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Medical Quiz: Laboratory profiles
Parasitic Infestation: Diagnosing Giardiasis
Intravenous Hydration Therapy: Replacement Fluids
Basic Medical Procedures: Nasal plugging
Neonatology: Care of the neonate at birth
Pediatrics: Rational Use of antipyretics in children
Health Care Administration: Health Care Waste Management
Pregnancy: Antenatal Care
Nutrition: Vitamin A deficiency: Prevention & control
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Cancer Medicine: Ultraviolet radiation & skin cancer
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Patho-physiology: Eosinophil & its abnormalities
Spices we use: Ginger
Psychology: Cognition
Original Research: Antibiotic resistance profile of UTI in Kashmir
A leaf from the history of Medicine: Louis Pasteur

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Medical Quiz 1:

Read the questions, think, pause, and don’t rush to the answer.

I) A woman who had a mastectomy 10 years ago complains of backache, bruising, and tiredness. She has received no treatment. Her investigations reveal:

- Hemoglobin 10.7 g %
- Platelets 50,000/c.mm
- Prothrombin time 26 seconds (Control 12 secs)
- Kaolin-cephalin clotting time: 55 seconds (Control 38 secs)

Q: 1) What is the hemotologic diagnosis?
   2) Name one test to confirm the diagnosis?

(Answers on page 18)

II) A man of 60 with vitiligo presents with tiredness. He is slightly jaundiced. His investigations reveal:

- Hemoglobin 6.0 g/dl
- MCV 112 fl
- MCHC 34g/dl
- WBC 3900/c.mm
- Bilirubin 25 μmol/l
- SGOT (AST) 20 U/l (Normal <25)
- SGPT (ALT) 11 U/l (Normal <20)
- Alkaline phosphatase 55 U/l (Normal 20-100)
- SHBD 2000U/l

Q: 1) What is the most likely diagnosis?
   2) Name 3 additional tests necessary to confirm the diagnosis.

(Answers on page 61)
Giardia lamblia occurs in the small intestine of the humans, producing mostly asymptomatic infections. However, sometimes it leads to diarrhoea especially in children. It is also an important producer of travelers to endemic areas. Several species of animals are naturally infected; some of these are implicated as source of epidemics.

**Geographic distribution:**
Giardia is a cosmopolitan organism with a worldwide distribution; the global prevalence of infection is 200 million! It is found in tropics as well as temperate areas. Interestingly, it is the only protozoon found in Eskimos! Prevalence in the less developed world is indeed very high – sometimes it is higher than 45% of the entire population, especially so in children. Malnourished children in Bangladesh had a prevalence of 51%.

Temperate climates are also not spared: in the USA, currently it is the highest diagnosed parasite and its prevalence is increasing. Lately more than 7% of the American stools had giardia!

Prevalence is particularly high in day-care centres and creches: in Brazil, a prevalence of 70% was found.

Prevalence is quite high among the male homosexuals.

In temperate zones, the prevalence among children may be seasonal, with higher rates during autumn.

Many outbreaks because of contamination of drinking water systems have been reported from developed countries, including some Scandinavian countries.

Some recent outbreaks have been attributed to zoonotic transmission from wild animals but till date there is no evidence of spread from pets.

**Morphology:** There are 2 stages: a trophozoite stage and a cystic stage.

<table>
<thead>
<tr>
<th>Trophozoite</th>
<th>Cyst</th>
</tr>
</thead>
<tbody>
<tr>
<td>Size: 21 x 15 x 4 μm</td>
<td>Size: 8-12 x 7-10 μm</td>
</tr>
<tr>
<td>Rounded anteriorly, Pointed posteriorly</td>
<td>Ovoid</td>
</tr>
<tr>
<td>Symmetrical internal organization</td>
<td>(Same)</td>
</tr>
<tr>
<td>Have 2 nuclei anteriorly</td>
<td>Have 4 nuclei</td>
</tr>
<tr>
<td>Have 4 pairs of flagella (anterior, posterolateral, ventral &amp; caudal)</td>
<td>No flagellum</td>
</tr>
<tr>
<td>Ventral surface has a suction disc which attaches the parasite to the intestinal mucosa</td>
<td>Have a readymade disc for the new host’s intestine</td>
</tr>
</tbody>
</table>

**Life cycle:**
Mature cysts are evacuated with the faces into the environment (water, soil), and eventually may gain to a new host with contaminated water or food. Cysts survive outside the body for 4 days at 37°C but for as long as 2 months at 4°C.
The cyst of giardia lives for months in cold environment, and thus is more problematic in temperate than in tropical climates. This is the only protozoon found in Canadian Eskimos.

Once ingested, cysts commence excystation probably within 5-10 minutes. A break appears at one end of the cysts and flagella appear. Cell division occurs and within 30 minutes two trophozoites are formed from one cyst. These trophozoites immediately attach to the brush border. They move down in the intestine and secrete a cell wall for themselves.

10 cysts are sufficient to produce infection in adults. Thus outbreaks can occur even with few cysts being isolated from drinking water.

Most of the outbreaks of giardiasis have been from lack of filtration, which is the best method for removal of various cysts. Chlorination alone, at the usual recommended doses, is ineffective in inactivating the cyst.

Pathogenesis:
Giardia trophozoites attach themselves to the brush border and damage to the brush border and atrophy of the villi is partly responsible for diarrhoea. There may be marked damage to the jejunal villi without causing diarrhoea. Laboratory evidence suggests that damage to brush border may lead to deficiency of brush border enzymes, which returns to normal once the infection is eradicated. Disturbance of IgA locally may contribute to infection. It is pertinent to mention that some 10% of general population is deficient in IgA. Other factors inside the mucosa or lumen may be contributory in causation of symptoms.

Various intracellular lesions include ultrastructural damage to or reduction in height of villi, reduced disaccharidase deficiency, mucosal inflammation & immature villous enterocytes due to rapid turn over of epithelial cells. Various intra-luminal factors are bacterial overgrowth, uptake of bile salts by the parasite and inhibition of host hydrolytic enzymes. Uptake of bile salts by giardia stimulates growth and encystations.

Clinical features:
Symptoms & signs vary with
- The age of the host
- Immunologic status &
- previous exposure to the parasite.

In endemic areas, giardia produces symptoms during childhood, and early exposure confers some immunity, since adults are rarely affected. On the contrary, because of lack of exposure in the developed world, giardiasis occurs more frequently in adults than in children. After an incubation period of 12-15 days, nausea, anorexia, epigastric fullness, and malaise occur followed by sudden, explosive, foul-smelling, watery diarrhoea, which within a few days changes into bulky, semisolid stools. Abdominal distension with increased foul flatulence, foul belching and epigastric cramps occurs.

The acute symptoms which mimic, acute viral enteritis, bacterial enteritis, or food poisoning, usually last for only a few days. Patients may have mild to moderate weight loss; with malabsorption the weight may even exceed 10 kg. X-ray of abdomen may show duodenjejunitis.
Chronic infections may lead to recurrent intestinal cramping, bloating, and bulky stools with fat and undigested food, showing absorptive deficiency of small intestine. Gastrointestinal symptoms. Course is more protracted and severe in immuno-compromised patients who develop malabsorption and remarkable weight loss. Therefore it is recommended in the developed world that all patients with chronic giardiasis undergo immune studies.

Patients may present with atypical features ie vitamin B12 deficiency, pancreatic insufficiency, hypokalemia etc.

**Immunity:**
Giardia affords immunity, thus in places with childhood exposure adults rarely get the overt disease. Immunity allows spontaneous resolution and re-infection without symptoms. In endemic areas, giardiasis generally occurs in pediatric age group (infants & children), and in patients with immuno-suppression (α-γ-globulinemia or hypogammaglobulinemia).

Giardial trophozoite remains in the lumen attached to the brush border and does not invade the mucosa. Thus primary immune stimulation occurs at the mucosal surface, being modulated by the lymphoid tissue in the intestinal wall, and is thus mainly humoral. Although some cell-mediated immune response is also produced in the local lymphoid tissue, the main response is via the antibody stimulation. In addition to local IgA, plasma IgE & IgG also increase. Stimulation of IgE explains various allergic reactions in giardiasis. Infection is severe & chronic in those with B-cell defects.

Local cell-mediated immunity entails increase of T8 in lamina propria and mucosas, which are replaced by T4 cells once infection is eradicated. Macrophages also engulf trophozoites and kill them by oxidative burst.

**Diagnosis:**
Diagnosis is made clinically but needs confirmation by demonstration of parasites in stools, duodenal aspirates or small intestinal biopsy specimen.

The method of choice, because of its convenience and low cost, is the direct examination of fresh or stained smears of fresh or fixed stool samples. As a general rule, examination of 3 stool samples collected at 2-3 day intervals will detect nearly 100% of infections. Evacuation of giardia in stools is cyclical, with daily periods of positivity alternating with those of negativity. Then, some persons excrete large number of parasites while others eliminate few numbers. Thus when giardiasis is suspected, one stool test should be ordered. If it is positive, treat the patient. If negative 2nd & 3rd may be ordered. If all the 3 are negative, 4th sample at an interval of 7-10 days is collected. Some studies suggest that yieldwise duodenal aspirates may be inferior to properly done stool examinations.

Direct microscopy of stool test is still the gold standard, and in experienced hands it should detect all cases of giardiasis. When a stool sample is examined, a search for all kinds of parasites should be undertaken. Data on the character of stool sample, presence of red blood cells, polymorphonuclear cells, should also be given.

Poor yield is because of
- A single stool examination,
- Poor methodology,
• Or incompetence at the microscope.
  Trophozoites are found in loose or liquid stools (& duodenal aspirates) while cysts are found in formed stools.

WHO recommendations for treatment of giardiasis:
Giardiasis may be treated with tinidazole in a single dose or with another 5-nitroimidazole such as metronidazole; both are highly effective and should be offered when practicable to all infected patients. Family and institutional contacts should also be treated.

Larger epidemics are difficult to eradicate because of the high proportion of symptomless carriers and because excreted cysts can survive for long periods outside the human host.
Drugs used to treat giardiasis:

Bashir Gaash

Various drugs used for treating giardiasis include metronidazole, tinidazole, ornidazole, secnidazole, nimarozole and satranidazole.

Metronidazole has been used extensively for the last 38 years. It is a derivative of 5-nitroimidazole discovered as back as 1955. This drug has an extremely broad spectrum of antiprotozoal and antimicrobial activity.

Metronidazole is effective against many parasites including trichomonas, amoeba and giardiasis. Trophozoites of giardia are affected at a concentration of 1-50 μg/ml in vitro. Metronidazole is also highly effective against all anaerobic cocci, anaerobic gram negative bacilli (as bacteroides) and anaerobic spore-forming gram-positive bacilli.

Other important effects of nitroimidazoles are suppression of cell-mediated immunity, mutagenesis, carcinogenesis, and sensitization of hypoxic cells to radiation.

Mechanism of action: Metronidazole is a prodrug since it requires metabolic activation by sensitive organisms. Once the drug has diffused into the cells, the nitro group accepts electrons from electron-transport proteins with sufficiently low negative redox potentials eg ferridoxins or their equivalents in protozoa and bacteria, and flavoproteins in man. The reactions are catalyzed respectively by iron-sulphur complexes and nitroreductase, and electrons are supplied by NADPH or sulfide. The main effect of metronidazole is through formation of labile, chemically reactive intermediates during the four-reduction of nitro group to hydroxylamine. The molecular steps by which these intermediates destroy cells involve reaction with cellular macromolecules as DNA, proteins, and membranes.

Metabolism: Metronidazole is promptly and completely absorbed after oral administration and within 1 hour reaches a plasma concentration of 10 μg/ml (which exceeds the therapeutically effective concentration of 8 μg/ml). The half-life in plasma is 8 hours, therefore the drug should not be given more often. The drug penetrates well into the body tissues and fluids, and 10% is bound to plasma proteins. Liver is the main site of metabolism, and both metronidazole & its metabolites are excreted in urine, which may colour it reddish-brown.

Dose: The dose required for giardia is same or even less than that for trichomonas. The required dose is 250 mg (adult) or 5mg/kg (child) three times daily for 7 days. It is available as 400 mg tablet and given thrice daily. A daily single dose of 2 g daily for 3 days is also sufficient. Some recommended a single oral dose of 2 g.

Side effects: Only rarely are these severe enough to discontinue therapy. The most common are headache, nausea, dry mouth, and a metallic taste. Vomiting, diarrhoea and abdominal distress are occasionally experienced. Intensification of moniliasis is associated with furry tongue, glossitis, and stomatitis. Side
effects which warrant discontinuation of metronidazole generally relate to the nervous system as dizziness, vertigo, numbness or paresthesia of the extremities or very rarely convulsions, incoordination, ataxia or encephalopathy. Urticaria, flushing, pruritus, dysuria, cystitis, and a sense of pelvic pressure have been reported. There may be disulfiram-like reaction if alcohol is consumed with the drug. Other reactions are seen with concurrent use of anti-coagulants (prolonged effect), cimetidine (prolongs half-life) and phenobarbitone (accelerates hepatic metabolism). Most of the adverse effects are reversible with discontinuation of therapy but sensory neuropathies may be irreversible.

Metronidazole should be used with caution in patients with active involvement of the CNS because of its neurotoxicity. Dosage is reduced in patients with severe obstructive hepatic disease, alcoholic cirrhosis and severe renal dysfunction.

High doses for prolonged periods are carcinogenic in mice and mutagenic in bacteria. However, therapeutic doses of metronidazole pose no significantly increased risk of cancer. Although no teratogenic effect has been demonstrated, metronidazole is not recommended during first trimester.

Ornidazole: It is similar to metronidazole and is used in doses of 1.5 g once daily for 1-2 days; children receive 40 mg/kg for 2 days). The side effects and precautions are as with metronidazole; however, metallic taste is less frequent.

Tinidazole: Its metabolism is slower, thus duration of action is longer than metronidazole which makes it more suitable for once daily therapy. Dose is 2 g as a single dose or 600 mg twice daily for 5 days. Children receive 30-50 mg/kg.

Secnidazole: Dose is 2 g (children 30 mg/kg) in single dose for 1 day.

Satrnidazole: For giardiasis, it is twice as potent as other nitroimidazole derivatives. Dose is 600 mg in single dose. Unlike other related drugs it does not produce nausea, vomiting, or metallic taste in mouth. Other side effects may occur.

There is not much to choose between various nitroimidazoles except cost and convenience. In the USA, metronidazole was introduced for treatment of giardiasis as late as 1994, while other derivatives have still not been cleared by the FDA for giardiasis. However, they are widely used for trichomoniasis & anaerobic infections. Baring the USA, all these drugs, especially tinidazole & ornidazole are used globally for giardiasis. The WHO recommends use of metronidazole or any of its cousins for giardiasis for all those infected with giardiasis. This is especially relevant to the developing world, where giardiasis is very common among children & compounds malnutrition. (Ed)
Epistaxis (nose bleed) often occurs from the plexus of veins in the anterior part of the nasal septum. In children it is often due to nose picking; other causes include trauma, a foreign body, Burkitt’s lymphoma, and nasopharyngeal carcinoma.

A patient bleeding from the nose is apprehensive. There is a tendency to lie at the back. In this position blood flow to the head, and thus the area of bleed, increases which is apt to worsen epistaxis. Therefore, we should manage epistaxis with the patient in a sitting position.

1) Remove blood clots from the nose and throat to visualize the site of bleeding and confirm the diagnosis. Pinch the nose between your fingers and the thumb while applying ice packs to the nose and forehead. Continue to apply pressure. Bleeding will usually stop within 10 minutes. Pack

2) If bleeding continues, pack the anterior nares with petroleum impregnated ribbon gauze. An inexperienced person may tend to insert smaller wicks into the nares, which are not able to press on the bleeding points. Sufficient gauze must be taken which can fully press upon the area. Lubricate it with liquid paraffin and pack the nares slowly with the help of the forceps. The nostrils feel distended once sufficient gauze is inserted. To stop sneezing during the insertion of oiled gauze in to the nostril, press on the upper lip of the patient. Generally it helps to abort a sneezing episode. Some insert a cut finger removed from a latex glove into the nostril; and then fill it with sufficient gauze to block the nares.

3) If bleeding continues after packing, the posterior nasopharynx may be the source of bleeding. Apply pressure using the balloon of the Foley’s catheter. Lubricate the catheter, and pass it through the nose till the tip reaches the oropharynx. Withdraw it a short distance to bring the balloon in to the nasopharynx. Inflate the balloon with water, enough to exert pressure but not to cause discomfort (5-10 ml of water is usually adequate for an adult, but use no more than 5 ml for a child). Gently pull the catheter forward until the balloon is held in the posterior choana. Tape the catheter to the forehead or check in the same manner as a nasogastric tube. With the catheter in place pack the anterior nares with petroleum gauze. Deflate the Foley catheter after 48 hours and if the bleeding does not recur, remove it.

4) If bleeding still occurs, refer to an otorhinolaryngologist.
Care of the Neonate at Birth

Farooq Fazilli

Most of deaths in children take place during the infantile period, majority occurring in the first postnatal week itself. The major causes of these deaths are birth asphyxia, hypothermia and infections. Babies born with a low birth weight (<2500gms) are at higher risk of dying due to these causes. Essential new born care is required to reduce the neonatal and infant deaths. Ideally this care should be available as close to the antenatal mother’s home as possible. Under the Reproductive & Child Health Programme, the first referral unit, the sub-district hospital, or community health centre, is supposed to provide this essential neonatal care, which includes: care at birth, provision of warmth, prevention of infection, care of LBW and sick new born, and early identification of new born needing referral.

1) Care at birth:

The delivery room should be clean, well ventilated, and adequately lighted. It is the responsibility of the management, ANMs and other concerned to ensure the 5 cleans during the delivery:
- Clean hands
- Clean surface
- Clean scissors / blade
- Clean cord tie
- Clean cord stump (no application

2) Provision of warmth:

The baby should be received in a dry pre-warmed and clean cloth. Place the baby preferably under the source of warmth ie a 200 watt bulb. Dry the neonate immediately after the birth, but do not remove the vernix (it protects the baby from hypothermia, and infection). After drying the baby should be wrapped in a clean dry cloth.

Bathing a baby immediately after birth is not advised. It not only removes the protective vernix caseosa but also exposes the baby to droughts and sudden heat loss. Our experience in leading hospitals, including the Lalded, has been contrary to the medical advice. Sometimes the neonates are washed like dirty linen by midwives. This practice should be stopped forthwith .(Ed)

A normal baby who is crying after the birth must be placed in close contact with the mother. The maternal body heat will provide the extra warmth required to keep the baby warm. It also assures the mother regarding the well being of her baby.

Loss of body heat or hypothermia (temperature <36°C) can be prevented by having well maintained temperature in the delivery room. If the baby’s feet or trunk are cold, the temperature must be recorded and if hypothermic (ie less than 36°C) it must be immediately treated. If after one hour the temperature does not rise, refer the baby to a nearby referral clinic but baby must be transferred preferably in a transport incubator and if it is not available then the baby must be fully wrapped. Throughout the baby must remain dry.
Cord care:

The umbilical cord must be cut with a sterile scissors / blade, about 2.5 cm above the abdominal skin surface. The cord should be tied with a sterile cord tie. Inspect the cord for any bleeding; if there is bleeding apply another cord tie. The umbilical cord should be left dry without antiseptic or dressing. The umbilical cord should be inspected after 2-4 hours after clamping. The cord usually falls after 5-10 days but it may take more time if kept moistened.

Eye care:

The eyes should be cleaned with clean cotton swabs, using one for each eye. The eyes should be cleaned from medial to lateral side. There is no role of prophylactic eye applications. The practice of applying Kajal/Surma in the eyes is not recommended as there are chances of transmitting the trachoma infection or may even cause lead poisoning. Some children may develop persistent epiphora due to blockage of nasolacrimal duct by epithelial debris. The mother should be advised to massage the nasolacrimal duct area by massaging the outer side of the nose adjacent to medial canthus 5-8 times each day.

Recording birth weight:

The weight of all babies at birth should be recorded on an infant weighing scale. Low birth weight babies (ie those weighing less than 2.5 kg at birth) need special attention and referral if required. Most healthy term babies lose up to 7-10 % of birth weight during 1st week of life. This physiological weight loss is due to the removal of vernix caseosa, mucus and blood from the skin, passage of muconium, and reduction of the extra cellular blood volume. Delayed feeding and unsatisfactory feeding schedule is also a contributory factor. Babies who are adequately fed are contended, playful, have good sleep, and are satisfied for at least for 2-3 hours after a feed. Birth weight is regained at the end of 1st wee. The average daily weight gain in a term baby is around 30 g, 20g, and10 g during the 1st, 2nd, 3rd and 4th month periods respectively. Most infants double their weight by 4-5 months of age and triple it by their 1st birthday.

