gynecological care, closed reduction of fractures and care of trauma within the available limited resources. He is the doctor working in the government CHCs or builds his own small hospital in peri-urban and rural areas in the private sector. He trains up local boys and girls into running the hospital. To that extent, he has to gain managerial experience as well, and also has to have a basic knowledge of sociology and economics to make his institution into a sustainable one.. In lieu of tertiary care surgery in one speciality, preventive and promotive health care forms a part of his work. He thus acts as a filtering institution between primary healthcare(which also he performs) and tertiary healthcare institutions near his area of activity. The diploma course in rural surgery has been made to contain all these elements and thus would come as a big support of the government's National Rural Health Mission.

Thirteen years ago, an Association of Rural Surgeons of India was formed with seven members. The first president was Prof.Balu Sankaran, retired professor of

orthopedics and an ex Director General of Health Services. The next president was Dr.N.H.Antia, plastic surgeon, who spearheaded the ICSSR/ICMR report on "health for all, an alternative strategy" to the parliament. Today the Association has 400 members and has matured through 13 annual conferences in small towns and in rural hospitals across the country, (The first conference was held at the MGIMS Wardha under the leadership of the late Dr.Sushila Nayar.) The course design has been drawn from the experience of many senior surgeons who have spent their lives working in rural areas of our country and met under the banner of this association(website arsi-india.org).

The Nobel laureate economist Gunnar Myrdal had mentioned in the chapter on education in his epoch making book "Asian Drama" - "In all forms of education, improvement of attitudes is at least as important as imparting skills"[4] Making a rural surgeon through relevant skill training together with attitudes, would thus be a boon to the rural population of our country on whose services depends the supply of our daily bread. Prof. Wilfried Lorenz is more precise on this issue. He mentions:- "The role of the scientist is no longer that of a precise methodologist or a sophisticated thinker but also of the provider, a person whose primary concern reflects the needs of the individual and of society.".[2] The NBE, by introducing the rural surgery course, is certainly living upto this role for the country.

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References

1. Banerjee.J.K.,Analysing outcome of Surgical development-rural surgery as an example, Ind.J. Surg, 2003, Vol65, No1, 68-72.
2. Lorenz.W., Outcome, definition, methods and evaluation, chapter in "Surgical Research, Basic principles and clinical practice, edited by Troidl et al, 3rd edition, Spinger Verlag, New York 1998, 513-519.
3. Krishnan T.N. Centre for developmental economics, Thiruvananthapuram, paper read in the 2nd National conference of rural surgery, SHIMOGA, 1994.
4. Gunnar Myrdal, Asian Drama,an enquiry into the poverty of nations, abridged by Seth S. King published by Allen Lane, The penguin press, 1978, 295.
5. Shipra Banerjee, Human resource development in rural surgery: Developing the paramedic training programme, Ind. J. Surg 2003, vol.65, No.1, 60-64.

Kangaroo Mother Care(KMC)

Kangaroo Mother Care or KMC has become an integral part of caring for the newborn , specially the low birth weight neonate. As the name would indicate this method of caring for the baby has been a 'return to nature' approach after observing nurturing practices for the joey (baby kangaroo) by the mother. Despite its Australian zoological origin, the KMC owes status in neonatal care to this practice in countries of the South American continent. In this method, the neonate is kept in direct skin to skin contact with an adult. The baby has caps on to prevent loss of heat from the head. The infant is often provided with socks and gloves as additional thermal support clothing. It must be remembered that the minimum contact period should be atleast one hour.This method is ideal for all Low birth weight babies and should be continued till the infant is about 2500 gm. Often the infants start 'creeping out' by the time they are about 1800 grams. It is quite possible to comfortably breast feed a baby undergoing kangaroo mother care.KMC can be given when the mother/adult is sitting or lying down. Appropriate 'pouches' or bag could be easily designed and locally made in facilitate KMC even when the adult is ambulatory. Once the infant is stable, KMC could be initiated for VLBW babies in the Neonatal Intensive Care unit itself. CPAP or ventilator support

need not be a hindrance to KMC is the infant is physiological stable.