Breast feeding:

Breast feeding is the first food for the baby and it is very important for both baby and mother to start breast feeding as soon as possible. It should be initiated within half an hour of birth. The delivery room staff should ensure that the mother puts the baby on her breast in their presence.

If a baby scale is not available, the attendant may hold the baby when both are weighed together. Then her weight is subtracted to give the baby’s weight.

Breast feeding is a fundamental right of every baby. Exclusive breast
feeding is desirable for at least 4-6 months. Breast feeding should be initiated as early as possible - preferably within half an hour after normal vaginal delivery and 4-6 hours after delivery by LSCS. *Frequent suckling by the baby promotes milk production and prevents breast engorgement.*

First feed is yellowish and is called colostrum. It is rich in vitamins, antibodies, proteins, fats etc. This provides natural immunity to the child and is truly the *first immunization of the child.*

**Advantages of early breastfeeding:**

- *very convenient method of feeding contains exactly the nutrients the baby needs*
- *Is easily digestible & assimilable*
- *Protects the child from various infections*
- *Is highly economical*
- *Is a natural way to promote mother baby bonding*
- *Prevents allergic reactions & also subsequent risk of development of congenital heart disease.*
- *Helps the baby’s physical and intellectual development of baby*
- *It causes early involution of the uterus after the delivery*
- *It reduces the risk of cervical cancer and breast.*
- *Breast fed babies are free from dental caries.*

No water is required (nor advised) in a breast fed baby up to 4-6 months of age (*Exclusive breast feeding*). Water reduces milk intake and also leads to infections when contaminated. Prelacteal feeds like honey, sugar, glucose are also harmful.

**Position of mother:**

The mother can adopt any position comfortable to her during feeding the baby. Baby is to be held close to the breast, face facing towards the breast with nose opposite to the nipple; 2/3rd of the areola should go inside of the baby’s mouth so to press the milk containing lactiferous ductules. Suckling on nipple can cause injury to the nipple causing pain to the mother and growth failure in the infant since sufficient milk is not sucked. Premature and low-birth weight babies can suckle the breast successfully.

First time mothers generally don’t know how to suckle their baby. It is the responsibility of the doctor or midwife to prepare her for successful lactation. Mothers have a tendency to put nipple in the baby’s mouth, who sucks with force and denudes the epithelium of the nipple. It draws blood and the ensuing pain discourages the mother from guiding the baby during suckling. *(Ed)*

A mother should be confident enough to feed her baby. Feeding should be on demand. He may need 8-12 feeds /day in first two weeks, slowing to 8-9 feeds /day at one month of age. The frequency may decline to 6-7 times per day by four months. Mothers are advised not to reduce it below 6 times in 24 hours during the first three months. During day hours a three hour interval may be allowed between two feeds.
There must be at least two feeds during the night.

The usual duration of nursing is highly variable from 4-20 minutes per breast. If a baby is still feeding after 25-30 minutes at each breast then that reflects inadequate milk production or ineffective lactation. There may be problems with the mother like inverted nipples, mastitis, not willing to feed her baby or she may ill. Major part of milk (80%) is being consumed within first 4 minutes of nursing at each breast. Before moving to second he should be allowed to finish suckling at the first breast to get the fat rich hind-milk.

Bottle feeding should be strongly discouraged. Bottle fed babies are 14 times more prone to get diarrhea and 8 times more vulnerable to get pneumonia.

Milk volume increases rapidly during the first two weeks after delivery. Average milk production in an exclusive breast feeding mothers is about 750 ml/day! - a level that is maintained for 4-6 month. The quantity is boosted by the touch of nipple & areola (hand, baby’s tongue, or suck). A good sleep or regular exercises of the mother which stimulates release of the milk secreting prolactin hormone. Even infants cry is sufficient to initiate milk ejection in some women.

Working mothers, who are unable to feed during working hours may resort to expressed breast milk which is collected in a sterile utensil and can be refrigerated for up to 24 hours. It can be transported on ice and is warmed by gentle shaking under warm running water immediately before feeding to the baby.

Practice point: (First AID)
RECOGNIZING EMERGENCIES

- Emergencies can often be recognized because of unusual sights, appearances or behaviours, odours, and noises.
- It may be challenging to recognize an emergency or sudden illness in some situations. The signals are not always obvious or easy to identify.
- A victim may deny anything is seriously wrong.
- If you think something is wrong, check the victim. Ask questions. Questions may help you determine what is wrong.

Once an emergency has been recognized, be calm and follow the emergency action steps:

- **Check-Call-Care**
  - **Check the scene** (for safety; to find out what happened; to determine how many victims there are; & bystanders who can assist). **Check the victim** (for consciousness.)
  - **Call** (emergency; the hospital; or the doctor)
  - **Care**: (for life-threatening conditions)

Source: American Red Cross Society
Rational Use of Antipyretics in Children

(Condensed from the paper presented by Dr Y. K. Amdekar at the Indo-UK Symposium on “Hot Topics in Pediatrics” held in February 2003.)

Rationality is exercised on the basis of reasoning and logical derivation. However, final conclusion should be such that is beneficial to the community at large while not deviating from collective evidence. Use of antipyretics is universal though riddled with several questions.

Fever is body’s response to mostly an infection, though a variety of other factors may induce similar reactions. It results from an immune response mediated through action of cytokines on thermo-regulatory centre of brain. Peripheral mechanisms play a role by either conserving heat through vaso-constriction manifesting as chills or generating heat by active muscular presenting as rigors.

It is important to realize that fever is a beneficial response in favour of the host. Then should fever be ever suppressed and if so when? There are in fact a few studies which have shown that suppression of fever may lead to persistence of viral shedding or malarial parasitemia leading to prolongation of illness and delayed recovery. The World Health Organization recommends suppression of fever only if exceeds 39°C. However, most of the studies have not been able to substantiate such a conclusion. No study has been able to document adverse effect of suppression of fever on immune system. Therefore, if it is not harmful to suppress fever, any way is it necessary?

Fever is beneficial but beyond a certain degree it leads to discomfort and at times to febrile convulsions. There is a level where hyperpyrexia can lead to brain damage. In general, fever up to 102°F may be considered beneficial, safe and not discomforting, and so may not be intervened. Fever between 102° and 104°F may be beneficial but discomforting and hence reduction of fever to a level below 102°F may be ideal to comfort the child. It could be brought down by simple measures not necessarily including use of antipyretics. However, if fever rises beyond 104°F, it may prove harmful and hence should definitely be brought down by prompt action.

Feeling of comfort is subjective and hence may be unpredictable in spite of reduction of fever. Though febrile convolution occurs commonly at higher degree of fever, mere reduction of fever does not guarantee against such an event. However, attempt to reduce fever offers moral confidence of parents and the physician.

Suppressing Fever:
It is customary to use oral antipyretics for their convenience and acceptance. Generally paracetamol, ibuprofen or nimuslide are used. However, fever may be suppressed through physical cooling methods, which include tepid water sponging, bath or fanning. Well-designed studies have demonstrated equal beneficial effects with either of the methods. It is important to remember that cause of fever decides the response to an antipyretic, thus patients respond
differently to various methods of suppression of fever.

Well-designed studies have shown that suppression of fever by use of antipyretics or through physical cooling is equally effective.

**Which antipyretic to use?**
Since all antipyretics are equally efficacious, it is the safety profile that should determine the choice of a particular antipyretic.

1) **Aspirin** is not used for fear of Reye’s syndrome and risk of metabolic acidosis and coma.

2) **Paracetamol** is a time-tested antipyretic. It has a short duration of action and hence the drug can be repeated every 4-6 hours. Thus paracetamol is a perfect fit for symptomatic relief. Most of the cited side-effects, including hepatotoxicity, have been from overdose than therapeutic usage. Hypersensitivity is very rare. In therapeutic doses, paracetamol is safe even in liver disease.

3) **Ibuprofen** is considered safe in children and may be used as an alternative to paracetamol; however, it may lead to gastrointestinal problems including nausea, vomiting, dyspepsia, and GI bleeding. Because of a longer duration of action it is used every 6-8 hourly (cf paracetamol 4-6 hourly).

4) **Nimuselide** is long acting, and has to be given 12 hourly. Its therapeutic dose is smaller than that of others (5 mg/Kg/d as against 60 mg/kg/d for paracetamol), thus overdose can occur easily. It is relatively more potent and may cause lowering of body temperature to subnormal levels which can be harmful. There can be serious side effects and many countries have either not introduced it as antipyretic or have withdrawn it after initial introduction.

Maternal ingestion can lead to end-stage renal failure in neonates. Nimuselide shares the toxic profile of other NSAIDs. Hematuria, renal toxicity, platelet dysfunction and periorbital edema have been reported in children. *Experts opine that nimuslide as an antipyretic is best avoided.*

More frequent dosing of nimuslide is rampant and is definitely dangerous. Same is true of overdosing. The pediatric formulation contains 50 mg/5 ml; thus a 15 mg dose for a young child weighing 10 kg will equal 1/3rd of a teaspoonful, and thus overdose can occur in any family. On the contrary, less frequent dosing of Paracetamol is widely practiced by pediatricians. That is why physicians think that paracetamol is not as efficacious as ibuprofen or nimuslide. The short-acting Paracetamol given 4-6 hourly is the best choice for pediatric antipyresis.

**Dosage:**
Equipotent doses of the 3 commonly used antipyretics are:

1) **Paracetamol:** 10-15 mg/kg (to be given 4-6 hourly)
2) **Ibuprofen:** 8-10 mg/kg (to be given 6-8 hourly)
3) **Nimuslide:** 2.5 mg/kg, 12 hourly, or 1.5 mg/kg 8 hourly. Should never be given at intervals of less than 8 hourly

Fixed dose combinations are better avoided, since optimum dosing intervals are different. Studies have shown no advantage in combining antipyretics. Similarly adding the so-called enhancers as metoclopramide is of no therapeutic benefit. Such practices only increase the cost of the formulation without any advantage. Oral route is as effective as any other route, thus the best. Rectal route of paracetamol has no added benefit.
Fever is friend & not an enemy. Suppression of fever, especially when using long-acting antipyretics, may mislead the physician especially when some dangerous underlying infection (as meningitis, pneumonia) is producing fever. It masks the natural course of the infection which would give clue to diagnosis.

In summary,
1) Fever upto 102F may be considered beneficial, safe and therefore may not be intervened with antipyretics.
2) An antipyretics should be used to prevent fever from rising to dangerous level without interfering with body’s natural immune mechanisms. It should not be used just to bring fever down to the normal.
3) Paracetamol is still the first and the best choice for childhood antipyresis, because of its short-acting, symptomatic relief and therapeutic safety.
4) Physical cooling measures are as effective as antipyretics in reducing fever. Mere sponging of forehead (!) is not going to help reduce fever. Bathing in tepid water and fanning are very useful in getting rid of extra heat.

Answer to Medical Quiz 1:
1) The hematological diagnosis is Disseminated Intravascular Coagulation (DIC), probably due to carcinomatosis. Prolongation of prothrombin time and kaolin cephalin clotting time indicates deficiency of more than one clotting factor. This, in presence of thrombocytopenia, suggests DIC. The formation of thrombi in small blood vessels consumes platelets and clotting factors. The fall in hemoglobin is due to hemolysis.

The process may be initiated by:
- Release of thromboplastic factors into the blood stream from damaged tissues.
- Extensive endothelial damage.

Fibrin Degradation Products (FDPs) circulate in DIC. This single test thus can confirm presence of DIC. Other helpful tests include fibrinogen level (which is reduced in DIC) and blood film (for evidence of fragmented red cells).

<table>
<thead>
<tr>
<th>Causes of DIC:</th>
<th></th>
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</thead>
<tbody>
<tr>
<td><strong>Acute</strong></td>
<td><strong>Chronic</strong></td>
</tr>
<tr>
<td>Obstetric accidents</td>
<td>Disseminated carcinoma</td>
</tr>
<tr>
<td>Abruption placentae</td>
<td>(particularly pancreas, stomach, breast)</td>
</tr>
<tr>
<td>Amniotic fluid embolism</td>
<td>Acute leukemia</td>
</tr>
<tr>
<td>Heart &amp; lung surgery</td>
<td>Intrauterine fetal death</td>
</tr>
<tr>
<td>Haemolytic transfusion reaction</td>
<td></td>
</tr>
<tr>
<td>Septicemia – especially meningococcal</td>
<td></td>
</tr>
<tr>
<td>Pulmonary embolism</td>
<td></td>
</tr>
<tr>
<td>Snake bites</td>
<td></td>
</tr>
<tr>
<td>Anaphylaxis</td>
<td></td>
</tr>
<tr>
<td>Diabetic ketoacidosis</td>
<td></td>
</tr>
</tbody>
</table>

2) Following fibrinolysis ‘Fibrin Degradation Products (FDPs)’ circulate. Small amounts can be detected in normal people but increased amounts of FDPs help to diagnose DIC. Other helpful tests include fibrinogen level (which is reduced in DIC) and blood film (for evidence of fragmented red cells).
Health Care Waste: An Introduction

Muzaffar Ahmad

Definition

Health-care waste includes all the waste generated by health-care establishments, research facilities, and laboratories. In addition, it includes the waste originating from “minor” or “scattered” sources - such as that produced in the course of health care undertaken in the home (dialysis, insulin injections, etc.).

Between 75% and 90% of the waste produced by health-care providers is non-risk or “general” health-care waste, comparable to domestic waste. It comes mostly from the administrative and housekeeping functions of health-care establishments and may also include waste generated during maintenance of health-care premises. The remaining 10-25% of health-care waste is regarded as hazardous and may create a variety of health risks. This handbook is concerned exclusively with hazardous health-care waste (also known as “health-care risk waste”); general wastes should be dealt with by the municipal waste disposal mechanisms.

Infectious Waste

Infectious waste is suspected to contain pathogens (bacteria, viruses, parasites, or fungi) in sufficient concentration or quantity to cause disease in susceptible hosts. This category includes:

- cultures and stocks of infectious agents from laboratory work;
- waste from surgery and autopsies on patients with infectious diseases (e.g. tissues, and materials or equipment that have been in contact with blood or other body fluids);
- waste from infected patients in isolation wards (e.g. excreta, dressings from infected or surgical wounds, clothes heavily soiled with human blood or other body fluids);
- waste that has been in contact with infected patients undergoing haemodialysis (e.g. dialysis equipment such as tubing and filters, disposable towels, gowns, aprons, gloves, and laboratory coats);
- infected animals from laboratories;
- any other instruments or materials that have been in contact with infected persons or animals.

Note: Infected “sharps” are a subcategory of infectious waste.
### Table 1 Categories of health-care waste

<table>
<thead>
<tr>
<th>Waste category</th>
<th>Description and examples</th>
<th>Wastes with high content of</th>
<th>Pressurized containers</th>
<th>Radioactive waste</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infectious waste</td>
<td>Waste suspected to contain pathogens e.g. laboratory cultures; waste from isolation wards; tissues (swabs), materials, or equipment that have been in contact with infected patients; excreta</td>
<td>Batteries; broken thermometers; blood-pressure gauges; etc. heavy metals</td>
<td>Gas cylinders; gas cartridges; aerosol cans</td>
<td>Waste containing radioactive substances e.g. unused liquids from radiotherapy or laboratory research; contaminated glassware, packages, or absorbent paper; urine and excreta from patients treated or tested with unsealed radionuclides; sealed sources</td>
</tr>
<tr>
<td>Pathological waste</td>
<td>Human tissues or fluids e.g. body parts; blood and other body fluids; fetuses</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sharps</td>
<td>Sharp waste e.g. needles; infusion sets; scalpels; knives; blades; broken glass</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Pharmaceutical waste</td>
<td>Waste containing pharmaceuticals e.g. pharmaceuticals that are expired or no longer needed; items contaminated by or containing pharmaceuticals (bottles, boxes)</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Genotoxic waste</td>
<td>Waste containing substances with genotoxic properties e.g. waste containing cytostatic drugs (often used in cancer therapy); genotoxic chemicals</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Chemical waste</td>
<td>Waste containing chemical substances e.g. laboratory reagents; film developer; disinfectants that are expired or no longer needed; solvents</td>
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</tbody>
</table>

Cultures and stocks of highly infectious agents, waste from autopsies, animal bodies, and other waste items that have been inoculated, infected, or in contact with such agents are called **highly infectious waste**.

### Pathological waste

Pathological waste consists of tissues, organs, body parts, human fetuses and animal carcasses, blood, and body fluids. Within this category, recognizable human or animal body parts are also called **anatomical waste**.

This category should be considered as a subcategory of infectious waste, even though it may also include healthy body parts.

### Sharps

Sharps are items that could cause cuts or puncture wounds, including needles, hypodermic needles, scalpels and
other blades, knives, infusion sets, saws, broken glass, and nails. Whether or not they are infected, such items are usually considered as highly hazardous healthcare waste.

**Pharmaceutical waste**

Pharmaceutical waste includes expired, unused, spilt, and contaminated pharmaceutical products, drugs, vaccines, and sera that are no longer required and need to be disposed of appropriately. The category also includes discarded items used in the handling of pharmaceuticals, such as bottles or boxes with residues, gloves, masks, connecting tubing, and drug vials.

**Genotoxic waste**

Genotoxic waste is highly hazardous and may have mutagenic, terato-genic, or carcinogenic properties. It raises serious safety problems, both inside hospitals and after disposal, and should be given special attention. Genotoxic waste may include certain cytostatic drugs, vomitus, urine, or faeces from patients treated with cytostatic drugs, chemicals, and radioactive material.

Cytotoxic (or antineoplastic) drugs, the principal substances in this category, have the ability to kill or stop the growth of certain living cells and are used in chemotherapy of cancer. They play an important role in the therapy of various neoplastic conditions but are also finding wider application as immunosuppressive agents in organ transplantation and in treating various diseases with an immunological basis. Cytotoxic drugs are most often used in specialized departments such as oncology and radiotherapy units, whose main role is cancer treatment; however, their use in other hospital departments is increasing and they may also be used outside the hospital setting.

<table>
<thead>
<tr>
<th>Most common genotoxic products used in health care*</th>
</tr>
</thead>
<tbody>
<tr>
<td>aClassified by working groups of the International Agency for Research on Cancer (IARC).</td>
</tr>
</tbody>
</table>

**Classified as carcinogenic**

- **Chemicals:**
  - benzene
- **Cytotoxic and other drugs:**
  - azathioprine, chlorambucil, clornaphazine, ciclosporin, cyclophosphamide, melphalan, semustine, tamoxifen, thiopeta, treosulfan
- **Radioactive substances:**
  - (radioactive substances are treated as a separate category in this handbook)

**Classified as possibly or probably carcinogenic**

- **Cytotoxic and other drugs:**
  - azacitidine, bleomycin, carmustine, chloramphenicol, chlorozotocin, cisplatin, dacarbazine, daunorubicin, dihydroxymethylfuratrizine (e.g. Panfuran S - no longer in use), doxorubicin, lomustine, methylthiouracil, metronidazole, mito-myacin, nafenopin, niridazole, oxazepam, phenacetin, phenobarbital, phenytoin, procarbazine hydrochloride, progesterone, sarcolysin, streptozocin, trichlormethine
**Harmful cytostatic drugs** can be categorized as follows:

alkylating agents: cause alkylation of DNA nucleotides, which leads to cross-linking and miscoding of the genetic stock;

antimetabolites: inhibit the biosynthesis of nucleic acids in the cell;

mitotic inhibitors: prevent cell replication.

Cytotoxic wastes are generated from several sources and can include the following:

contaminated materials from drug preparation and administration, such as syringes, needles, gauges, vials, packaging;

outdated drugs, excess (leftover) solutions, drugs returned from the wards;

urine, faeces, and vomit from patients, which may contain potentially hazardous amounts of the administered cytostatic drugs or of their metabolites and which should be considered genotoxic for at least 48 hours and sometimes up to 1 week after drug administration.

In specialized oncological hospitals, genotoxic waste (containing cytostatic or radioactive substances) may constitute as much as 1% of the total health-care wastes.

**Chemical waste**

Chemical waste consists of discarded solid, liquid, and gaseous chemicals, for example from diagnostic and experimental work and from cleaning, housekeeping, and disinfecting procedures. Chemical waste from health care may be hazardous or non-hazardous; in the context of protecting health, it is considered to be hazardous if it has at least one of the following properties:

toxic;

corrosive (e.g. acids of pH < 2 and bases of pH > 12);

inflammable;

reactive (explosive, water-reactive, shock-sensitive);

genotoxic (e.g. cytostatic drugs).

Non-hazardous chemical waste consists of chemicals with none of the above properties, such as sugars, amino acids, and certain organic and inorganic salts.

The types of hazardous chemicals used most commonly in maintenance of health-care centres and hospitals and the most likely to be found in waste are discussed in the following paragraphs.

**Formaldehyde**

Formaldehyde is a significant source of chemical waste in hospitals. It is used to clean and disinfect equipment (e.g. haemodialysis or surgical equipment), to preserve specimens, to disinfect liquid infectious waste, and in pathology, autopsy, dialysis, embalming, and nursing units.

**Photographic chemicals**

Photographic fixing and developing solutions are used in X-ray departments. The fixer usually contains
5-10% hydroquinone, 1-5% potassium hydroxide, and less than 1% silver. The developer contains approximately 45% glutaraldehyde. Acetic acid is used in both stop baths and fixer solutions.

**Solvents**

Wastes containing solvents are generated in various departments of a hospital, including pathology and histology laboratories and engineering departments. Solvents used in hospitals include halogenated compounds, such as methylene chloride, chloroform, trichloroethylene, and refrigerants, and non-halogenated compounds such as xylene, methanol, acetone, isopropanol, toluene, ethyl acetate, and acetonitrile.

**Organic chemicals**

Waste organic chemicals generated in health-care facilities include:

- disinfecting and cleaning solutions such as phenol-based chemicals used for scrubbing floors, perchlorethylene used in workshops and laundries;

- oils such as vacuum-pump oils, used engine oil from vehicles (particularly if there is a vehicle service station on the hospital premises);

- insecticides, rodenticides.

**Inorganic chemicals**

Waste inorganic chemicals consist mainly of acids and alkalis (e.g. sulfuric, hydrochloric, nitric, and chromic acids, sodium hydroxide and ammonia solutions). They also include oxidants, such as potassium permanganate (KMnO₄) and potassium dichromate (K₂Cr₂O₇), and reducing agents, such as sodium bisulfite (NaHSO₃) and sodium sulfite (Na₂SO₃).

**Wastes with high content of heavy metals**

Wastes with a high heavy-metal content represent a subcategory of hazardous chemical waste, and are usually highly toxic. Mercury wastes are typically generated by spillage from broken clinical equipment but their volume is decreasing with the substitution of solid-state electronic sensing instruments (thermometers, blood-pressure gauges, etc.). Whenever possible, spilled drops of mercury should be recovered. Residues from dentistry have a high mercury content. Cadmium waste comes mainly from discarded batteries. Certain “reinforced wood panels” containing lead are still used in radiation proofing of X-ray and diagnostic departments. A number of drugs contain arsenic, but these are treated here as pharmaceutical waste.

**Pressurized containers**

Many types of gas are used in health care, and are often stored in pressurized cylinders, cartridges, and aerosol cans. Many of these, once empty or of no further use (although they may still contain residues), are reusable, but certain types - notably aerosol cans - must be disposed of.

Whether inert or potentially harmful, gases in pressurized containers should always be handled with care; *containers may explode if incinerated or accidentally punctured.*
**Most common gases used in health care**

**Anaesthetic gases:**

- nitrous oxide, volatile halogenated hydrocarbons (such as halothane, isoflurane, and enflurane), which have largely replaced ether and chloroform.

*Applications* - in hospital operating theatres, during childbirth in maternity hospitals, in ambulances, in general hospital wards during painful procedures, in dentistry, for sedation, etc.

**Ethylene oxide**

*Applications* - for sterilization of surgical equipment and medical devices, in central supply areas, and, at times, in operating rooms.

**Oxygen**

- Stored in bulk tank or cylinders, in gaseous or liquid form, or supplied by central piping.

*Application* - inhalation supply for patients.

**Compressed air**

*Applications* - in laboratory work, inhalation therapy equipment, maintenance equipment, and environmental control systems.

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**Practical Points:**

**Cleaning up a blood spill**

*If a blood spill occurs –*

- Clean up the spill immediately or as soon as possible after the spill occurs.

- Use disposable gloves and other personal protective equipment when cleaning spills.

- Wipe up the spill with paper towels or other absorbent material.

- After the area has been wiped up, flood the area with a solution of ¼ cup of liquid chlorine bleach to 1 gallon of fresh water, and allow it to stand for at least 20 minutes.

- Dispose of the contaminated material used to clean up the spill in a labeled biohazard container.
Antenatal Care

Rehana Kausar

Antenatal care began as a social service in Paris in 1788 for women who had the double inconvenience of being both pregnant and destitute. The problem of disposal seems to have been a more pressing objective than treatment or preventive care.

Antenatal clinics constitute screening clinics because they are often the only time a healthy young woman will visit her doctor. It may be the first time a woman has been physically examined in her life. Breast palpation and cervical smears should be included in routine examination during such visits. Incidental diseases such as diabetes, HIV and renal disorders should be detected at a very early stage and the necessary treatment be given. General advice and education should be given when ever possible to both mother and father on what to expect and do in pregnancy and labour and about the care of the infant.

Aims of Antenatal Care

• Assessment and management of maternal risk and symptoms
• Assessment and management of fetal risk
• Prenatal diagnosis and management of fetal abnormality
• Diagnosis and management of perinatal complications
• Decision regarding timing and mode of delivery
• Parental education regarding pregnancy and childbirth
• Parental education regarding child rearing

Schedule of Antenatal visits during pregnancy:

A pregnant woman must have at least 3 antenatal visits during pregnancy other than registration. First before 16-20 weeks, second at 32 weeks and third at 36 weeks. The traditional pattern, a monthly examination until 28 weeks, then fortnightly until 38 weeks and weekly thereafter, has much to recommend it.

Booking visits (8-14 weeks): - The main aim of a booking visit (registration visit; enrolment visit) is to obtain a comprehensive history, to establish the gestational age and identify maternal and fetal risk factors. Enquiry about maternal age is one of the oldest screening test in the history of antenatal care. The mother’s age is particularly important because of increased risk of chromosomal abnormalities with maternal age, while the incidence of spontaneous abortion is also higher among older women.

Table 1. shows a checklist of the most common problems that can be identified at a booking visit. It is important that women are given an opportunity to discuss problems at an early stage in the pregnancy and that remedial action is initiated. Acceptance of the pregnancy, emotional support, and strengthening of the women’s social network help to
promote health of the mother and prospective baby.

**Menstrual history**

For the majority of pregnancies, the most important question is "how old is the fetus?" This can be established by knowing the date of the last menstrual period.

- Date of last menstrual period
- Whether it was normal in amount and duration?
- Whether it came at the correct time?
- The cycle length
- Whether O.C had been taken recently?
- When the first symptoms of the pregnancy occurred and how these compared to their time of quickening?

Calculate the expected date of delivery (EDD) using Naegle’s rule: 280 days from the first day of the last menstrual period (LMP). This is easily done by adding 7 days to the date of the LMP and then going forward 9 months. This rule is based on a menstrual cycle of 28 days and assumes ovulation occurred mid-cycle. Where the cycle is regularly greater than or less than 28 days the calculation has to be adjusted accordingly, e.g. add a further 7 days for a 35 day cycle and subtract a further 7 days from a 21 day cycle.

**Obstetric history**

The previous obstetric history has an important bearing on outcome of her present pregnancy. A detailed account of her past pregnancies, date and year of their occurrence, outcome of each pregnancy and any obstetric complications at the time should be documented. Details about the baby i.e. sex, gestational age, mode of delivery, weight at birth, should be asked.

A *gravida* is a woman who is or has been pregnant, irrespective of the pregnancy outcome. With the establishment of first pregnancy she becomes a *primigravida*, and with successive pregnancies she becomes a *multigravida*.

A *nulligavida* is a woman who is not now and never has been pregnant.

A *primipara* is a woman who has been delivered only once of a fetus or fetuses who reached viability.

A *multipara* is a woman who has carried two or more pregnancies to viability. *It is the number of pregnancies reaching viability and not the number of fetuses delivered that determines parity.*

A *nullipara* is a woman who has never completed a pregnancy beyond an abortion. She may or may not have had an abortion.

It is customary to describe the patient by her parity and gravidity as G, P. e.g. a G3 P1 would mean the patient is pregnant for the third time but has carried only one pregnancy to viability.

**Contraceptive history**

- Details of method used
- If hormonal, when was the pill discontinued?
- Was the pregnancy planned?
- Length of time trying to conceive.
Family history

Hypertension
Diabetes in 1st degree relative
Genetic disorder
Twins

Social history
Marital status
Working
Alcohol intake
Smoking
Home & family situation

General recommendations at the booking visit

Prenatal diagnosis
The facilities for prenatal diagnosis and screening should be explained if available for high-risk patients.

Diet, smoking and alcohol
A good balanced diet should be advocated, within the mothers’ purchasing power. The routine use of iron and folic acid supplements to prevent anemia is now less common than formerly. As many women, have poor iron reserves in pregnancy iron should be routinely prescribed.

Exercise and work
Most mothers should be encouraged to see pregnancy as a healthy state and normal activity, both domestic and recreational, should be continued. Outside employment usually continues till term-increasingly women, especially professional groups continue to work until term. They should make efforts to ensure adequate rest.

Coitus

Intercourse is not contraindicated in pregnancy.

Drugs
Mother should be advised to refrain from taking any medicine unless authorized by her physician.

Bowel action
Constipation is common in pregnancy and should not be a cause for concern. A diet high in fruit and vegetables helps and mild laxatives may be taken as required.

Visits in the last 2 trimesters

The 2nd trimester is usually a quite time when attention is focused upon:

- The observation for gestational age and occurrence of multiple pregnancies.
- Uterine irritability, amniotic fluid volume, occurrence of IUGR
- Early detection of anemia and hypertension

Visits in the last trimester: Attention is focused upon:

- Fetal age, growth and maturity
- Fetal well being
- Maternal complications of pregnancy and maternal well-being
- Mechanics of pregnancy
- Preparation for labour-induced labor
- Education for pregnancy, labour, breast feeding, infant care and counseling in family planning

At each visit the precise gestational age should be calculated. If the date of the LMP is certain; if there are reliable observations in early pregnancy; if USG has been performed
before the 28th week; and if all observations are in agreement, the calculation is a matter of routine. If not, the clinician must weigh the evidence and make the best estimate, as it is against the gestational age than most other observations are assessed.

The assessment of fetal well-being is important and can be done by measurement of fetal movements by study of fetal heart, antenatal cardiograph, non-stress test and by the bio-physical profile. However, under field conditions a simple yet accurate assessment can be done by identification of risk factors and simple clinical observation of weight gain, fetal movements and uterine height.

**EXAMINATION:**

**Abdominal Examination:** Make sure that the patient looks comfortable, is lying semi-recumbent and has a sheet covering her waist and legs. One must examine from the woman’s right side.

**Inspection:**
Assess shape and size of the uterus, any obvious asymmetry of the abdomen, & fetal movements.
Look for surgical scars.

**Palpation:** Firstly, measure the fundal height by placing the ulnar border of the left hand gently in the fundus of the uterus, and measuring with a tape in cm to the symphysis pubis. The measurement in cm should give an estimation of gestational age in weeks i.e. +/- 2 cm from 20-38 weeks. The bladder must be emptied before any measurement. A full bladder can make the fundal height 3 cm higher.

Then palpate for fetal poles to determine presentation and lie.
To establish head engagement in 3rd trimester, it is better to gently palpate with both hands facing down over the abdomen as shown in the Fig. 2.
After you have palpated the uterus, gently palpate for kidney tenderness and liver and spleen enlargement.
Measure fundal height from top of symphysis pubis:

- 12 weeks: Palpable abdominally just at the symphysis pubis
16 weeks: Palpable midway between the symphysis and the umbilicus
20 weeks: Palpable at the umbilicus
20 to 32 weeks: Height in centimeters above symphysis parallels gestational age in weeks.

Auscultation: One should auscultate for fetal heart with a foetoscope. Normal fetal heart rate is 120-160 beats/min. Heart rates above 160/min or less than 120/min indicates fetal abnormality. In essentially all pregnancies the fetal heart sounds can be auscultated between 16 and 19 weeks using a Dee Lee stethoscope. By 22 weeks the fetal heart sounds are audible in pregnant women.

Blood Pressure: Measure B.P in the semi-recumbent posture (45°). The diastolic blood pressure is taken at Kortokoff (IV) (muffling) and not V (disappearance) of sound. Taking Kortohoff V, some women may have diastolic B.P of zero.

Edema: Edema is characterized by pus of face, swollen fingers and swelling of abdominal pain. (Stethoscope will leave an impression). Pre-tibial edema is checked by pressure for 15 seconds and seen if a pit is formed.

Breast examination: The real value of breast exam is to pick up any suspicious masses. The 5-year survival in breast cancer detected in pregnancy is 50% of that in age-matched non-pregnant women. Detection of inverted or retracted nipples is done and the woman advised accordingly.

Thyroid: Examination of thyroid gland is an essential part of the first assessment. Although rarely found, a goiter could be present.

A typical exam at each antenatal visit should include:

- B.P
- Check for edema, fingers, pre-tibial
- Symphysis Fundal height
- Presentation
- Lie
- Engagement
- Fetal heart auscultation

INVESTIGATION

Booking [8-14 weeks]

- Blood
- Hemoglobin and full blood count
- Microbiological: hepatitis B
- VDRL for syphilis
- Rubella
- USG:- A mid trimester scan provides the most detailed study of the fetus and uterine contents. It is the most comprehensive examination an individual will ever receive for the remainder of her life. The aim of this scan is to provide an accurate measurement of the gestational age if an early scan has not been improved by measurement of biparietal diameter,
  1. First trimester: crown-rump length predicts the estimated date of confinement. to within 7 or 10 days.
  2. Second trimester: Biparietal diameter (BPD) or femur length predicts EDC to within 7 to 10 days.
3. Third trimester: Scans postponed to this time period are not very helpful in predicting the EDC and are accurate only to within 3 weeks either way.

Carry out detailed anatomical survey to rule out any structural abnormalities.

Establish presence of multiple pregnancy and determine chorionicity locate to placenta.

**ADVICE GIVEN IN PREGNANCY**

1. Iron and folic acid to be taken for at least 100 days.
2. Two injections of T.T to be taken 4-6 weeks apart; first dose whenever the patient comes for antenatal visit. Only one dose of T.T is required if previous childbirth was within three years.
3. To avoid hard and strenuous activity She should take extra meals including fruits, vegetables, carbohydrates and proteins
4. Should sleep for 8 to 10 hours at night and 2 hours in day time
5. She should immediately consult the obstetrician if she has any of the following whether during the day or night (box).

   - Delay could have severe implications for both mother and the baby.

   - Acute leg pain and swelling
   - Vaginal bleeding
   - Abdominal pain including contractions
   - Severe or continuous headache
   - Swelling of face or fingers
   - Persistent vomiting
   - Chills and fever
   - Dysuria
   - Cessation or marked change in frequency or intensity of fetal movements
   - Collapse including convulsions.
   - Escape of fluid from vagina

**Internal examination**

A pelvic examination is usually not necessary unless specifically indicated or prior to induction of labor. To perform a digital pelvic examination, ask the patient to lie comfortably on her back, usually with a tilt and the knees down up with the ankles together. Both hands should be gloved, the fingers of the left hand gently part the labia, with the index and forefinger of right hand gently introduced within the vagina. This may be advanced till cervix is reached. In later pregnancy, the cervical length and consistency will provide information on the stage of labor. [Bishop’s score] and this allows an assessment of favorability for induction of labor.

A digital examination should not be performed with suspected placenta previa [risk of precipitating hemorrhage] or when there is preterm rupture of membranes [risk of introducing infection]. Same applies when consent is withheld.
### Advice on use of various vaccines during pregnancy:

<table>
<thead>
<tr>
<th><strong>Live virus vaccine</strong></th>
<th><strong>Inactivated bacterial vaccine</strong></th>
<th><strong>Hyper immune globulin</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Measles: contraindicated</td>
<td>Cholera: to meet international travel requirements</td>
<td>Hepatitis B: post exposure prophylaxis; give along with Hepatitis B vaccine initially, then vaccine alone at 1 and 6 months</td>
</tr>
<tr>
<td>Mumps: contraindicated</td>
<td>Pneumococcus: same as non pregnant</td>
<td>Rabies: post-exposure prophylaxis</td>
</tr>
<tr>
<td>Poliomyelitis: not routine; increased risk of exposure</td>
<td>Plague: selective vaccination of exposed persons</td>
<td>Tetanus: post-exposure prophylaxis</td>
</tr>
<tr>
<td>Yellow fever: travel to high risk areas only</td>
<td>Typhoid: travel to endemic areas</td>
<td>Varicella: Consider for post exposure (within 96 hours)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Inactive virus vaccines</strong></th>
<th><strong>Toxoids</strong></th>
<th><strong>Pooled immune serum globulins</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Influenza: underlying disease</td>
<td>Tetanus: diphtheria—same as non pregnant</td>
<td>Hepatitis A: post-exposure prophylaxis</td>
</tr>
<tr>
<td>Rabies: same as non pregnant</td>
<td></td>
<td>Measles: post-exposure prophylaxis</td>
</tr>
<tr>
<td>Hepatitis B: at high risk and negative for B antigen</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### RECOMMENDED INTERVALS FOR ROUTINE AND INDICATED TESTS AND PROCEDURES DURING PREGNATAL CARE

<table>
<thead>
<tr>
<th>TIME (WK)</th>
<th>ASSESSMENT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial</td>
<td>Hemoglobin</td>
</tr>
<tr>
<td></td>
<td>Urinalysis, including microscopic examination and infection screen</td>
</tr>
<tr>
<td></td>
<td>Blood group and D type</td>
</tr>
<tr>
<td></td>
<td>Antibody screen</td>
</tr>
<tr>
<td></td>
<td>Rubella antibody titer</td>
</tr>
<tr>
<td></td>
<td>Syphilis screen</td>
</tr>
<tr>
<td></td>
<td>Cervical cytology</td>
</tr>
<tr>
<td></td>
<td>Hepatitis B virus screen</td>
</tr>
<tr>
<td>8-18</td>
<td>Ultrasound</td>
</tr>
<tr>
<td></td>
<td>Amniocentesis</td>
</tr>
<tr>
<td></td>
<td>Chorionic villous sampling</td>
</tr>
<tr>
<td>16-18</td>
<td>Maternal serum alpha-fetoprotein</td>
</tr>
<tr>
<td>26-28</td>
<td>Diabetes screening</td>
</tr>
<tr>
<td></td>
<td>Repeat hemoglobin or hematocrit</td>
</tr>
<tr>
<td>28</td>
<td>Repeat antibody test for un sensitized D-negative patients</td>
</tr>
<tr>
<td></td>
<td>Prophylactic administration of anti-D immune globulin</td>
</tr>
<tr>
<td></td>
<td>Repeat hemoglobin</td>
</tr>
</tbody>
</table>
Spot the diagnosis

(Answer on pg 40)
Vitamin A deficiency

S. Manzoor Kadri

Vitamin A deficiency is a world wide problem that leads to eye diseases, severe infection and death in many people. Most of those affected live in low-income countries. Deficiency occurs in endemic proportions in developing countries and is considered to be the most common cause of blindness in children throughout the world. Besides its essential role in vision, vitamin A is also important in cellular differentiation (e.g., growth, reproduction, immune response) and in maintenance of epithelial integrity. No nutritional deficiency is more synergistic with infection than vitamin A. The 2 main mechanisms involved in the prevention of disease are the effect of vitamin A on the immune system and on epithelial integrity.

The history of vitamin A

Already in the early sixteenth century the Egyptians knew that ox liver was good for prevention of night blindness. Also fishermen from New Foundland have known for a long time that they navigate better at night if they eat cod liver. In 1913 the researchers found a substance that made humans grow and see better. They called it the fatty-lose A. Later they gave the substance the name vitamin A. Still, despite worldwide continuing research, all questions have not been answered about this vitamin.

Avitaminosis A generally accompanies states of severe malnutrition, such as kwashiorkor and marasmus, and it may be suspected in individuals with an unusual susceptibility to infectious diseases, such as measles. Various symptoms include

- Impaired vision, particularly at night (Because of the essential role of vitamin A in photoreceptor function, night blindness is the earliest and most common symptom of its deficiency.)
- Photophobia
- Erythema
- Dry, thickened skin (toad skin)
- Diarrhea

Signs: The most distinctive clinical features of VAD are manifest in the ocular system; however, numerous skin findings have also been reported. Clinical findings include the following:

- **Conjunctival xerosis** is typically found on the temporal, interpalpebral, and bulbar conjunctivae. Characteristically, it is seen as a dry, granular patch that can exhibit thickening, wrinkling, or loss of pigmentation and transparency.

- **Bitot spots** are triangular, perilimbal, gray plaques of keratinized conjunctival debris overlying an area of conjunctival xerosis.

- **Xerophthalmia** is instability of the precorneal tear film, which can lead to a dull corneal appearance and a superficial punctate keratopathy noted with the use of fluorescein.

- **Corneal ulcerations** can be partial or full thickness. Keratomalacia is a full-thickness
liquefactive necrosis of the cornea. Clinically, it is a sharply demarcated lesion with an opaque, grayish yellow appearance. The stroma can slough, either leaving a descemetocele or, in severe cases, causing perforation and loss of the anterior chamber.