The advantages of this innovative and cost effective care are- thermal Synchrony- temperature of infant almost constant at 37°C; 1°C drop in infant's temperature results in mother's contact skin temperature rising by 2 °C ; similarly 1°C rise of infant results in1°C drop in maternal contact skin temperature. KMC stimulates and satisfies all 5 senses- touch - skin contact; hearing - mothers' heart beat and voice; taste – breastfeeds; vision – eye contact with mother; olfaction – mother's natural odor. Needless to say many believe that KMC would be an ideal psychosocial motivator for the neonate.

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Workshops on research methods for DNB candidates and consultants

NBE has been holding workshops for the NBE faculty members/ consultants of various Accredited hospitals/institutions running DNB training programmes. During interactions with them it was felt that many consultants/ faculty members need to be given exposure to research methods, so that they are able to provide better guidance to DNB candidates in their thesis work. In that context NBE had conducted a pilot workshop at Maulana Azad Medical College, New Delhi from 20th July to 22nd July 2006. Based on this feed back more workshops will be conducted for Consultants and for DNB candidates in near future.

DNB (Rural Surgery)

National Board of Examinations has launched DNB (Rural Surgery), on pilot basis from June 2006. The concept of rural surgery has evolved in India over the past decade based on the ground reality of surgical practice of surgeons practicing outside high-tech institutions in our country. In India, 400 million people have no access to basic surgical care, termed by the WHO as "essential surgical care". The aim of this course would be to create a cadre of basic multipurpose surgeons, who would acquire the expertise to provide basic and emergency and lifesaving surgical care to rural population of our country. They can form the back bone of health care delivery system and can play a vital role in fulfilling the Rural Health Mission announced by the Government of India.

Goal: After qualifying the final examinations the candidate should be able to function as a consultant (specialist) in Rural Surgery (multiple surgical disciplines) within the constraints of limited resources.

Objectives: At the end of the training period, the candidate should be able to acquire following competencies:

- Basic & general surgery with emphasis on open surgeries.
- Basic orthopaedics including trauma care.
- Obstetrics and Gynaecology.
- Basics of anesthesia, ultrasound and X-Ray.
- Emergency care

Training for DNB in Rural surgery will take place in two kinds of hospitals:

1. Multi specialty hospital which will be called as **Nodal Rural Surgical Training Center:** 2 years of training will take place here. This institute will take primary responsibility for the candidate in terms of- Organizing & scheduling the training program for the entire 3 years in consultation with the peripheral institutes. A co-ordinator from both the institutions will be appointed to look after the total training of the candidates; Providing hands on experience to the candidate thus imparting practical surgical skills. Candidate should eventually be able to perform procedures independently and not merely be a first assistant; Placement of the candidate to a peripheral rural surgical centre where the candidate is regularly monitored for skills training and for preparation of the dissertation.

2. **Peripheral Rural Surgical Centre**: 1 year of training will take place here. This will train the candidate to work in resource limited situations and develop his/ her capability to learn to innovate and manage a rural surgical practice; This is also the setting in which the candidate will write up a dissertation based on a topic which is relevant to the rural surgical practice. The candidates will be posted in peripheral Rural Surgical Center for 3-4 months in first, second and third years of training