- Generalized xerosis with fine wrinkles and scales may be present.
- Phrynoderma (follicular hyperkeratosis) is characterized by red-brown follicular papules that are approximately 2-6 mm in diameter, with a central keratotic spinous plug. These lesions are usually found clustered around the bony prominences of the elbows and the knees, although they may extend up the thighs and the arms.

Magnitude & frequency

It is estimated that about 750 million people are affected by vitamin A deficiency globally. Vulnerable groups are:

- Children from six months to six years.
- Pregnant women.
- Lactating women.

Vitamin A deficiency is largely limited to developing countries especially Africa, Asia and Western Pacific. In 39 countries vitamin A deficiency is a clinically significant public health problem. 5-10 million children develop xerophthalmia, of which 25 % to 50 % go blind.

Globally, an estimated one fourth to one half million children annually develop keratomalacia and become partially or totally blind, and 13-14 million children exhibit xerophthalmia of lesser severity. The World Health Organization (WHO) estimates that approximately 190 million preschool-aged children live in areas where VAD is known to occur. These areas are mainly in the developing world where an estimated 40% (70-80 million) of the children are likely to be sub clinically deficient. Thus, 90-100 million children worldwide are likely to be vitamin A deficient, with the consequence that their health and likelihood of survival are compromised.

Mortality rates of 30-60% or more are seen in children with keratomalacia and mild xerophthalmia, and the fatality risk for those even sub clinically deficient is increased by 20-30%. At any one time, as many as 230 million children are at risk of clinical / sub clinical VAD, and, annually, more than 1 million deaths in children are associated with VAD. Females and males are affected equally.

Avitaminosis A is most common in children aged 1-6 years, with the most severe, blinding complications affecting children aged 6 months to 3 years. The incidence is skewed toward children because infants born to mothers who are vitamin A deficient have small vitamin A stores at birth and, subsequently, get little from breastfeeding. Furthermore, the demands of rapid growth and susceptibility to infectious disease place an even greater demand on the meager body stores of vitamin A they do possess.
Pathophysiology

When ingested in the presence of fat, vitamin A is well absorbed from the intestinal lumen. It is metabolized, in part, in the intestinal mucosa and is then carried via chylomicrons to the liver and other tissues. Most of the vitamin A in the liver is stored as retinyl esters in specialized cells termed stellate cells. Retinol is transported in the plasma on a specific protein called retinol-binding protein.

Once within tissues, retinol is bound by cellular retinoid-binding proteins, ein I (CRBPI) and II (CRBPII). In these complexes, retinol may be either esterified or further oxidized via retinol to retinoic acid. The cycling between the major storage organs, such as the liver, and epithelial tissues that require vitamin A for cellular differentiation is extensive and efficient.

When vitamin A intake is low, the absorption efficiency remains high, carotenoid cleavage is enhanced, the plasma transport remains at essentially normal levels, recycling and utilization mechanisms become more efficient, and the excretion of metabolites markedly decreases. Marked reductions in absorption efficiency, whether due to disease, parasitic infestation, or lack of fat in the diet, and impaired liver and kidney functions adversely affect vitamin A status.

Deficiencies of vitamin A depress both humoral immunity and cell-mediated immunity. The principal effects of vitamin A inadequacy on immune function may be a consequence of impaired growth and differentiation of myeloid tissues. Vitamin A has been labeled the anti-infection vitamin. Vitamin A is particularly important for the integrity of the epithelium and the maintenance of mucosal secretions, which, if impaired, may increase exposure to microorganisms and the risk of infection.

Epithelial tissues of the eyes, the lungs, and the gut are impaired by vitamin A deficiency (VAD). These are all tissues where epithelial cell turnover is high. In humans, numerous studies using the impression cytology test have shown that low circulating vitamin A levels are associated with an increased risk of epithelial damage in the eye. Impaired gut integrity is common in malnutrition. Damage to the integrity of epithelia and mucosal barriers facilitates translocation of microorganisms and contributes to the increased severity of infections. Thus, low plasma vitamin A levels may compromise immune function by impairing epithelial integrity and by depressing lymphocyte numbers, and, although the capacity of immune cells may still be normal, the overall immune response is depressed.

Vitamin A has essentially 2 roles in ocular metabolism. First, in the retina, vitamin A serves as a precursor to the photosensitive visual pigments that participate in the initiation of neural impulses from the photoreceptors. Second, it is necessary for conjunctival epithelial cell ribonucleic acid (RNA) and glycoprotein synthesis, which helps to maintain the conjunctival mucosa and the corneal stroma.

The retina contains 2 distinct photoreceptor systems, the rods and the cones. The rods are responsible for...
vision in dim or low light, and the cones are responsible for color vision and vision in bright light. Vitamin A is the backbone of the visual pigments for the rods and the cones. In rod cells, the aldehyde form of vitamin A (retinol) and the protein opsin combine to create rhodopsin, which is the photosensitive pigment. When light hits the rod cells, the pigment isomerizes, which leads to the nerve impulse and results in the visual signal.

Vitamin A is necessary for the maintenance of the specialized epithelial surfaces of the body. A lack of vitamin A leads to atrophic changes in the normal mucosal surface, with loss of goblet cells, and replacement of the normal epithelium by an inappropriate keratinized stratified squamous epithelium. In addition, the substantia propria of the cornea breaks down and liquefies, resulting in keratomalacia.

**Food sources of vitamin A**

Everyday our body needs about 500-600 mg of vitamin A. Sources of vitamin A can be divided in vegetable and animal foods. In animal foods the vitamin is present as retinol, which is the active form of vitamin A, and in vegetables it is present as provitamin A. One has to eat six times as much provitamin A to get the same amount of vitamin A as in retinol. It is easier for the body to take up vitamin A if the food is cooked and eaten together with some fat or oil.

Animal food sources include liver, small fish as sardines, fish liver oil, egg yolk, milk and milk products as cheese, food with milk fat as margarine and butte, & breast milk.

**Vegetable food sources:**

- Dark green leaves for example spinach, cassava and mustard.
- Yellow and orange vegetables for example carrot, coloured yams, yellow squash and sweet potatoes.
- Yellow and orange fruits for example papaya, apricots and mangoes (but not citrus fruits).
- Red palm oil.

Cassava and mustard leaves are common food in many low income countries. The same is true for sweet potatoes and yams. Red palm oil is used in many African countries.

**How much food do you need to eat to get enough vitamin A?** Some 50 g of green leafy vegetables are sufficient to provide full day of supply. In one day one has to eat one of these examples to get 500mg or more of vitamin A:

- Two slices of cheese, one peach and half a mango.
- Seven sardines.
- The butter on three sandwiches, one egg and one ice cream made of cream.
- One big portion of spinach
- One carrot

**Prevention of vitamin A deficiency**

*The tragedy of such an easily preventable blindness should be averted by educating people on the importance of vitamin A.*

An understanding of the dietary and socio-economic determinants of vitamin A deficiency is necessary in order to design appropriate intervention programmes for each country. It is important to establish the magnitude of the problem and risk groups.
The ultimate goal for any prevention programme must be adequate dietary intake of vitamin A and elimination of all forms of vitamin A deficiency. Some of the current interventions used are:

- Increased intake of dietary sources of vitamin A.
- Administration of large doses of vitamin A.
- Dietary fortification and enrichment.
- Supplementation
- Public health measures

**Availability of therapeutic vitamin A (as retinol palmitate):**

<table>
<thead>
<tr>
<th>Tablets (Sugar - coated)</th>
<th>10,000 units</th>
</tr>
</thead>
<tbody>
<tr>
<td>Capsules</td>
<td>200,000 units</td>
</tr>
<tr>
<td>Oral solution (oily)</td>
<td>100,000 units/ml</td>
</tr>
<tr>
<td>Water miscible injection</td>
<td>50,000 units/ml</td>
</tr>
</tbody>
</table>

**Increased intake of dietary sources of vitamin A**

- Encourage breast feeding; the first milk (colostrum) contains a lot of vitamin A.
- Promote cultivation and consumption of vitamin A rich foods.
- Improve preservation and cooking methods to decrease losses and to improve bioavailability.
- Use mass media to educate people on the importance of vitamin A.

**Prevention of Vitamin A deficiency:**

(WHO guidelines)

1. Infants < 6 months: 50,000 units before 6 weeks of age, followed by 2 further doses of 50,000 units at intervals of 1 month (total of 150,000 units)

2. Infants 6-12 months: 100,000 units, preferably at the time of measles vaccination.

3. Child over 1 year (preschool): 200,000 units every 4-6 months.

4. Adults: i) Women of child-bearing age or pregnant: maximum of 10,000 units daily or maximum of 25,000 units weekly.

   ii) Adults in high-risk regions and mothers at or soon after delivery: 200,000 units followed by another dose after 6 weeks. [All doses are oral]

**Administration of large doses of vitamin A**

This involves giving vitamin A by mouth or injection in order to provide sufficient stores for about four to six months. Here in India we resort to what is called ‘target prophylactic dosing’. Children up to 3 years of age are given six monthly doses of retinol palmitate; the first dose is given at the time of measles vaccination i.e. at 9 months of age.

**Dietary fortification and enrichment**

- Fortification is addition of vitamin A in the food where the vitamin is absent.
- Enrichment is addition of vitamin A to a food in which the vitamin is present in small amounts.

Vitamin A has been used to fortify sugar, monosodium glutamate and dried skimmed milk. Margarine has been enriched with vitamin A. Dietary
vehicle for fortification should be wisely chosen to ensure that the population is well covered and at the same time prevent toxicity.

It can well be said that vitamin A plays a central role in the body’s immunity to infectious diseases. When there is a lack of vitamin A in the body the damaging effects of infections are pronounced and the consequences are much more severe. It is also known that if children with an infectious disease, for example measles, are given vitamin A supplementation both morbidity and mortality are reduced and that the vulnerability to other illnesses is reduced as well. The diseases that are associated with vitamin A deficiency are: measles, acute respiratory infections (ARI), diarrhoea, and HIV/AIDS.

Relation with measles

Vitamin A deficiency makes measles a very serious, killing disease in low-income countries. Due to the deficiency one’s immune responses are impaired, which makes the infection much more severe. Children with measles are also likely to develop pneumonia that is often lethal. It is known from studies that the smaller the vitamin A intake is from the diet the bigger the risk of getting measles is.

Treatment Schedule (for xerophthalmia):

**WHO Recommendation***

<table>
<thead>
<tr>
<th>Category</th>
<th>Dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Infants &lt; 6 months</td>
<td>50,000 units</td>
</tr>
<tr>
<td>2. 6-12 months</td>
<td>100,000 units</td>
</tr>
<tr>
<td>3. Child over 1 year &amp; adults</td>
<td>200,000 units</td>
</tr>
</tbody>
</table>

*The WHO guideline is immediate dosing, with the same dose repeated next day and then after 2 weeks. For women of childbearing age, having severe signs of xerophthalmia, recommendation is as for other adults. For less severe cases, (as night blindness), 5000-10,000 units daily for 4 weeks or 25,000 units weekly.

# Oral vitamin A preparations are preferred for the prevention and treatment of vitamin A deficiency. However, in situations, where patients have severe anorexia or vomiting or are suffering from malabsorption, a water-miscible injection preparation may be administered intramuscularly.

**Side effects of Vitamin A administration:**

No serious or irreversible adverse effects are encountered in recommended doses. High levels may cause birth defects, transient increased intracranial pressure in adults or a tense and bulging fontanelle in infants (with massive dosage). Massive overdosage can cause rough skin, dry hair, enlarged liver, a raised ESR, raised serum calcium and raised serum alkaline phosphatase concentration.

**Treatment of complications**

- Secondary eye infection is treated with tetracycline eye ointment three times a day for 5-7 days plus the vitamin A bolsters.
- Corneal ulcers are treated with atropine eye ointment or drops to prevent prolapse of the iris plus the vitamin A dosage and the patient is referred to eye specialist for special care.
- Patients are advised on the importance of using of vitamin A rich food.

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Osteogenesis Imperfecta - An Inherited Collagen Disorder

As its name implies osteogenesis imperfecta is a disease caused by defects in the formation of bone. This disorder, sometimes known as "brittle bone disease," affects approximately 1 in 10,000 individuals in all ethnic groups. Nearly all cases of osteogenesis imperfecta are caused by defects in type I collagen, a major component of bone that provides much of its structural stability. The function of collagen in bone is analogous to that of the steel bars incorporated in reinforced concrete. This is an especially apt analogy because the tensile strength of collagen fibrils is roughly equivalent to that of steel wires.

When type I collagen is improperly formed, the bone loses much of its strength and fractures easily.

<table>
<thead>
<tr>
<th>Subtypes of Osteogenesis Imperfecta</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Mild bone fragility, blue sclerae, hearing loss in 50% of patients, normal stature, few bone deformities</td>
</tr>
<tr>
<td>2. Most severe form, with extreme bone fragility, long bone deformities, compressed femurs; lethal in the perinatal period (most die of respiratory failure)</td>
</tr>
<tr>
<td>3. Severe bone fragility, very short stature, variably blue sclerae, progressive bone deformities, dentinogenesis imperfecta common</td>
</tr>
<tr>
<td>4. Short stature, normal sclerae, mild to moderate bone deformity, hearing loss in some patients, dentinogenesis imperfecta common; bone fragility is variable</td>
</tr>
</tbody>
</table>

Patients with osteogenesis imperfecta may suffer hundreds of bone fractures, or they may experience only a few, making this disease highly variable in its expression. In addition to bone fractures, patients may have short stature, hearing loss, abnormal tooth development (dentinogenesis imperfecta), bluish sclerae, and various bone deformities. Osteogenesis imperfecta is commonly classified into four types (Box above).

There is currently no cure for this disease, and management consists primarily of the repair of fractures and, in some cases, the use of external or internal bone support (e.g., surgically implanted rods). New, yet unproven, approaches include the use of bisphosphonates to decrease bone resorption and human growth hormone to facilitate growth. Physical rehabilitation also plays an important role in clinical management.

Type I collagen is a trimeric protein (i.e., having three subunits) with a triple helix structure. It is formed from a precursor protein, type I pro-collagen. Two of the three subunits of type I pro-collagen, labeled proα(I) chains, are encoded by a gene on chromosome that is about 18,000 base pairs (18kb) in length. The third subunit, the proα2(I) chain, is encoded by a 38-kb gene on chromosome 7. Each of these genes contains more than 50 exons. After transcription and splicing, the mature mRNA formed from each gene is only 5 to 7 kb in length. The mature mRNAs proceed to the cytoplasm, where they are translated into polypeptide chains by the ribosomal machinery of the cell.

At this point, the polypeptide chains undergo a series of post-translational modifications. Many of the proline and lysine residues are hydroxylated (i.e., hydroxyl groups are added) to form hydroxyproline and hydroxylysine, respectively. The three polypeptides, two proα(I) chains and one proα2(I) chain, begin to associate with one another at their COOH termini. This association is stabilized by sulfide bonds that form between the chains near the COOH termini. The triple helix then forms, in zipper-like fashion, beginning at the COOH terminus and proceeding towards the NH₂.
terminus. Some of the hydroxylysines are glycosylated (i.e., sugars are added), a modification that commonly occurs in the rough endoplasmic reticulum (Fig. 2 -1). The hydroxyl group in the hydroxyprolines help to connect the three chains by forming hydrogen bonds, which stabilize the triple helix. Critical to proper folding of the helix is the presence of a glycine in every third position of each polypeptide. This occurs because every third residue must fit into the center of the helix, and only glycine is small enough to do so.

Once the protein has folded into a triple helix, it moves from the endoplasmic reticulum to the Golgi apparatus (see Fig.) and is secreted from the cell. Yet another modification then takes place: the pro-collagen is cleaved by proteases near both the NH$_2$ and the COOH termini of the triple helix, removing some amino acids at each end. The amino acids performed essential functions earlier in the life of the protein (e.g., helping to form the triple helix structure, helping to thread the protein through the endoplasmic reticulum) but are no longer needed. Cleavage results in the mature protein, type I collagen. The collagen then assembles itself into fibrils, with adjacent molecules outside the cell to form the covalent crosslinks that impart tensile strength to the fibrils.

The path from the DNA sequence to the mature collagen protein involves many steps. The complexity of this path provides many opportunities for mistakes (in replication, transcription, translation, or posttranslational modification) that can cause disease. One common mutation produces a replacement of glycine with another amino acid. Because only glycine is small enough to be accommodated in the center of the triple helix structure, substitution of a different amino acid causes instability of the structure and thus poorly formed fibrils. This type of mutation is seen in most cases of type II osteogenesis imperfecta. Other mutations can cause excess posttranslational modification of the polypeptide chains, again producing abnormal fibrils.

**FIGURE:** The process of collagen fibril formation. After the pro-alpha polypeptide chain is formed, a series of post-translational modifications takes place, including hydroxylation and glycosylation. Three polypeptide chains assemble into a triple helix, which is secreted outside the cell. Portions of each end of the procollagen molecule are cleaved, resulting in the mature collagen molecule. These molecules then assemble into collagen fibrils.
Skin cancers occur in easily accessible sites and are caused by well-defined environmental agents; consequently, their formation illustrates numerous salient features of carcinogenesis. Skin tumors in man account for approximately 30% of all new cancers reported annually. There is epidemiologic and laboratory evidence of a direct causal role of sunlight exposure in the induction of cancer, and the high rate of skin carcinogenesis is a direct result of the high dose rate from the ultraviolet light component. Both basal cell and squamous cell carcinomas typically are found on sun-exposed parts of the body (eg, the face and trunk in men, face and legs in women) and their incidence is correlated with cumulative sunlight exposure. Tumor incidence and mortality increase with decreasing latitude, corresponding to exposure; skin cancers are less frequent in dark-skinned populations than in lighter-skinned people; and tumor incidence increases with occupational exposure, such as in ranchers and fishermen. Melanoma, although also associated with sunlight exposure, shows a weaker dependence on total exposure to sunlight and a distribution over the body that is not correlated to exposed areas but is more closely related to intermittent exposures and sunburn in childhood. Under lab conditions, exposure to direct sunlight at lower latitudes results in the accumulation of a mean lethal dose within approximately 30 min that is equaled only by cigarette smoke in very heavy smokers.

Variations in individual susceptibility are also clearly observed in skin carcinogenesis. Human skin can be classified into types I to IV, ranging from individuals who always burn and never tan, to those who tan but never burn; skin cancer susceptibility varies accordingly. But

The most dramatic examples of variations in human susceptibility occur in certain human genetic disorders, especially xeroderma pigmentosum (XP), Cockayne syndrome (CS), trichothiodystrophy (TTD), basal cell nevus syndrome (BCNS), the porphyrias, and phenylketonuria. Other disorders associated with acquired sun sensitivity include polymorphous light eruption, actinic reticuloid and prurigo, solar urticaria, lupus erythematosus, and Darier disease, as well as medication and immunologic status.

Sunlight has immunosuppressive effects also; it may lead to loss of antigen-presenting Langerhans cells and the appearance of dyskeratotic keratinocytes (apoptotic sunburn cells) in the upper epidermis, together with the erythematous sunburn response associated with vasodilation caused by a release of prostaglandin. Recent surveys have shown that ultraviolet B (UVB) can elicit a wide range of increases or decreases in gene expression, especially involving adhesion, apoptosis, inflammatory responses, proteases, stress responses, and translation.

**Epidemiology**

The ultraviolet component of sunlight is the major environmental agent that precipitates the clinical symptoms of skin carcinogenesis. This is well-established for squamous and basal cell cancers, but is still controversial for melanoma. The former (Non-melanoma) skin cancers are by far the most common cancers in the United States comprising 30 to 40% of all cancers. At the same time, their incidence is increasing at an alarming rate, and melanoma may be considered a quiet 21st century epidemic. Epidemiologic data has shown variable risks associated with geographic locations, skin
type, and various photosensitizing, enhancing, and protective applications. There is also a possibility of greater risk when the exposure is received during childhood and adolescence. The relationship of melanoma to sun exposure and the possible action spectrum are less clear, but may be related to acute burns rather than to accumulated dose.

The importance of deoxyribonucleic acid (DNA) as a chromophore for the shorter wave-lengths is illustrated by the autosomal recessive disease XP. In this disease, a failure in one cellular protective mechanism, DNA repair, is associated with a major increase in the rate of onset of squamous and basal cell carcinoma and melanoma. Median onset for skin cancer in the general United States population occurs at 50 to 60 years of age; in XP patients, carcinogenesis is accelerated and median onset is within the first decade. This early onset is a direct consequence of sunlight-induced changes in DNA of skin cells.

**SUNLIGHT SPECTRUM AND WAVELENGTHS RESPONSIBLE FOR SKIN CANCER**

Ultraviolet radiation (UVR) is divided into three wavelength ranges based on differences in photochemistry and biological importance. UVA (320 to 400 nm) is photocarcinogenic and involved in photo-aging but is weakly absorbed in DNA and protein. UVB (290 to 320 nm) overlaps the upper end of the DNA and protein absorption spectra and is the range mainly responsible for skin cancer through direct photochemical damage to DNA. Ultraviolet C (UVC; 240 to 290 nm) is not present in ambient sunlight but is readily produced by low-pressure mercury sterilizing lamps. Absorption of UVR by strato-spheric ozone greatly attenuates these wave-lengths, so that negligible radiation shorter than 300 nm reaches the earth’s surface. Hence, although ultraviolet A (UVA) and UVB light constitute a minute portion of the emitted solar wavelengths, they are primarily responsible for the sun’s pathologic effects. Physical shielding of the critical cells of the skin is achieved by melanin pigment and keratin layers; intracellular defenses depend upon repair of DNA damage, antioxidant enzymes (superoxide dismutase, glutathione reductase, etc), endogenous free radical quenchers, and inducible detoxifying enzymes and biochemical systems.

**SUNLIGHT-INDUCED PHOTOPRODUCTS IN DNA**

Action spectra for squamous cell carcinoma indicate that DNA is the target molecule. Nucleotide excision repair (NER) is the most important repair process concerned with UV damage. It removes pyrimidine dimers and large chemical adducts in DNA, replacing the damaged site with a newly synthesized polynucleotide patch. The continuous excision and resynthesis of DNA is associated with a very low net frequency. It takes only minutes to complete repair of an individual lesion. Excision repair is a heterogeneous process, and A dynamic balance is set up between excision and repair. Although UV-induced lesions are required for mutagenesis, mutation hotspots are determined by other factors also.

1 of the PGK1 gene varied 15-fold with much

**Genetic Disorders of DNA Repair**

A series of genetic loci that control the response of mammalian skin to damage have been identified. These loci are all characterized by significant increases in sensitivity to UVC or UVB radiation and include the disorders XP, C, TTD, and BCNS. Most of these disorders represent increased sensitivity to UVB and UVC wavelengths due to recessive mutations associated with a series of genes that regulate human cell DNA repair.
XERODERMA PIGMENTOSUM
XP is a rare autosomal recessive disease and affected homozygous patients have sun sensitivity resulting in progressive degenerative changes of sun-exposed portions of the skin and eyes, often leading to neoplasia. Some XP patients have, in addition, progressive neurologic degeneration. Obligate heterozygous parents are generally asymptomatic. The median age of onset is 1 to 2 years of age, with skin rapidly taking on the appearance of that seen in individuals with many years of sun exposure. Pigmentation is patchy, and skin shows atrophy and telangiectasia with development of basal and squamous cell carcinomas. The frequency of cancers is about 2,000 times that seen in the general population under 20 years of age, with an approximate 30-year reduction in life span.

COCKAYNE SYNDROME
CS is an autosomal recessive disease characterized by cachectic dwarfism, retinal abnormalities, microcephaly, deafness, neural defects, and retardation of growth and development after birth. Carcinomas of the skin as a result of enhanced photosensitivity are not seen in patients with CS, setting this disease apart from XP. The characteristic cellular changes in CS include a failure of DNA and RNA synthesis to recover to normal levels after UV irradiation.

TRICHOThIODYSTROPHY
TTD is a rare autosomal recessive disorder characterized by sulfur-deficient brittle hair and ichthyosis. Hair shafts split longitudinally into small fibers, and this brittleness is associated with 15-50% higher levels of cysteine/cystine in hair proteins. Patients also show physical and mental retardation of varying severity and often have an unusual facial appearance, with protruding ears and a receding chin. Mental abilities range from low normal to severe retardation.

CARCINOGENESIS
Carcinogenesis often appears to proceed by a multistep process, the first being an initiation event with subsequent promotional events that can often occur much later. Initiation implies the induction of a small number of somatic mutations in a few critical genes, and promotion involves further alterations in gene expression, copy number, and karyotype. Carcinogenesis appears to involve a process that destabilizes the genome with resulting variations in the activity of a large number of genes that change and develop over time. These include genes for cell-cycle regulation, check-point and damage response, detoxifying carcinogenic chemicals, DNA repair, including some 50 or more dominantly acting proto-oncogenes activated by mutation, deletion, translocation, or amplification, and tumor-suppressor genes whose loss may contribute to the development of cancer. Two molecular mechanisms can be important in the initiation of carcinogenesis — activation of proto-oncogenes and inactivation of tumor-suppressor genes—and both are vulnerable to the lethal and mutagenic effects of UVR. Skin cancers include at least three categories of tumor type: squamous cell carcinoma, basal cell carcinoma, and melanoma. These have distinct origins, molecular changes, and prognoses, and each has characteristic genetic and solar components in their development. Squamous cell carcinomas and basal cell carcinomas appear to originate from different locations in the skin, and melanoma from the pigment cells. The initial damage produced by solar UVB to the skin is eliminated either by repair or by proliferation and exfoliation from the skin’s surface. Some cells in the skin also die by apoptosis following exposure (“sunburn cells”) resulting in the elimination of damaged cells. Stem cells for the epithelium are thought to reside in the bulge region of the hair follicles, but there are also secondary stem cells at the base of each column of epidermal transit amplifying cells in the epidermal proliferative units. A very low frequency of quiescent cells has been observed to retain DNA damage for long periods, seemingly
with-out repair or proliferation. The carcinogen-retaining cells may be stem cells, or damaged cells with the potential to become mutants once stimulated to proliferate. The progression of molecular changes involved in squamous cell carcinoma appears to be initiated by inactivating mutations in the p53 gene that result in expanding clones in sun-exposed skin that are initially confined within the proliferating units. These clones can be very frequent and can break out of the confines of the columnar structure of the proliferative units after chronic UVB irradiation. More than 90% of sunlight-induced squamous cell carcinoma have cytosine-to-thymine transition mutations or cytosine-cytosine-to-thymine-thymine double transitions in the p53 gene. About 10% are caused by activating mutations in the Ha-ras and N-ras oncogenes at codon 61, from solar UV exposure. The Cytosine-to-thymine transitions occur at Thymine/cytosine or cytosine/cytosine dimers, the Ha-ras and N-ras activations occurred in tumors at thymine/thymine sites. Subsequent to the expansion of p53 mutant clones, additional factors come into play; changes have been observed in EGF, ras, NΦb, JNK2, presenilin, and MMP9, as well as in various chromosomal regions identified by allelotyping that control tumor initiation and papilloma to carcinoma conversion. There may be an important role for the immune system in squamous cell carcinoma formation because immune suppression in organ transplant patients enhances squamous cell carcinoma formation. Suppression of apoptosis by induction of DNA repair by the cytokine IL-12 may also play a role in immuno-suppressed individuals. Basal cell carcinomas are exemplified by the hereditary disease BCNS. Many tumour-suppressor factors have been shown to be involved. More than 50% of basal cell carcinomas and 90% of squamous cell carcinomas also contain mutations in p53 with a specific signature induced by ultraviolet light and many other gene amplifications and deletions have been detected. Melanoma occurs in a hereditary form among approximately 5 to 12% of all patients. Although this is clinically and histologically indistinguishable from nonfamilial melanoma, there are differences in the age of diagnosis, lesion thickness, and frequency of multiple lesions. The two known melanoma predisposition genes are CDKN2A and CDK4. CDKN2A is located on the short arm of chromosome 9 (9p21) and functions as a primary cutaneous melanoma shows a complex pattern of chromosomal gains and losses.

There are frequent deletions of chromosomes 9p, 10q, 6q, and 8p, as well as gains of chromosomes 7, 8, 6p, and 1q. Amplifications of chromosomal regions containing potential oncogenes occur at 4q12, 5p14.3-pter, 7q33-pter, 8q12-13, 11q13.3-14.2, and 17q25. Losses of chromosomes 9 and 10 occur early in melanoma progression, whereas gains of chromosome 7 occur later. Chromosome 9p, the site of the p16 gene, is frequently lost early in primary melanoma. Spitz nevus is a relatively benign melanocytic neoplasm that often occurs in childhood and is difficult to distinguish histologically malignant melanoma. Although the majority of Spitz nevi have a normal chromosomal complement, some contain gains of 11p that corresponds to amplification of the HRAS gene. The genomic changes in melanoma are complex, but a general pattern has emerged of a major role for the p16 gene on chromosome 9p both in familial and sporadic melanoma. In addition, other genes may be involved, including PTEN, and the p53, mdm2 pathway.**

*****************************************************************************
Measuring the TB problem:

Tajammul Hussain

Various well-known epidemiologic indices are utilized to assess the magnitude of the problem in a community and to plan & evaluate the relevant control measures. These include:

A) Measurement of infection:

a. Prevalence of infection: The cumulative experience of the community to infection, whether recent or remote, determined by tuberculin positivity is the prevalence of infection. It represents the proportion of individuals infected with M. tuberculosis at a given point of time and is expressed as a percentage.

Significance: Reflects the epidemiologic situation since the proportion of people infected depends on the intensity of exposure of the susceptible population to the open cases. Also, the cases of active tuberculosis emerge from the pool of infected people.

Crude prevalence is far inferior an indicator to the age-specific prevalence rates, which provide a measure of the cumulative effect of exposure of a cohort to tubercular infection up to a given age.

Universal BCG vaccination and cross-sensitivity to atypical mycobacteria has complicated interpretation of Mantoux test, though it still is the only community tool for estimating prevalence of infection in a population. Therefore, prevalence is usually estimated from tuberculin- test results among individuals without BCG scar by cross-sectional surveys in a representative sample of population. For assessment of epidemiologic situation of TB in a community, tuberculin survey is preferably conducted among children (0-9 years), since prevalence rate among them represents comparatively recent levels of transmission. Also, interpretation of results is easier & more accurate in them. Later on a large proportion of persons are likely to be infected with MOTT ie mycobacteria other than M. tuberculosis.

The widely taught cut-offs for interpreting tuberculin reaction globally have been: less than 5 mm (negative); 5-9 mm (borderline); & 10 mm or more (positive)

Thus, a 10 mm reading has customarily been considered as positive. However, the WHO has recommended that, for epidemiological purposes or tuberculin surveys in a community, there should be a standard criteria for every country to read a test result as positive.

For our country the cut-off for interpretation of tuberculin test is as under:

Less than 10 mm: negative
10 mm: borderline
More than 10 mm: positive

b. Incidence of infection: (Also called the Annual Risk of Infection
(ARI), annual rate of infection, annual incidence of infection, and tuberculin conversion index. It reflects the proportion of population under study who will be newly infected by M. tuberculosis among the non-infected of the preceding survey during the course of one year. It is the probability of acquiring new infection during the course of one year, ie the annual risk of being infected or re-infected for a community. Grossly it reflects upon the attacking force of tuberculosis in a given community but that is not the only implication.

ARI is a comprehensive indicator which expresses the overall impact of various factors influencing the transmission of TB bacilli viz:

- the load of infectious cases in the community
- perpetual circumstances which favour transmission in the community
- efficiency or inefficiency of case-finding & treatment programme

Risk of infection is, thus, an index representing the direct & a near-immediate consequence of the presence of bacteriological cases (Infectious, active disease), which in turn is the pool of cases left-over & carried over time, thus an index of the failure of programme efforts. It has been estimated that in developing countries, every 1% of ARI corresponds to 50 new cases of smear-positive pulmonary tuberculosis per year for 100,000 general population. Extensive research in epidemiology of tuberculosis has revealed that ARI, rather than disease rates, reflects the current epidemiological situation in an area - the higher the annual risk of infection, the bigger the TB problem. Currently, therefore, ARI is the chief indicator used to monitor & evaluate TB problem & trends globally, since any effective anti-tuberculosis programme should reduce the risk of new infection in the community. That is also the prime epidemiological objective of DOTS strategy.

The annual risk of infection may be estimated directly or indirectly. In the direct method, the proportion of tuberculin converters (the non-reactors in the earlier survey conducted 1 year back who turn positive in the subsequent survey) is used to calculate the annual incidence. The test is limited by the possibility of:

- boosting reaction (exaggeration of reaction by previous testing)
- waning of tuberculin allergy in some children and
- new infection with mycobacteria other than M. tuberculosis (MOTT) which, by conferring a moderate positivity, interferes with interpretation of test

Raj Narayan’s modification, which calculates the difference between two reactions elicited more than 18 months apart, is more appropriate to India: the children with a large increase in size (more than 16 mm) are considered as having been newly infected. In this method, all the limitations are minimized. The indirect method does not need repeated survey in the same cohort (which is a disadvantage with direct method), since estimations can be made from prevalence of infection by using the formula:

\[
ARI = 1 - (1-P)^{1/A},
\]
(Where P is the prevalence of infection in the representative sample of children without a BCG scar, & A is the mean duration of exposure (ie the mean age of children)

Repetition of tuberculin surveys at regular intervals (12 months, 18 months) yields the epidemiologic trend of tuberculosis in a community and can be used for monitoring the efficacy of the concurrent anti-tuberculosis programme.

**B) Measuring Tuberculous Disease:**

**Prevalence of disease** (also called the case-rate) represents the disease burden at a given point of time. It is expressed as a rate per 1000 population.

\[
\frac{\text{Total number of old as well as new cases at a point of time}}{\text{Total population investigated}} \times 1000
\]

A representative sample is screened with chest x-rays & all abnormal radiographs are tested for sputum positivity and culture. Children under 5 years are excluded since they are non-productive on x-ray or sputum microscopy. Identification of sputum positive cases is more reliable as well as important since they are the ones who infect others. Since radiography is less specific, precise estimation of abacillary cases (x-ray positive, sputum negative) is less accurate. Indian researchers have suggested alternative methods for estimating prevalence of sputum positive cases. Here screening is done for people with symptoms suggestive of pulmonary TB, who are directly subjected to sputum microscopy/culture. The exact prevalence of extra-pulmonary cases can not be obtained because of the difficulty in diagnosis.

For purpose of DOTS, case-rate is the percentage of people whose sputum is positive for M. tuberculosis on microscopy. Although not as informative as ARI, it is the best available practical index for estimating the number of infectious cases (the case load) within a given community.

The **Incidence of new disease**, defined as the number of new cases occurring in a previously healthy population within a year, is also expressed per 1000 population.

\[
\frac{\text{Number of new cases in a year}}{\text{Population at risk (mid-year population)}} \times 1000
\]

Calculation of the incidence of disease in developing countries is very difficult since case detection as well as reporting is erratic. Repeat disease surveys (ie conducted at yearly intervals) is the only reliable method. The number of new bacillary cases detected at subsequent survey represents incident sputum positive cases during the intervening period. Similarly, the number of new radiologically active cases who were x-ray negative in the previous annual survey gives the annual surveys is always an underestimation.

The accurate method of estimation is the complete reporting of all cases of TB in
a community as occurs in the developed world.

Bacteriologic case-prevalence, in being the pool of cases left-over and carried forward, is more an index of a failure of the anti-tubercular efforts, while as the incidence of sputum positive cases is an epidemiologic index for evaluation of the overall tuberculosis situation. Styblo (1985), established a linear relationship between incidence of infection & incidence of disease in developing world and Netherlands – ie 50 smear positive cases per lakh population per year for every 1% annual risk of infection. Murray (1990) made an estimate of 1.22 cases of smear negative pulmonary and extra-pulmonary cases for every new case of smear positive tuberculosis in developing countries.

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**Good News About RNTCP:**

The Revised National TB Control Programme(RNTCP), based on the DOTS strategy, has seen a rapid expansion in the last five years. From a coverage of ~130 million population in 1999, the present coverage is 778 million (around 75% of the population). Thirteen States or Union Territories have been fully covered.

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**Achievements under RNTCP, 2003 (till December 31, 2003)**

<table>
<thead>
<tr>
<th>Indicator</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Population coverage, cumulative</td>
<td>778 million</td>
</tr>
<tr>
<td>Total number of cases put on DOTS</td>
<td>9,06,472</td>
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<tr>
<td>New smear positive patients put on DOTS</td>
<td>3,58,496</td>
</tr>
<tr>
<td>Cure rate (expected 85%)</td>
<td>86%</td>
</tr>
<tr>
<td>No.of NGOs involved</td>
<td>&gt;700</td>
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<tr>
<td>No of private practitioners involved</td>
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</tbody>
</table>
NEWER & FUTURE VACCINES

Rubina Shaheen

Accelerating research and development for vaccines and devising mechanisms to bring them to those who need them most - i.e., the impoverished and marginalized populations in developing countries - requires a concerted effort. During the past 200 years - since the time of Edward Jenner - vaccination has controlled the major diseases. The impact of vaccination on the health of the world’s people is hard to exaggerate. With the exception of safe drinking water, no other modality, not even antibiotics, has had such a major effect on mortality reduction & population growth.

Technologies for making new vaccines

The number of technological approaches for making new vaccines has been growing rapidly for over 20 years. Most technical applications have been directed towards developing new vaccines for diseases not previously approachable by immunologic intervention. The majority of vaccines now being developed use new technologies because they appear to offer greater safety. The focus is on subunit (purified proteins or polysaccharides), genetically engineered, or vectored antigens, because the target pathogens are intracellular and difficult to immunize against. However older methods such as attenuation and inactivation continue to yield new vaccines.

New vaccine delivery technologies

Research and development of novel vaccine delivery technologies aim at improving logistics, safety and coverage of vaccination. This will mainly be accomplished through:

- Rendering vaccines more temperature stable and therefore abolishing the need for the cold chain;
- Rendering vaccination needle free, and
- Reducing the number of doses necessary for full vaccine protection from two to three (e.g. tetanus and Hep B) down to one.

Diseases under focus for vaccine development

<table>
<thead>
<tr>
<th>viral</th>
<th>bacterial</th>
<th>parasitic</th>
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</thead>
<tbody>
<tr>
<td>HIV infection</td>
<td>Tuberculosis</td>
<td>Leshmaniasis</td>
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<tr>
<td>Rota viral diarrhea</td>
<td>Shigellosis</td>
<td>Malaria</td>
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<td>Dengue</td>
<td>Pneumococcal pneumonia</td>
<td>Schistosomiasis</td>
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<tr>
<td>Japanese encephalitis</td>
<td>Meningococcal meningitis</td>
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<tr>
<td>HPV-associated cervical ca</td>
<td>ETECdiarrhoea</td>
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<tr>
<td>Herpes simplex virus</td>
<td>Staphylococcus aureus</td>
<td></td>
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<tr>
<td>Respiratory Syncetial Virus</td>
<td></td>
<td></td>
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</tbody>
</table>
Type of vaccines and the status of development made by different technologies

Live vaccines
Live vaccines have some peculiar characteristics: They are
- Able to replicate in the host (thus they multiply from a smaller dose).
- Attenuated in pathogenicity. (thus will not cause disease)
- Elicit antibodies and cell mediated immunity. (immunogenic)

Classical virus vaccines:
The term classical refers to technical strategies that do not utilize recombinant DNA technology.

Attenuation in cell culture:
The wild type virus isolated from a natural human infection is passaged in vitro through one or more cell types that the virus ordinarily does not encounter in vivo, with the goal of attenuating (= weakening) its pathogenicity. The success of this empirical approach, has been applied to both oral vaccines i.e. poliovirus vaccine and to parenteral vaccines like measles-mumps-rubella & varicella.

Variants from other species:
Small pox, the first vaccine, is the prototype of this vaccine type. An animal virus that causes a veterinary disease similar to a human disease can be isolated and cultivated; anticipating that the animal virus will be attenuated for humans to elicit protective immunity to human virus. Based on this model, first generation vaccines for rotavirus consisted of non-reassortant viruses isolated from rhesus monkeys and cows. However, such rotavirus vaccines were not reproducibly efficacious as human vaccines and were abandoned as development candidates

Reassorted genomes
A reassortant virus, which contains genes from two parental viruses, is derived following co-infection of a cell with two viruses with segmented genome. To improve the efficacy of animal rotaviruses, reassortant rotaviruses were isolated that contain mostly animal rotavirus genes, which confer the attenuation phenotype for humans, as well as the genes for human rotavirus surface proteins that elicit serotype-specific antibodies for human rotavirus. The quadrivalent reassortant rhesus rotavirus vaccine, which was being used in the United States, was withdrawn from distribution as it was observed that the vaccine caused an increased incidence of intussusceptions of approximately 1 in 10,000 vaccinees immediately post-vaccination. The same approach has been applied to influenza vaccines

Temperature –sensitive mutants
Viruses, unable to grow at elevated temperatures (ts), or cold adapted (ca), have been selected for growth in vitro at lower than physiologic temperatures. The strategy behind this approach is that ca or ts viruses will be less vigorous in their in vivo growth than their wild-type parental virus, hence less virulent and phenotypically attenuated. A ca influenza vaccine based on reassortants, has been developed for intranasal administration. A ca influenza vaccine has been used widely in Russia, and a double ts respiratory syncytial
virus (RSV) vaccine has been tested clinically.