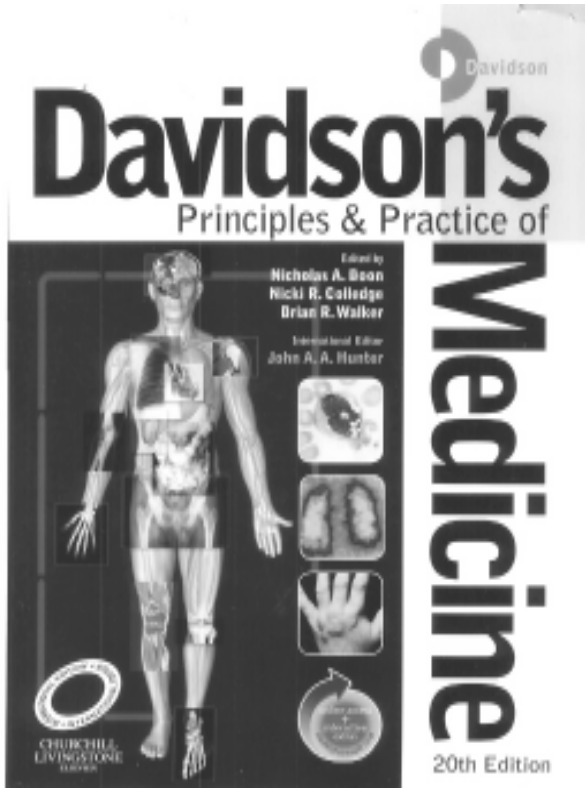
Eligibility criteria for the Candidates

1. Essential- Any medical graduate with MBBS qualification, who has completed internship and is registered with MCI/State Medical Council can register with the Accredited Institutions for 3 years of training.

2. Desirable- 1 year experience after completing internship in a peripheral/rural set up. In service candidates from Defence, Central/ State Government, Railways, Public sector institutions may also be given preference.

Davidson's Principles and Practice of Medicine: (eds) Boon NA, Colledge WR, Walker BB, Hunter JAA.20th edn. Edinburgh, Elsevier, 2006. Pages xvi + 1381

Late Sir Stanley Davidson conceived in the later 1940s Principles and Practice of Medicine based on the lecture notes he gave in Edinburgh. A medium-sized, comprehensive book was published in 1952. Though the subsequent editions have witnessed many changes in its format and presentation, they have retained the original vision and objectives of Sir Stanley Davidson. The current book is its 20th edition. The book has a large readership consisting of medical students, doctors and other health professionals all over the world. The successive editions have evolved to meet the changing needs of health professionals.



The 20th edition has been divided into two sections. The first section with 7 chapters deals with Principles of Medicine describing the basis on which medicine is practiced and the fundamental mechanisms determining health and disease. The second section with 27 chapters deals with Practice of Medicine pertaining to the relevant medical specialties. The book though has 1400 pages, yet it is concise giving an updated knowledge of clinical medicine. This multi-authored book numbering 60 includes Prof. Shyam Sunder of Banaras.

A problem-based approach has been followed in section 1 with 171 pages, bringing together the modern medical practice and clinical practice. It begins with a new chapter on Good Medical Practice highlighting the professional and ethical principles underlying medical practice. Art of medicine hinges on the ability to recognize and respect the differences in belief, attitudes and expectations between patients and doctors, and to treat every patient as an individual. There are subsections on doctor-patient relationship, clinical and communication skills, personal and professional development, clinical ethics, complementary and alternative medicine (CAM). Though the authors mention 'big five' CAM therapy, *Ayurveda* does not find a place! There is discussion on good prescribing. It is essentially prescription only when necessary to cure or ameliorate disease or to alleviate symptoms.

There are new chapters on Molecular mechanisms of diseases, immunological factors, environmental and nutritional factors in disease, and principles of infectious diseases. Molecular mechanisms of disease discuss cell cycle and the structure of DNA, genetics and cell biology that have revolutionized our understanding of the inheritances and molecular basis of disease. The chapter on immunology provides a general understanding of immunology and its influence on human disease. There is discussion on clinical presentation of the most common forms of immune dysfunction. The molecular and cellular mechanisms of disease which are intrinsic to the individual patients are modified with the influence

of external environment. Exposure to infectious agents is the major environmental determinant of health. There are detailed write-ups on nutritional factors in disease, dietary recommendations, micronutrients and principles of infectious diseases. Infectious diseases continue to be greatest killers of mankind. The interaction between human and other microorganisms in nature results in disease. All systems of body are susceptible to infections. There is a section on the antimicrobial therapy.

The initial chapters in section 2 deal with critical care and emergency medicine, poisoning, psychiatry and oncology, and infectious diseases affecting various systems, HIV/AIDS, sexually transmitted infections, chemical biology and metabolism, and palliative case management.