Recombinant Virus Vaccines
Specific modifications or deletions can be made in viral genes so that the virus is more stably attenuated, that is, unable to revert to virulence. Herpes simplex virus (HSV) has been genetically engineered to be attenuated, to provide for antibody markers of wild-type HSV infection, and to protect against both the types 1 and 2 virus (HSV-1 and HSV-2).

Recombinant Viral Vector Vaccines
Recombinant DNA (rDNA) technology has been applied to develop novel live vaccines that have been engineered into carriers or vectors of foreign polypeptide antigens from other pathogens. This strategy has a potential advantage of amplification of the immunogenic signal when the live vector initiates multiple rounds of replication. If the vector virus is a commonly used vaccine, one could immunize simultaneously against the the vector virus and the pathogen, ideally in a single dose.

The prototype viral vector is vaccinia virus, in which dozens of foreign polypeptides have been expressed. Recombinant vaccinia virus expressing HIV-1 glycoprotein (gp) 160 has been tested clinically for prophylactic and therapeutic applications. Such a virus expressing carcino-embryonic antigen has been evaluated clinically for colorectal cancer.

Other mammalian viruses have been engineered into live vectors, which includes, Adenovirus, members of the pox family i.e. fowl pox and canarypox viruses.

Advantages associated with poxvirus based vectors:
- Capacity for multiple foreign gene inserts.
- Simple method of in vitro recombination
- Cytoplasmic replication.
- Authentic gene expression.
- Robust production process.
- Good stability profile.
- Pancytotropic.

Classical bacterial vaccines
It has been difficult to develop live, attenuated bacterial vaccines by classical strategies, because there has been relatively little success in culturing bacteria for attenuation while maintaining immunogenicity and because of reversion. The one widely available bacterial vaccine based on serial in vitro passage is for tuberculosis (TB) and cancer. This vaccine is a live, attenuated strain of Mycobacterium bovis, also known as Bacille Calmette-Guerin (BCG). The BCG vaccine was developed into a vaccine for the treatment of superficial bladder cancer by intra-vesicular instillation.

A major research effort is being made to develop new tuberculosis vaccines. Much of this work is aimed at improved understanding of the immunopathogenesis of TB by studying both the infecting organism and its human host. Researchers have sequenced the complete genome of M. tuberculosis, which will provide new opportunities to address questions of virulence, pathogenesis, and persistence (i.e., the ability of bacilli to achieve long-lasting dormancy following infection). Researchers also have more knowledge of both host and microbial genetic factors related to increased resistance and susceptibility to TB and are working
to better understand the human protective immune response to the disease. At the same time, new vaccine candidates (e.g., subunit vaccines, DNA vaccines, and attenuated strains of living mycobacteria) are being developed and tested in animal models. Within the next few years, several candidate vaccines should be available for human testing. Several critical steps must be taken to reach the goal of developing a new vaccine and establishing its use in public health programs.

Chemical mutagenesis followed by selection was employed to derive the attenuated Ty21a strain of *Salmonella typhi*. This vaccine was licensed for preventing typhoid fever based on its record of safety and efficacy after a regimen of three to four doses.

**Recombinant bacterial vaccines**

The engineering of bacteria for attenuation is much more complex than that of viruses because bacterial genomes are approximately 100-fold larger than those of viruses. It may be possible to over-attenuate the bacterial strain to the point that it no longer replicates sufficiently in vivo to be effectively immunogenic. *V. cholerae* strains have been developed as live cholera vaccines. Attenuation of these cholera strains has been accomplished by the rDNA-directed deletion of genes encoding virulence factors like cholera toxin. Live, attenuated cholera vaccine candidates prepared in this fashion have been evaluated clinically, and one has been licensed.

There have been attempts to develop *Shigella* strains into live vaccines by mutating particular chromosomal or plasmid-based genes in order to reduce pathogenicity.

**Inactivated/Subunit Vaccines**

**Characteristics:**

- Unable to replicate in the host.
- Elicit mostly antibodies.
- Cannot revert to pathogenicity. (thus there is no risk of vaccine-induced disease)
- Immunogenicity enhanced by administration with an adjuvant or a delivery system.

**Whole-pathogen vaccines**

**Bacterial**: Inactivation of whole bacterial cells with heat or chemical agents (e.g., thimerosal or phenol). The vaccine doses not undergo further purification. The examples of this are:

- Pertussis vaccine.
- Inactivated whole-cell *V. cholerae* vaccine.
- Enterotoxogenic *Escherichia coli* (ETEC) vaccine. (under clinical evaluation)

**Recombinant bacterial vector vaccines**

Suitable strains of pathogenic bacteria have been engineered into live vectors for expressing foreign polypeptides. The most common development has been to engineer enteric pathogens for inducing mucosal immunity against the foreign polypeptide following oral delivery. *Salmonella* typhi vectors have been commonly developed strains in terms of immunology, molecular design, and clinical testing. Strains of *V.cholerae*, *Shigella flexneri* and *Listeria monocytogenes* have been engineered likewise. The BCG vaccine strain also has been engineered as a live vector to express foreign polypeptides. *Streptococcus gordonii*, a gram positive commensal, has been engineered to express foreign polypeptides on its surface by genetic fusion to attachment sequences of *S.gordonii* M protein.
**Viral:** Viruses are shed into cell culture media, this cell-free media from infected culture are collected, enriched readily by simple purification techniques. Examples include:

- Poliovirus vaccine
- Influenza virus
- Rabies virus
- Japanese encephalitis virus
- Hepatitis A virus

**Whole human cell vaccines**
The use of inactivated allogenic whole tumor cells as a vaccine affords the opportunity to present a wide array of tumor specific antigens to the immune system. Tumor cell lines are expanded in vitro, pooled and inactivated. Vaccination with melanoma vaccine, using a synthetic adjuvant, has been licensed.

**Protein-based vaccines:**
- **Natural antigen:**
  The first protein-based vaccines relied on natural sources of antigens. The hepatitis B virus vaccine is unique in utilizing a human source (plasma) or the vaccine antigen. This vaccine is well-tolerated and highly efficacious. Protein purified from cultures of B.pertussis have been combined to formulate acellular pertussis vaccines, which eventually are expected to replace whole-cell pertussis vaccine for routine pediatric vaccinations in most developed countries.
- **Chemical inactivation:**
  Toxins produced by various bacteria (e.g., B. pertussis, Clostridium tetani, and Corynebacterium diphtheriae), is detoxified with formalin or glutaraldehyde, and are converted into toxoids. Thus represents two of the vaccines in DPT combination vaccine.
- **Genetic inactivation:**
  The chemical ‘toxiding’ procedure has the disadvantages of potential alteration of protective epitopes, with ensuing reduced immunogenicity, and the potential for reversion to biologically-active toxin. rDNA technology has been employed to produce a stable toxoid. As applied to pertussis vaccine, the toxin was mutated for reducing the enzymatic activity responsible for its toxicity. A genetic approach to derive a diphtheria toxoid, following mutation was found to be successful. This genetic toxoid (CRM197) is the protein carrier for a licensed Haemophilus influenzae type b (Hib) conjugate vaccine and pneumococcal conjugate vaccine. This technology also has been applied to V. cholerae toxin and ETEC toxin to produce candidate mucosal adjuvant.
- **Recombinant polypeptides:**
  The expression of recombinant polypeptides as subunit vaccines has been the most extensively used application of rDNA technology to the development of new vaccines. The first application of rDNA technology to the production of new vaccine was for HBV through the expression of HBsAg gene in baker’s yeast (Saccharomyces cerevisiae), and in E.coli. HBsAg has also been expressed in transgenic potato tubers; the purified HBsAg was immunogenic. Another example of the effective use of virus-like particle (VLPs) is for human papillomavirus (HPV), expressed in E.coli, and the vaccine is in Phase III clinical trials.

  There are innumerable ongoing applications of rDNA technology to produce proteins as candidate vaccine antigens for viral, bacterial, and parasitic infections. The major *Borrelia burgdorferi* outer membrane protein (OspA), expressed in E.coli as a recombinant lipoprotein, has been
licensed for the prevention of Lymes
disease. Recombinant HIV-1 gp120
expressed in Chinese hamster ovary
(CHO) cells has been formulated into a
vaccine that is in Phase III clinical
studies.

Vaccine applications outside of
infectious diseases have become
increasingly diverse, for allergy,
ocology, autoimmunity, and infertility.

**Hosts for Expression of Recombinant
Protein**

**Bacteria**
- Escherichia coli
- Bordetella pertussis
- Vibrio cholerae

**Yeast.**
- Saccharomyces cerevisiae
- Henseula polymorpha

**Mammalian cells**
- Chinese hamster ovary
- African green monkey kidney

**Mammals.**
- Goat
- Sheep
- Cow

**Plants.**
- Tomato
- Potato
- Tobacco

**Peptide-based vaccines**

B-cell epitopes against which
neutralizing antibodies are directed can
be precisely identified in a polypeptide.
These peptides would be effective
vaccine antigens if they are rendered
more immunogenic than they are as
native peptides. There are several
technologies for increasing the
immunogenicity of a linear B-cell
neutralization epitope. The
pre-erythrocytic vaccine for Malaria is one
such example, where circumsporozoite
protein (CSP) is a major protein of the
sporozoite. The SPf66 vaccine candidate
was a synthetic multiepitope, multistage
peptide vaccine tested in several Phase
III trials involving tens of thousands of
people.

**Carbohydrate- and Polysaccharide-
based Vaccines**

Antibodies directed against capsular
dy saccharides are found to be
protective for most encapsulated
bacteria, thus establishing capsular
dy saccharides as vaccine antigens;
components of lipopolysaccharide on
Gram-negative bacteria, are used as
vaccine antigens.

- **Plain polysaccharides:**
  The polysaccharide preparations
  are usually immunogenic in adults and
  children over 2 years of age. Polysaccharide
  vaccines have been licensed for Hib (monovalent), N.
  meningitis (quadrivalent), and Streptococcus pneumoniae. The
  limitations of these vaccines is that the
  polysaccharides being T-cell
  independent immunogens they are
  poorly immunogenic in children
  younger than 2 years owning to the
  immature status of their immune
  systems.

- **Conjugate polysaccharides:**
  Conjugation of polysaccharide
to a carrier protein converts the
  polysaccharide from a T-cell
  independent to a T-cell dependent-
  immunogen. Polysaccharide conjugate
  vaccines can elicit protective
  immunoglobulin G (IgG) and elicit
  protective immunologic memory in
  infants and young children. This
  strategy has been applied in preparing
  licensed vaccines against H. influenzae
type b; there are four licensed Hib
  conjugate vaccines, with different
carrier proteins e. g; Tetanus toxoid,
diphtheria toxoid, CRM 197, and an
outer membrane protein complex from
N. meningitidis. A heptavalent pneumococcal conjugate vaccine has been licensed for pediatric use. A conjugate of group B streptococcal polysaccharides can be used to immunize pregnant women for the prevention of neonatal group B streptococcal meningitis.

**Anti–idiotype antibody vaccines:**
The idiotype is associated with the hyper-variable region of the antibody molecule and represents the unique antigenic determinants of that antibody. The idiotype (Id) on antibody (Ab-1) itself can act as an immunogen that can elicit an immune response; the Abs that bind to the Id on Ab-1 are referred to as anti-idiotype antibodies (anti-Id) or antibody 2 (Ab-2) by virtue of the anti body-binding site of the anti-Id mimicking the conformation of the particular antigen. Anti Id molecules themselves can be used as vaccine candidates in which an epitope is presented on Ab-2, the carrier molecule. An anti-Id for the parasite Schistosoma mansoni that mimics a schistosome carbohydrate epitope has shown promise as vaccine candidates.

**Nucleic-Acid-Based Vaccines**
DNA encoding a vaccine antigen is a technology that came into existence during the 1990s. DNA immunization can be employed as a technology, known as expression- library immunization. In this technique, a microbial DNA genome is cloned as a library of DNA expression plasmids. By successive fractionation and testing in the challenge model, protective plasmids can be identified.

**Characteristics:**
- Stimulate synthesis of antigens only in cells.
- Elicit mostly cell-mediated immunity.

**Naked DNA Vaccines:**
Naked DNA encoding a vaccine antigen is injected intramuscularly. Cells take up the DNA, transcribe its expression cassette, and synthesize the antigen, which may be processed similarly to a live viral infection.

Several DNA Vaccines for influenza, HIV, and malaria have shown these vaccines to be well tolerated. One new type of experimental DNA vaccine for HIV/AIDS is made from the genetic material of HIV itself. Genes coding for viral proteins of HIV are injected directly into the body. This enables the body to produce the viral proteins, which than stimulate the immune system to produce antibodies against HIV.

**Facilitated DNA Vaccines:**
Facilitation can be at the level of cellular uptake of DNA, expression of messenger RNA, or immunological activation. DNA has been incorporated into micro projectiles that then are “shot” directly into cells, which produce the encoded antigen that stimulates an immune response. This “gene gun” technique has been reported to be potent at eliciting immune responses. For increasing uptake, DNA has been coated with cationic lipids, lipospermines for facilitating transfer across membrane.

**viral DNA Vaccine Delivery:**
For DNA vaccine delivery by fowl pox or canary pox virus, the expression cassette for recombinant protein is integrated into the viral genome. Canary pox virus expressing HIV-1 rgp 160 or rgp 120 has been used as apart of a prime-boost HIV-1 vaccination regimen.

**Bacterial DNA vaccine delivery:**
Bacteria that replicate intracellularly can be engineered to deliver plasmid DNA into host cell for expressing vaccine antigens. Shigella flexneri has been attenuated by a deletion mutant in the *asd* gene, an essential gene.

**Mixed strategies:**
More recently, vaccines have been developed that use either mixtures of vaccines made by different technologies (mixed vaccines) or different types of vaccines given during the overall dosing regimen (mixed regimens).

- **Mixed vaccines:** Oral inactivated whole-cell cholera (WCC) vaccine which lacks cholera toxin (CT) and its toxic effect, has been shown to be well tolerated and to have a rate of efficacy of approximately 60% for 3 years. In order to elicit CT-neutralizing antibodies, recombinant CTB is independently expressed, purified, and added back to the WCC vaccine. This combined WCC+ recombinant CTB vaccine has been shown to have a higher rate of efficacy than WCC vaccine alone.

- **Mixed regimens:** Cannarypox virus expressing recombinant HIV-1 rgp 160 or rgp 120 has been administered in two priming doses followed by boosting with rgp 160 protein; this regimen induced higher levels of neutralizing antibodies than immunizing with rgp 160 alone.

**PASSIVE VACCINES (ANTIBODIES)**
Preparation of polyclonal or monoclonal antibodies is referred to as passive vaccine. The protective effect mediated by most of these antibody preparations is to:

- Neutralize virus infectivity.
- Bind to bacteria, which than are destroyed by phagocytic cells;
- Bind to and neutralize molecules such as toxins elaborated by the pathogen.

**Polyclonal antibodies:** The earliest preparation of antibody or immune globulin that were effective for antimicrobial therapy were made in species such as horses, which had been injected with bacterial toxoids. A more recently developed product, equine rabies globulin, is widely used as a life-saving therapy in developing countries. Nevertheless, such preparations tend not to be used in humans, except in emergencies when no alternative therapy is available.

A range of human polyclonal IG products has been available for human use. Depending upon the IG under consideration, these products are prepared by pooling plasma from voluntary healthy volunteers. The pooled plasma is fractionated with alcohol to enrich for antibody. The preparations are heat treated under conditions that are known to destroy the infectivity of human pathogens.

**Monoclonal antibodies:**
The preparation of monoclonal antibodies came into existence after the invention of hybridoma technology in the mid-1970s.
Advantages:

- These proteins can be generated with exquisite selectivity and specificity.
- Antibodies have multiple effector functions in addition to their antigen combining abilities.
- Antibodies have a long serum half-life, this facilitates prophylactic treatment of the at-risk patients.
- Specific antibodies can be generated more rapidly and with far less efforts than that required for conventional low-molecular weight organic molecules.
- It is possible to test whether the neutralizing a given mediator with an antibody benefits the host.

**Therapeutic targets for which human monoclonal antibodies are known to be useful:**

- Red cell antigens: Rh(hemolytic disease of the newborn)
- White cell antigen: antilymocyte / thymocyte globulin
- Viral antigens: Hepatitis A and B, rabies, EBV, CMV, HSV, varicella zoster, HIV,
- Bacterial antigens: Tetanus, gram negative endotoxins, diphtheria toxin and pneumococcus.
- Elimination of circulating drugs (i.e. in over doses)
- Anti-snake venom.
- Fertility control (e.g., anti-B-human chorionic gonadotropin)

**Conclusion:**
Continued rapid technological developments over the past two decades have assured rapid expansion in the number of general strategies for making new vaccines. The number of approaches should continue to expand over the next decade, such that almost all antigens or epitopes can be presented in a highly immunogenic form in the context of a live to a non-live vaccine or be expressed through a DNA-based vaccine. Beyond all the technological advances, the limiting factor in developing new vaccines for human use will continue to be a more comprehensive understanding of immunology.******************

There is a tendency among doctors, especially the pediatricians, to immediately patron newer vaccines. There is no doubt that the pharmaceutical companies incur huge expenditure on research & development of vaccines and consequently expect quick returns. The practitioner should, however, take into consideration the following:

1. Is the vaccine essential? If not, why to give it?
2. Can the parents afford the huge cost of an unnecessary vaccine? If not, why to prescribe it?

Vaccines like those against Hepatitis A are definitely totally unnecessary in situations where water-borne infection is highly prevalent, and the vast majority of children become immune by their 10th birthday. Also, hepatitis A is a mild, mostly subclinical infection in the pediatric age. Then what is the rationale of continuing prescribing it?? (Ed)
Complementary Feeding

Rohini Bhan

Importance of nutrition as a foundation for healthy development is often underestimated. Poor nutrition leads to ill-health and ill-health contributes to further deterioration in nutritional status. These effects are most dramatically observed in infants and young children, who bear the brunt of the onset of malnutrition and suffer the highest risk of disability and death associated with it. In 2001, 5–70% of the burden of diarrhoeal diseases, measles, malaria and lower respiratory infections was attributable to malnutrition. The children who die represent only a small part of the total health burden due to nutritional deficiencies. Maternal malnutrition and inappropriate breastfeeding and complementary feeding represent major risks to the health and development of those children who survive. Deficiencies in the diet of vitamin A, iodine, iron and zinc are still widespread and are a common cause of excess morbidity and mortality. Over 50 million children under age five are wasted, and in low-income countries one in every three children suffers from stunted growth. Indeed, many children never reach this age. The effects of poor nutrition and stunting continue throughout life, contributing to poor school performance, reduced productivity, and impaired intellectual and social development.

Inappropriate feeding practices are a major cause of the onset of malnutrition in young children. Children who are not breastfed appropriately have repeated infections, grow less well, and are almost six times more likely to die by the age of one month than children who receive at least some breast milk. From six months onwards, when breast milk alone is no longer sufficient to meet all nutritional requirements, infants enter a particularly vulnerable period of complementary feeding during which they make a gradual transition to eating family foods. The incidence of malnutrition rises sharply during the period from 6 to 18 months of age in most countries, and the deficits acquired at this age are difficult to compensate for later in childhood.

During the past decade, there has been considerable progress in the implementation of interventions to improve breastfeeding practices. Clear recommendations and guidelines, combined with political commitment and increased allocation of resources, enabled many nations to establish programmes that combined the necessary actions to protect, promote and support breastfeeding. Consequently, improvements in breastfeeding rates have been demonstrated in various settings. However, similar progress has not been made in the area of complementary feeding. While research and development have contributed to an expanding evidence base for recommendations on appropriate feeding and effective interventions for children after six months of age, translation of new knowledge into action has lagged behind. To consider this gap and what could be done to fill it, WHO convened a global consultation on complementary feeding (Geneva, 11-13 December 2001). A group of scientists and programme managers reviewed and updated recommendations for appropriate complementary feeding, and to identify actions needed to accelerate programmatic efforts, including priorities for research and development of tools to plan and implement interventions. The gist of the final recommendations is given below.

1) Malnutrition is responsible, directly or indirectly, for over half of all childhood deaths. Infants and young children are at
increased risk of malnutrition from 6 months of age onwards, when breast milk alone is no longer sufficient to meet all nutritional requirements and complementary feeding needs to be started. Complementary foods are often of lesser nutritional quality than breast milk. In addition, they are often given in insufficient amounts and, if given too early or too frequently, they displace, rather than supplement, breast milk. Gastric capacity limits the amount of food that a young child can consume during each meal. Repeated infections reduce appetite and increase the risk of inadequate intakes. Infants and young children need a caring adult or other responsible person who not only selects and offers appropriate foods but assists and encourages them to consume these foods in sufficient quantity.

2) Global recommendations for appropriate feeding of infants and young children are:

- Breastfeeding should start early, within one hour after birth.
- Breastfeeding should be exclusive for six months.
- Appropriate complementary feeding should start from the age of six months with continued breastfeeding up to two years or beyond.

3) The scientific review on complementary feeding that WHO and UNICEF commissioned in 1998 provided age-specific guidance on nutritional requirements from complementary foods in healthy breastfed children. Lately new estimates have been made for energy and nutrient requirements for infants and young children (FAO/WHO/UNU), warranting an update of previous recommendations. The latest estimated energy requirements from complementary foods, assuming an average breast-milk intake, are 200 kcal/day for infants aged 6–8 months, 300 kcal/day for infants aged 9–11 months, and 550 kcal/day for children aged 12–23 months.

2. Scientific and empirical data are not yet sufficiently robust to warrant a change in estimated nutrient requirements from complementary foods described in the scientific review. However, a comparison of average nutrient intakes of children aged 6-24 months and new dietary reference intakes published by the Institute of Medicine, USA shows that the diets of infants and young children in most populations in low-income countries are consistently deficient in some nutrients, including iron, zinc and vitamin B6.

3. Adequate energy and nutrient intakes for this age-group are the result of a balance between appropriate breastfeeding and complementary feeding. There is no evidence of a
preferential order between breastfeeding and complementary feeding at a given meal. Support for sustained breastfeeding as part of efforts to improve complementary feeding is critical. Increasing complementary feeding frequency, for example, may impair breastmilk intake with the potential risk of reducing total energy and nutrient intake if not enough attention is paid to sustaining breastfeeding.

4. On a population basis, recommended meal frequencies – assuming a diet with energy density of 0.8 kcal per gram or above and low breastmilk intake – are:
   - 2-3 meals per day for infants aged 6-8 months;
   - 3-4 meals per day for infants aged 9-11 months and children 12-24 months
   - additional nutritious snacks may be offered 1-2 times a day, as desired.

5. Complementary foods should be varied and include adequate quantities of meat, poultry, fish or eggs, as well as vitamin A-rich fruits and vegetables every day. Where this is not possible, the use of fortified complementary foods and vitamin mineral supplements may be necessary to ensure adequacy of particular nutrient intakes. As infants grow, the consistency of complementary foods should change from semi-solid to solid foods and the variety of foods offered should increase. By eight months, infants can eat ‘finger foods’ and by 12 months, most children can eat the same types of food as the rest of the family.

4) Reducing childhood malnutrition requires a multi-sectoral approach that includes a variety of interventions to address its major causes. There is increasing evidence for the positive impact of feeding-counselling on energy and nutrient intakes and growth in children less than two years of age. To support changes in individual behaviour, supplemental interventions will be needed in many settings to ensure the availability and utilization of adequate micronutrient-rich complementary foods. Given the close link between maternal health and child health outcomes, in particular the contribution of low birth weight to childhood malnutrition, interventions should also address the health and nutrition of mothers.

**Improving feeding behaviours**

1) Improving complementary feeding requires attention to foods as well as to feeding behaviour of caregivers. Infants and young children need assistance that is appropriate for their age and developmental needs to ensure that they consume adequate amounts of complementary food. This is called **responsive feeding.**

<table>
<thead>
<tr>
<th>Critical dimensions of responsive feeding are:</th>
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<tbody>
<tr>
<td>• feeding with a balance between giving assistance and encouraging self-feeding, as appropriate to the child’s level of development;</td>
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<tr>
<td>• feeding with positive verbal encouragement, without verbal or physical coercion;</td>
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<tr>
<td>• feeding with age-appropriate and culturally appropriate eating utensils;</td>
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<tr>
<td>• feeding in response to early hunger cues;</td>
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<td>• feeding in a protected and comfortable environment;</td>
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</table>
feeding by an individual with whom the child has a positive emotional relationship and who is aware of and sensitive to the individual child’s characteristics, including changes in physical and emotional state.

Inappropriate feeding behaviours are an important determinant of malnutrition. Caregivers often are unaware of the importance of responsive feeding, or do not know how to practise it. They need support from health professionals and community-based workers to acquire the necessary knowledge and skills.

11. Feeding behaviours are anchored in a wider belief system that influences what, when, where and how people feed their children. The most effective interventions are based on an in-depth assessment of this system; they address major barriers, using various channels and resources to support behaviour change.

Current strategy emphasizes focusing on the family rather than on individual caregivers in designing interventions to improve complementary feeding. Assessing time allocation and time constraints in relation to food preparation and feeding are critical, as is estimating the real costs associated with implementing new feeding recommendations.

12. It is also important to promote safe preparation, feeding and storage of complementary foods in efforts to improve complementary feeding. Contamination and the proliferation of pathogens in food are major underlying causes of childhood diarrhoea.

Answer to Medical Quiz II

1) The diagnosis is pernicious anemia. The typical 4 features are:
   - Vitiligo (autoimmune)
   - Macrocytic anemia
   - Elevation of SHBD (Elevation to this extent is only found in hemolysis, leukemia and myocardial infarction).
   - Mildly raised bilirubin in the presence of normal liver function tests, suggesting low-grade hemolysis.

2) The 3 additional tests required are bone marrow examination, serum B12 level and the Schilling Test.
   a) Bone marrow: This would reveal megaloblastic changes. Megaloblasts differ from normoblasts in being larger and in having more open nuclear chromatin patterns.
   b) Serum B12 level is low
   c) Schilling test: Following saturation of B12 binding sites with intramuscular B12 (1000μg), an oral dose of 1 mg labeled B12 is given and the percentage excreted in the urine is measured over 24 hours. This will be low if oral absorption is impaired or in renal failure. Malabsorption of B12 due to pernicious anemia can be corrected by concurrent administration of intrinsic factor. This forms the 2nd part of Shilling test.
Eosinophils & their abnormalities:

Shabnam Bashir

Eosinophils are derived from the common precursor of the granulocytes, myeloblast, measuring 15-20 μm in diameter, which on Romansky stain, exhibits scanty basophilic cytoplasm and a large nucleus with open fine chromatin and 2-5 nucleoli. These give rise to promyelocyte, a larger cell (20-25 μm), with more abundant cytoplasm in which granules appear for the first time. Subsequently differentiation into neutrophils, basophils and eosinophils occurs.

For the eosinophil, the in-marrow post-tmitotic process takes some 2.5 days. Peripheral blood kinetics is very complex. The eosinophils exhibit re-circulation: the initial half life is 4 hours, with reappearance within 6-24 hours, and the 2nd phase of slow disappearance spanning 4 days.

Eosinophils resemble neutrophils, with a size of 12-17 μm and bilobed or trilobed nucleus. They have granules which stain deep red with eosin - each one has approximately 20 large refractile granules. Electron microscopy shows that each granule is surrounded by double membrane and contains amorphous material with a dense crystalline core and a less dense matrix. They constitute less than 5% of the total circulating leucocytes, ie count 40-440 /μl. This level shown some diurnal physiologic fluctuation that is inversely correlated with adrenocortical activity.

The contents of the granules is of particular interest: half the total protein is a strongly basic substances of molecular weight 11,000 (the major basic protein). In addition, the granules contain a peroxidase, acid phosphatase, alkaline phosphatase, aryl sulfatase, β-glucuronidase & ribonuclease, & also typical lysosomes. Their exact role is unknown.

Eosinophil function: Exact function of this complex cell is unknown. They share some properties with neutrophils. They respond to complement-mediated or other chemotactic stimul, but show selective migration to to sites of parasitic infestation or allergic reaction. Many substances including antigen-antibody complexes and lymphokines attract eosinophils. Another substance which is especially chemotactic for eosinophils is released from the granules of basophils in response to the interaction of antigen and basophil-bound IgE (ie during immediate hypersensitivity reactions). This factor is called the eosinophil-chemotactic factor of anaphylaxis (ECFA).

Eosinophils have lesser phagocytic activity than neutrophils, but can consume mycoplasma, bacteria, antigen-antibody complexes, zymosan particles, and mast cell granules. Eosinophil is also able to discharge their granular chemicles to the exterior and can kill helminth larvae without need for phagocytosis. Eosinophils are involved in the containment and modulation of immediate hypersensitivity reactions by
their ability to phagocytose some of reaction-products. They also neutralize heparin released from the basophils.

**Eosinophilia:** An increase in eosinophil count has long been recognized in various allergic conditions and as an accompaniment of a variety of parasitic infestations.

<table>
<thead>
<tr>
<th>Various causes of eosinophilia:</th>
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<tbody>
<tr>
<td>Parasitic infestations</td>
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<tr>
<td>Allergic disorders:</td>
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<tr>
<td>Asthma</td>
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<tr>
<td>Hay fever</td>
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<tr>
<td>Drug &amp; other hypersensitivity reactions</td>
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<tr>
<td>Skin disorders:</td>
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<tr>
<td>Eczema</td>
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<tr>
<td>Urticaria</td>
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<td>Pemphigus</td>
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<tr>
<td>Dermatitis herpetiformis</td>
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<tr>
<td>Pulmonary disorders:</td>
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<tr>
<td>Astma</td>
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<tr>
<td>Parasitic infestations</td>
</tr>
<tr>
<td>Polyarteritis nodosa</td>
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<tr>
<td>Malignancy:</td>
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<tr>
<td>Hypereosinophilic syndrome</td>
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<tr>
<td>Sarcoidosis</td>
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<tr>
<td>Hypoadrenalism</td>
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Increased eosiphil production with blood and tissue eosinophilia is seen in most disorders with an immune basis. It is seen in all invasive metazoan infestations. However, it is less predictable when the process is confined to the gastrointestinal tract or when larval forms get encysted (as with Taenia solium).

Allergic disorders associated with eosinophilia include bronchial asthma, allergic rhinitis, certain drug allergies, and skin allergies as eczema, contact dermatitis, and urticaria.

The presence of metazoan larvae in the lung is a regular cause, but eosinophilia also occurs with hypersensitivity to inhaled organic dusts and in pulmonary involvement with polyarteritis nodosa.

Less frequently eosinophilia may be seen in malignancy or inflammatory conditions (inflammatory bowel disease and collagen-vascular disease). Mild eosinophilia is characteristic in patients with adrenocortical failure.

In hypereosinophilic syndrome, there is a progressive massive blood and tissue eosinophilia with splenomegaly and endomyocardial and pulmonary fibrosis. Tissue damage occurs from eosinophilia, which in turn is a reaction to an unidentified stimulus.

**Eosinopenia:** A reduction is seen with physiologic or pathologic increase in adrenocortical activity or after the administration of adrenocortical trophic hormone (ACTH) or adrenal steroids.

<table>
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<tr>
<th>Causes of eosinopenia:</th>
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<tr>
<td>Hypercorticoid states:</td>
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<tr>
<td>Cushing’s disease</td>
</tr>
<tr>
<td>Glucocorticoid adminstration</td>
</tr>
<tr>
<td>Stress</td>
</tr>
<tr>
<td>Epinephrine administration</td>
</tr>
<tr>
<td>Congenital (rare)</td>
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</table>

No patients have been described with pure absence of eosinophils. A few patients have been described with hypogamma-globulinemia, eosinophilia, and thymoma. A patient with absent eosinophils & basophils & reduced levels of IgA & IgE had repeated infections, rhinitis and asthma.

Peripheral eosinophils are particularly sensitive to adrenocortical activity, and their numbers may be greatly reduced or absent in periods of stress, in patients with Cushing’s disease and those on corticosteroid treatment. **
Ginger
(Condensed from ICMR Bulletin)

Ginger, a most widely used spice, belongs to Zingiberaceae family. The edible part of the plant is the rhizome. The plant produces an orchard like flower with petals that are greenish yellow streaked with purple colour. Ginger is cultivated in areas of abundant rainfall. Ginger is native to southern Asia, but it is widely cultivated in tropical areas also such as Jamaica, China, Nigeria and Haiti. It is an important spice crop in India; in 2001, 9000 metric tones costing Rs 4.5 crore was exported from India. In the country it is mainly cultivated in Kerala, Karnataka, Tamil Nadu and North Eastern states.

Sanskrit is known by many local names. In India, it is called Sonth; in Kashmir, Shonth. Hakims & Tabibs remember it as Adrak, its Persian name. Ayurveda has named it ‘Maha Aushadhi’, ie the great medicine. In Sanskrit, it is called Sringavera, and in Greek, Zingiberi. Its botanical name is Zingiber officinale (Latin Zingiber is ginger).

Nutritive value:
- Moisture: 80.9%
- Carbohydrates: 12.3%
- Protein: 2.3%
- Fat: 0.9%
- Fibre: 2.4%
- Minerals; 1.2%
- Iron
- Calcium
- Phosphorus

Vitamins:
- Thiamine
- Riboflavin
- Niacin
- Vitamin C

Chemistry:
1. In fresh rhizome, Gingerols are the main active components.
2. Powdered rhizome contains in addition to protein, carbohydrate, crude fibre, water and ash contains fatty oils & volatile oils.

**Volatile oils in ginger:**
- Alpha-zingeberine (30-70%)
- Beta-sesquiphellandrene (15-20%)
- Beta-bisaboline (10-15%)
- Alpha-farmesene
- Campene
- Beta-phellandrene
- Curcumene
- Cineole
- Geranyl acetate
- Terphineol
- Terpenes
- Borneol
- Geraniol
- Limonene
- Linalool

3. In dried ginger powder, shagoal (a dehydration product of gingeriol) is the main pungent constituent. Other pungent substances are gingerol, zingerone, and paradol. Aroma comes mainly from zingiberol.

Role of ginger in traditional medicine:
Ginger has been an essential ingredient in many traditional Chinese medicines since 4th century BC. The Chinese prescribed & took ginger for stomach-ache, diarrhoea, nausea, asthma, heart conditions, respiratory disorders, toothache and rheumatic complaints. In Ayurveda, the ‘maha aushadhi’ was recommended for use as carminative, diaphoretic, antispasmodic, expectorant, peripheral circulatory stimulant, astringent, appetite stimulant, anti-inflammatory agent, diuretic and digestive aid. The Greek physician Galen used ginger as a purificant of
body; he used it to treat conditions caused by imbalances in body. Africans & the west Indians also use ginger medicinally. In the USA, it is recommended to relieve and prevent nausea caused by motion sickness and morning sickness. In India ginger is used in preparation of most of the sauces, curry powder, pickles, and dishes.

**Pharmacology**

1) **Effect on the GIT**: Ginger increases muscular activity in the digestive tract thus stimulates digestion and absorption and relieves constipation & flatulence. Ginger has been found superior to dimenhydrinate (Dramamine) in preventing motion sickness. It prevents postoperative nausea and vomiting, where its effect equals that of metoclopramide. Ginger also reduces symptoms of morning sickness.

2) **Anti-inflammatory activity**: One of the features of inflammation in rheumatic disorders is increased oxygenation of arachidonic acid which results in the production of prostaglandins and leukotrienes. Ginger reduces inflammation & ameliorates symptoms by reducing the biosynthesis of prostaglandins & leukotrienes.

3) **Antimicrobial effects**: Ginger has antibacterial as well as antifungal activities. It inhibits colonic bacteria which otherwise ferment undigested carbohydrate leading to flatulence. Thus the spice has antiflatulent properties. Ginger can inhibit the growth of E coli, proteus, staphylococcus, streptococcus, and salmonella. Among the fungi, it inhibits aspergillus and mycoderma species.

4) **Effect on CVS**: Ginger stimulates blood circulation throughout the body by powerful stimulatory effect on the heart muscles and by diluting blood. The improved circulation increases the cellular metabolic activity, thus contributing to the relief of cramps. Ginger reduces blood pressure & decreases cardiac workload. It reduces the formation of pro-inflammatory prostaglandins & thromboxane, thus lowering the clotting ability of the blood. The inhibition of platelet aggregation by ginger has been found to exceed that of onion and garlic. Ginger has anticholesterol properties.

5) **Anticarcinogenic**: Ginger has antioxidant properties. It stimulates the levels of glutathione-s-transferase (GST), a group of cellular detoxification enzymes. There is high correlation between induction of these enzymes and inhibition of carcinogenesis. Ginger especially stimulates GST in liver, lungs and intestine, thus conferring protection against the toxic effect of xenobiotics. It also stimulates another phase II detoxification enzyme, quinone reductase, thus effectively counteracting the oxidative damage in tissues of liver and lungs.

6) **Antimigraine effect**: Studies have shown that ginger has preventive effect in migraine.

Spices & condiments are an integral part of our diet. They impart flavour, colour, food preservation, and enhance palatability. At the same time they have no side effects and have established medicinal properties. Ginger has been used in traditional medicine for thousands of years. Only recently have its multiple medicinal properties been established through scientific research. In addition to its established effects on the GIT, CVS & blood, it stimulates protective enzymes involved in xenobiotic metabolism and thus protects liver, lung and intestine from cancer.
Cognition, knowing, perceiving, and thinking - it is a defining property of what it is to be a human being and is studied by psychologists, neuroscientists, computer scientists, and philosophers who are interested in an organism’s ability to think. To understand cognition, the mental processes which result in a conscious understanding of our sensory world need to be studied. These include our ability to perceive, to remember, to attend, to communicate, and to plan. Cognition is a topic of primary interest to the fields of cognitive psychology (a branch of psychology that explores the workings of the mind using experiment, theories, and models of mental representation) and cognitive science (in which theories of intelligent behaviour are most commonly expressed on computers). It is also an aspect of the brain and its relation to consciousness as we are conscious of our ability to think and we believe that thought is dependent on activity of the brain.

Cognition was of interest to early philosophers, who were concerned with the classification of all things, the properties of such things, and the prime substances that make up any object. The ability to think evidently requires a very special classification. It requires an explanation of what it is to be able to explain, and therefore became part of the puzzling question of the nature and substance of mind and consciousness. So it remained until the end of the 19th century when “the father of psychology”, American physician and philosopher William James, introduced a degree of pragmatism into the question. The study of cognition became more closely associated with an active form of thinking, such as inferring outcomes from observations. This distinguished it from less concrete mental events such as moods, emotions, and feelings. Cognition therefore became closely related to the process of reasoning and knowledge of the world. There was, however, a movement in psychology called behaviourism that, from the early part of the 20th century onwards, regarded cognition as an unsound element of psychology. It was reasoned that internal mental states and the processes of reasoning could not be measured and could only be known through introspection. This caused psychologists such as John Watson in the 1920s and Burrhus Frederic Skinner in the 1950s to regard a concern with cognition as being less than scientific.

Contemporary interest in cognition is partly a reaction to these negative tendencies. It stems from a desire to develop a science of how the perceived world is represented in thought and how this involves the use of language and other informational processes. Where in the brain specific cognitive acts take place is of interest to the neurophysiologist and the psychologist alike. This question is rendered difficult by the fact that many functions are distributed over several identifiable parts or modules of the
brain. Successful studies will adopt a judicious mix of assuming both that functions are local, and that such local areas interact. There is general agreement that some cognitive functions can be traced to particular areas in the brain. For example, studies with injured patients indicate that thinking about space occurs in the central right hemisphere of the cortex (the outer layer which is folded into the skull), abstract mathematical thinking in the mid-left hemisphere, while planning involves the frontal lobes which lie behind the forehead. Reliance on such localization, however, should be considered with care, as recent brain imaging studies reveal that function may be more distributed throughout the brain than experiments with injured patients indicate. The way in which similar processes could be made to operate in a computer has been helpful in the development of the desired psychological science or cognitive science. Despite the pragmatism, the topic of cognition is and will continue to be controversial. While the brain is sometimes likened to a computer, the distinction between the two is important. For example, the brain is capable of cognition through its evolution and through learning. It is a dynamic, self-programmed, intricately sculptured cellular structure. This has created the most recent challenge for this science: the discovery of cognition as a property of the neural structure of the brain.

THE HISTORY OF COGNITION

To understand contemporary debates on cognition, historical influences are very important. They may be divided into the early classical influence of both the Milesian founders of Greek philosophy and, later, the great Greek philosophers, Socrates, Plato, and Aristotle. The next great influence was the religion of the Middle Ages and, later, two products of the Enlightenment—Cartesianism and Empiricism.

A Greek Philosophical Thought

As with most aspects of philosophy in the Western world, early interest in cognition may be traced to what is known of the ideas of Thales of Miletus. While his best-known pronouncement is that all things are made of water, he noted that some objects could move unaided and others could not. Those that could, he said, were alive and possessing a soul. Although this seems not to be linked to “thought”, it was the beginning of the interest in the “inner state” of a living being. This is precisely the central concern in studies of cognition. In general, living creatures express forms of behaviour through muscular movement, and cognition is that which is interposed between the senses and action. Objects such as a tree that bends in the wind do not possess cognition. But a human being who thinks about whether to plough the land early or late, does. So cognition entered philosophy at Miletus as deserving enquiry both about its substance and as an object of inner drive, hidden from other beings, but vital to the individual.