The second part is very extensive with 1140 pages. The editors have maintained a uniform approach throughout. The incorporation of evidence-based medicine has transformed the practice of clinical medicine and has provided a useful vehicle for the development of guidelines. The description of each system in different chapters is followed in this manner uniformly: review of relevant clinical examination including the examination techniques and the interpretation of physical signs, functional anatomy, physiology and investigations, presenting problems, and individual diseases. Such a presentation has made it easy to follow and understand the subject easily. There is a global perspective giving more detailed account of health problems in developing countries.

The book is profusely illustrated with a large number of tables, charts, boxes, clinical photographs, radiographs, echocardiograms, endoscopic pictures, CT, MRI, SPECT, angiograms, geographical distribution of diseases, and microphotographs. The illustrations exceed 1000. The eye-catching colour combinations highlight the salient features. The evidence-based medicine panels summarise the results of most recent systematic reviews or randomized controlled trials in key therapeutic areas.

At the end of each chapter, there is mention of books and journal articles for further information, and important websites providing more information. There is an appendix at the end giving biochemical values, haematological values and cardiovascular risk prediction charts. There is an extensive index of 54 pages.

The authors and editors deserve congratulations for bringing out the such an outstanding book with updated information. They are highly successful in making the work as one of the world's leading textbooks of medicine. Every medical student should possess this valuable book for use in day-to-day learning and practice. This comprehensive text has lived up to its reputation for providing a proper basis for the practice of medicine.

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M.R. Medical College, Gulbarga

Discovery of Insulin

In 1920, Canadian surgeon Frederick Banting visited the University of Toronto to meet new HOD of physiology, John J.R. Macleod. Macleod had studied glucose metabolism and diabetes, and Banting had a new idea to treat so-called "sugar disease."

Late in the 19th century, scientists found the connection between the pancreas and diabetes. It was further narrowed down to the islets of Langerhans, a part of the pancreas. In 1920, he realized that the pancreas' digestive juice was destroying the islets of Langerhans hormone before it could be isolated. If he could stop the pancreas from working, but keep the islets of Langerhans going, he should be able to find the stuff! Banting badgered him until finally Macleod gave him lab space, 10 experimental dogs, and a medical student assistant.

In August, 1921 they had the first conclusive results: when they gave the material extracted from the islets of Langerhans (called "insulin," from the Latin for "island") to diabetic dogs, their abnormally high blood sugars were lowered.

Macleod felt confident enough to try it on a human for the first time: a 14-year-old boy dying of diabetes. The injection indeed lowered his blood sugar and cleared his urine of sugars and other signs of the disease. Banting and Best published the first paper on their discovery a month later, in February, 1922. In 1923, the Nobel Prize was awarded to Banting and Macleod for the discovery, and each shared their portion of the prize money with the other researchers on the project.

The discovery of insulin was one of the most revolutionary moments in medicine. One year the disease was an automatic death sentence; the next, people-even children had hopes of living full and productive lives even with the disease. Estimates show there are more than 15 million diabetics living today who would have died at an early age without insulin.

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1. Standard journal article- Sharma AK, Singh S, Organ transplantation in HIV infected patients. N. Engl. J. Med. 2002; 347: 284-7
2. Books and Monograph- Murray RR, Rusenthal KS. Medical Microbiology. 4th ed. St. Lovis: Mosby; 2002.
3. Chapter in a book- Meltzen PS, Trent JM. Chromosome alternations in human solid tumors. In : Vogelstein B, editor. The Genetic basis of human cancer, Newyork: MC GrawHill; 2002. p. 93-113
4. Conference proceedings- Handen P, Jones W D, Editors. Germ cell Tumors. Proceedings of the 5th Germ cell tumor conference; 2001 Sept 13-15; Leads, U/C. Newyork: Springer; 2002.
5. Dissertation- Singh AK. Prevalence of hypertension in school children. Maulana Azad Medical College; 2003.
6. Internet article- Abood S. Quality improvement initiatives in running homes Am J Nurs, 2002 Jun; 102 (6), available from: http//www.muningworld.org/AJN/2002.nurseswatch.com

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