In the era of the great Greek philosophers Socrates, Plato, and Aristotle, the human capacity to think and in particular the ability to do mathematics and logic became acclaimed as marks of supremacy among human beings. Socrates practised dialectic, the method of enhancing knowledge through a process of question and answer. He believed that cognition was immortal and, having been put to death by the state of Athens for being “a curious person” and subverting the young, he pronounced that, in death, he would either sleep a dreamless sleep or be capable of thinking forever. For Plato, knowledge was a product of the intellect rather than the senses. Universal concepts such as the meaning of the word “cat” were for him eternal and created by God. The senses could only provide specific examples of cats, but the realization of the existence of the concept “cat”
is discovered by the intellect and appreciated as a divine gift.

In contrast, Aristotle’s view of cognition was less mystical but also harder to understand. Things are because they contain some material and have a particular shape or function. A tree trunk is made of wood, its “matter”, and is recognizable by its shape or its “form”. Soul is that which gives form (now best understood as “purpose”) to the body. It perishes with the body. So what kind of a thing is cognition? When we see something what is it that, within ourselves, does the “seeing” and visualizing (picturing things described by language)? “Mind”, taught Aristotle, “is that part of the soul that enables the body to think”, that is, it enables human beings to be cognitive. Mind is divine not in the sense of being a gift of God but more in the sense of being an experience during mortal life which is so exalted as to be shared with the highest of beings, that is, whatever Divinity there may be.

**Cognition and the Religions of the Middle Ages**

In the Middle Ages it was the Christianity of the Western world that defined attitudes to cognition. With St Augustine, the first acknowledged Christian philosopher, the notion of “will” came into philosophical discourse. That is, thought could lead to good or evil and would be judged by God. He returned to the Platonic idea of thought being a divine gift. Nine hundred years later, St Thomas Aquinas, an ardent scholar of Aristotle’s philosophy, persuaded the Church that Aristotle’s views were to be preferred to those of Plato. That is, “wisdom” as an element of cognition is a pleasurable pursuit of the intellect, a way of discovering the nature and the purposes of the universe. Such natural reasoning, Aquinas taught, led to the truths professed by the Catholic Church.

Muslims espoused the powerful philosophies of Avicenna and Averroës. As scholars of Aristotelian writings they believed that conceptual thought is a transformation of sensory thought mediated by cognition. That is, cognition transforms the experience of, say, many cats into the concept of “cat”. In contrast to the such interpretations of cognition arising from the Abrahamic religions, other powerful philosophies that stressed the importance of thought developed in the East. Buddhism for example, espouses the notion of a dual “self”—the occult and the sensory. Thought is to be directed towards the diminution of the latter to the eventual state of “nirvana”, where the self has become totally occult, that is, a perfect inner cognitive state.

**Cartesian Cognition and the Empirical Reaction**

The philosophy of René Descartes, known as Cartesianism, and the powerful reactions to this have dominated the philosophy of cognition from the 17th century to the present day. Descartes’s dictum, *Cogito ergo sum* (“I think therefore I am”), portrayed cognition as being generally not representative of truth: it contains inventions as well as observed facts. Accordingly there is only one certainty: that of existence. Without it, there would be no cognition at all. He returned to the Platonically inspired notion of innate ideas through which God reveals Himself to the thinker. He largely denied the physical basis of cognition, arguing that thought and action are weakly linked through the pineal gland. It is this view of mind that is called “dualist”. The reaction came from a group of philosophers known as the British Empiricists. John Locke developed a theory of ideas, which denied divine revelation and placed cognition firmly in the domain of experience, where abstraction was a result of mental operations on that which is experienced. David Hume, known for his sceptical views, endorsed Locke’s link of cognition to experience, but argued that one cannot think of abstractions. That is, we cannot think of the concept of a “cat”, but only of actual cats we have known or imagined. Thinking, he also argued, cannot encompass how one event causes another, but can only be concerned with frequently coincident or closely sequential occurrences of events. Confidence in the experiential basis of cognition came to an end with the writings of German philosopher Immanuel Kant. He suggested that cognition contains *a priori* (innate) ideas such as those of time, space, quantity, relation, and others, which are not divinely revealed, but are a function of the physical apparatus of the brain.

In summary, over the last two and a half millennia, enquiry into cognition has swung
between the Platonic notion of divine revelation and the Aristotelian dependence on sensory experience which, as its greatest feat, is capable of abstract thought. These features remain in the great debates of the present day, with the added quest, as initiated by Kant, to understand how cognition might depend on the physical apparatus of the brain.

COGNITION AND PSYCHOLOGY

Cognition has been a major element in the development of psychology. This includes both its acceptance, as in the work of William James, and its denial in the methods of behaviourists.

A William James and the Scientific Method

Psychology is now accepted to be an appropriate framework for the study of cognition as a science. In 1890, William James described psychology as “The science of mental life, both of its phenomena and its condition”, urging that it should be studied under rigorous conditions. That is, he encouraged those interested in mental life to carry out controlled measurements in order to build systematic theories of the behaviour and thought processes of human beings. This increased rigour was thought to be less prone to opinions and earned for its author the title of “pragmatist”, which made him the originator of what was to be called “pragmatism” in the philosophy of mind. While he was happy to study what was meant by human beings “being conscious”, his pragmatic outlook caused him to object strenuously to suggestions that human beings could “have” consciousness. He argued that while “being conscious” is part of our experience, “consciousness” itself is not something we can experience “having”, like a hand or a bicycle. His pragmatism led him to argue, as did the empiricists before him, that the content of our cognition can only arise from previous experience, current perception or imagination rather than mysterious or transcendental revelation.

Some rigorous studies of thought processes had taken place before James's instigation. Of particular note is the suggestion that was made by Charles Darwin that cognition develops through evolution. This suggestion has not received major attention until the 1990s. In the new field of evolutionary psychology questions are now being asked about how cognition may be shaped by the inherited physical features of the human being. One of the factors hampering development of an evolutionary theory of cognition is the very link between the physical structure of the brain (which can be influenced by inheritance) and the nature of cognition. This is the major unanswered question that underlies most modern work on the subject.

Another practitioner of precise methodology was the German academic Wilhelm Wundt of the University of Leipzig. He initiated a variety of experiments in which he trained his subjects to speak of their inner perceptions or introspections.

B The Behaviourist Denial of Cognition

Wundt’s technique was strongly criticized in the early part of the 20th century when John Watson urged psychologists to mistrust introspection, as the reports of subjects, even if trained, could not be corroborated. This led to the school of behaviourism, a type of psychology only concerned with an organism’s response to carefully designed stimuli. Well known is the work done in Leningrad by Ivan Pavlov, who showed that a dog would anticipate (be conditioned to) the arrival of food on sensing other events (such as the ringing of a bell) which normally preceded the food. Similarly, in the United States, B. F. Skinner measured the factors that affected animals in tasks where appropriate actions had to be chosen to receive food. The significance of behaviourist approaches on cognition is that they largely denied the existence of the inner state in behaving organisms. That is, behaviourists attempted to develop a theory of behaviour that is independent of cognition.

The omission of the inner state in psychology is now largely considered as being untenable. But it is also true that introspective reports by human subjects cannot be corroborated. This dilemma has been resolved since the 1950s through the process of modelling of internal activity, an approach that relies more on the consistency of models and less on
introspective reports. Such modelling owes much to engineering, where the modelling of complex machinery with internal states (such as aircraft controllers or processing plant) is commonplace. In cognitive psychology engineering notions of communication and control have been used in models, and in cognitive science, engineering theories used in computation feature strongly.

A significant realization of contemporary studies in psychology is that cognition is an aggregation of many mental facilities. Principal among these are memory, attention, and the use of natural language and planning. These are considered separately.

C Memory and Cognition

Most of the thoughts that occupy our mind, that is, the essence of cognition, appear to rely on mechanisms of memory. In the narrow sense this refers to our ability to remember things like telephone numbers or historical dates, while in the broadest sense it could be said to encompass all of thinking. Psychologists have classified memory in several ways: long- and short-term, episodic, semantic, and “working” memory.

C1 Long- and Short-Term Memory

In cognitive science, there is much measured information on how retentive the human brain can be in the short term and how memories transfer from the short duration to the relatively permanent. These tests usually refer to lists of objects. Cognitive models exist where short-term memory is seen as a “box” of limited capacity and a rehearsal loop. Memory of a list of objects is said to be retained in the box and “recycled” through the rehearsal loop. Eventually, this is transferred to another box, the long-term memory, which is like a filing cabinet within which the list can be retained for periods that can be as long as a lifetime. Such models have occasionally been criticized by neurobiologists as the boxes featured in the models do not exist in the neural makeup of the brain. However, the main role of such cognitive models is to act as a framework for observed behaviour rather than being biological explanations. One often quoted fact is that most people’s short-term memory span is a list of seven objects.

C2 Episodic, Semantic, and Working Memory

Episodic memory relates to events that are directly remembered, such as: “Last July I saw a horrific accident in the Kings’ Road.” In contrast, semantic memory is a way of describing our store of knowledge, much of which is shared with others. “A dog is a four-legged domestic animal” is an example of semantic memory. Work on memory in the UK by Alan Badderley and his colleagues in the mid-1980s, has demonstrated that memory can be dependent on context. For example, it is easier to remember quotations from Shakespeare during a conversation about the Bard and his works than had one been discussing football. That is, an area of knowledge comes into “working memory”, from which it is easier to access its elements than otherwise.

C3 Computer Memory

“Memory” has, of course, become the word used for the storage facility of computers. It is important to distinguish the functioning of memory in a living being from that of a computer. A computer has a vast store of memory locations organized like a filing cabinet. It requires a precise index (the address)
in order to retrieve information contained in an electronic “folder”. Human memory, on the other hand is a far more flexible and rapid instrument. There is no system of addressing, just an efficient system for performing associations. This is due to what are thought to be special emerging abilities of the neural networks in the brain. Despite the massive processing speed of a computer, the human brain, even if slower, can find some associations far more rapidly than the contemporary computer as a result of the brain’s highly specific parallel organization. The computer searches while the brain associates. A good example of this is the association of names and faces, and the ability to do this even if a face has changed considerably through ageing or hair alterations. The importance of this is not to deny that some day computers might achieve a performance similar to that of the brain, but to stress that cognitive memories operate on the basis of organizational principles that are very different from those of computer memories.

Some researchers have studied the effect of ageing on memory. This distinguishes between subjects who have been diagnosed as having a biochemical deficit (Alzheimer’s and Parkinson’s diseases) and those who do not. Diseases affect people in different ways, but generally it is short-term and episodic memory that suffers. Normal subjects, however, are unlikely to suffer severe short-term memory loss, although some loss is noted in the very elderly. Episodic recall is diminished in normal subjects while semantic memory remains relatively intact.

The human sensory system is constantly bombarded by information from its environment. To lead an orderly existence, much of it has to be ignored. The mental capacity for making choices between that which is noticed and that which is ignored is called “attention”. A human being can concentrate on a television play or listen to a musical concert, while ignoring other activities in his or her surroundings. This “taking in” of one object of sensation among many that are present at the time was considered and carefully recorded by William James and Wilhelm Wundt. So, in the early parts of the century, much became known about fluctuations of visual gaze due to distracting visions and the “coming into awareness” of rival visual events, depending on their order of occurrence. This became the basis for a post-behaviourist revival of work on attention in the 1950s. Much of the drive for these studies was practical, and stimulated by the desire to model human behaviour, made increasingly acute during World War II. How do mission controllers improve their performance? How do humans respond in situations where they have to maintain a clear view of their actions in the surrounding chaos of a battle? Two of the key workers associated with research on attention were both communication engineers in the UK—Donald Broadbent and Colin Cherry.

Broadbent’s model was based on the way that a communication system could be designed to cope with an information overload. He equated the brain to a communication channel with a limited throughput capacity. That is, in computing terms, a channel that can
transmit only a maximum number of bits per second: attempting to exceed this causes distortion and confusion of the information. Broadbent’s model acts as an automatic switch that selects streams of information that will not overload the system. The words “filter theory” are sometimes used in conjunction with this model as it filters through data that the automatic switch has selected.

**D2 The Cocktail Party Problem**

Colin Cherry is best known for having discussed the “Cocktail Party Problem”. At a cocktail party, a listener selects one person’s discourse while ignoring others that could be just as loud. Cherry found that there are many physical factors (such as the distance of the speakers and the position of the head) which determine the ability of a listener not to be distracted by speakers other than the selected one. An important result is that words or phrases with emotional content have a deep effect on attention switching. In the cocktail party context, for example, were someone to use the listener’s name, or use a word such as “sex”, it was likely to cause a switch of attention.

**D3 Visual Attention**

Visual attention is the phenomenon of the gaze being attracted to important events in the visual field. In 1968, Paul Kolers stimulated work on visual attention by studying the eye movements that take place while a subject is reading. Further assessment of visual attention during car driving and aircraft piloting followed. In recent years, visual attention has risen in importance as a central mechanism of cognition. The fact that the brain can provide a coherent sensation despite the fact that the eyes are moving between areas of interest has led researchers to look for sites in the brain where signals from eye muscles and the visual paths coincide reconstructing an experience of what is being seen. This is also a meeting point between cognitive science and neurophysiology that is becoming important in the understanding of cognition.

**E Natural Language**

Considerable controversy surrounds those areas of cognition which relate to our knowledge and use of language. How much of this knowledge is innate and how much learned during life? There is no doubt that the meaning of words and the details of how they are used is learned, but whether there is a certain deep grammatical structure in place in the brains of newly born children is the source of the controversy. American linguist Noam Chomsky is the major advocate for this nativist position while the leading opponent has been the Swiss psychologist Jean Piaget, who advocated a theory of language construction after birth.

**E1 Nativist Theories of Language and Cognition**

Nativist theories are based on the observation that children appear to use correct forms of language without much use of incorrect forms. It is not a matter of just learning rules and then following them. A child who learns the rule that the sentence “The ball is yellow” may be turned into the question “Is the ball yellow?” would learn that the verb needs to be brought to the front of the sentence. But then sentences such as “The ball which is in the bedroom is
yellow” could be wrongly turned into “Is the ball which in the bedroom is yellow?” As children hardly ever make errors of this kind, Chomsky concluded that they are endowed with an innate tendency to recognize “which is in the bedroom” as a “chunk” of language from which the verb should not be moved.

More recently, the American psycholinguist Steven Pinker has treated this and similar abilities as an instinct. It is not surprising that a child exhibits the instinct of recoiling in the presence of a large advancing object, so it should not be surprising that it possesses some form of instinctive use of language. Pinker’s argument is not that “chunking” is an instinct, but that the art of seeking efficient use of language is an instinct. Recognizing “chunking” as an efficient procedure is an example of such an instinctive act.

An alternative, nurture-based, theory of language, stems from Jean Piaget’s extensive experimentation with children. He noticed that they appear to understand the physical world in stages. They first notice that there are differences between the properties of things, such as the malleability of plasticine, the liquidity of water, and the solid nature of stones. At a later stage (around 7 to 10 years old) the child understands deeper principles such as a feeling for quantity—water in a glass does not change volume if poured into a bucket. Language, he argued, arrives at its structure in a way that shadows these stages of developing cognition. First, simple ways of using language are mastered and these are sufficient to match a simple physical understanding. More complex forms follow, building on simpler ones. More recently, a similar theory of development has been put forward by British psychologist Annette Karmiloff-Smith, a former pupil of Piaget’s. She calls this “Representational Redescription” to indicate a process of gradual internal redescription of knowledge. This starts with attending to sensory information, continues with discovering groupings (for example, striped animals are different from non-striped ones), to having a mental representations (being able to visualize these animals), to appending verbal labels (calling striped quadrupeds “zebras”). She suggests that during the development of an individual, several such representational processes may be proceeding at once, matched by language becoming increasingly sophisticated.

COMPUTATIONAL MODELS OF COGNITION

The development of artificial intelligence (AI) has had a profound influence on the study of cognition. AI may be defined as a set of computer programs that have a behaviour which, if exhibited by human beings, would be said to require intelligence. Computers that play chess are examples of this. So any program in AI could also be said to be a precise description of some particular cognitive process. Game playing, for example, does require cognition of a kind, and the step-by-step process of getting a computer to play chess is arguably a model of the cognitive act of a chess player engaged in the game. This methodology is also called cognitive science. Another
example is the modelling of visual perception. A successful computational model of visual perception has been developed by the British scientist David Marr.

A Marr’s Three Steps of Perception

Marr’s model comprised three progressive steps. The first, a “primal sketch”, is a description of the light intensity changes in the visual input which relates to blobs, edges, and contours. The next phase, the “2½-dimensional sketch”, includes information about the orientation of surfaces. This can be inferred from shading information. Finally, the 3-dimensional model links the previous two stages to knowledge about objects and the world. Marr suggested that in this last step objects could be represented in stylized ways—as “pipe-cleaner” wire models or like artists’ wooden puppets made of cylinders. Marr’s work was highly influential (after his death in 1980) on the design of computer vision systems, but eventually lost impact as a cognitive model due to the lack of plausibility of the 3-dimensional sketch.

B Databases, Knowledge, and Problem-Solving

The use of databases as models of stored knowledge is common in computational models of cognition. Called “semantic networks” these are conceptual networks of nodes and arrows. Nodes represent nouns of different levels of generality. For example, at a detailed level, nodes may be nouns such as “cat”, “bee”, “salmon”. At a higher level they might be “animal”, “insect”, and “fish”. Arrows indicate relations such as “is a” or “is not a”, allowing the network to represent phrases such as “a cat is an animal but is not a fish”. Problem-solving and reasoning have also received increasing attention in computational models of cognition. This includes several theories based on rules for searching knowledge represented as semantic networks. Alternatively, there is interest in the cognitive ability of a person to build scenarios in his mind. For example, what goes through a person’s mind in noticing a hole at the bottom of a rowing boat is not the result of the search of a network but an imagination of what will happen and how it might be stopped.

C Criticism of Computational Models: the “Chinese Room”

Do programming models “explain” how cognition works, or are they just a programmer’s way of solving a problem? The American philosopher John Searle has used an argument called the “Chinese Room” to direct an attack at computational work which claims to be a model of language understanding. Searle describes a room that is sealed except for a posting slot in its side. Chinese people outside the box feed stories written in Chinese symbols through the slot. They then post comprehension questions as further symbols. The box replies with symbols which are answers to these questions and the questioners conclude that if the answers are right, whatever it is that goes on in the box is a suitable model of whatever cognition is required to understand language. To make his point, Searle reveals that the box contains a human being (who speaks English but no Chinese) and a filing cabinet full of rules written in English. As the questions arrive, the person looks up rules in the filing cabinet. These state how the symbols in the story need to be rearranged to form the answers. Clearly this is a parody of how a computer works, but makes the point that there is nothing inside the box, particularly the human being, that “understands” Chinese. Searle contrasts this to the way in which human beings continuously relate language to their experience to obtain understanding and concludes that this process is missing in computer models. This criticism has led to the initiation of new research into the way that symbols could refer to experience. This is called “symbol grounding”. Initiated at Princeton University by cognitive scientist Steven Harnad, symbol grounding refers to connectionist methods (see below) to create symbols for an AI system which are decoded from sensory events. Whether this overcomes Searle’s objection is open to discussion.

D Connectionism and Cognition

Since the mid-1980s, models based on neural networks have increasingly been investigated for their ability to perform cognitive tasks. Neural networks are cellular systems loosely based on the networks of neural cells found in the brain. Their key attribute is that they build up their cognitive abilities through learning from examples rather than being programmed.
and they are claimed to represent cognitive processes which are more revealing of human cognition than the programmed models. Because the function of such systems depends on the learned strengths of connections between neurons, the approach is called “connectionist”.

Artificial neural networks were first proposed at Massachusetts Institute of Technology in 1943 by physician Warren McCulloch and logician Walter Pitts. They suggested that a neuron as found in the brain could be represented by a variable electrical device and that networks of these devices can learn to recognize patterns. In the early 1960s the technique was explored by Frank Rosenblatt, using a version of such artificial neurons called Perceptrons. He demonstrated their ability to learn to recognize simple patterns. After a setback due to a critical report by Marvin Minsky and Seymour Papert in 1969, a revival took place in the 1980s. The work of a group of scientists distributed across many universities in the United States drew attention to the unexplored power of such systems under the title of Parallel Distributed Processing. Models of several cognitive abilities featured in this new approach. Speech perception, linguistics, and deficits such as amnesia were shown to benefit from this modelling technique. In speech perception, a model called TRACE by Jay McClelland and Jeffrey Elman made effective use of context in a network for recognizing phonemes in a spoken sentence. McClelland and David Rumelhart explained mechanisms for creating past-tense forms of verbs from present-tense versions, and the same two authors showed that simulated deficits in neural networks lead to amnesia-like characteristics. In Europe, too, work had been done since the 1960s on cognitive modelling by the Italian physicist Eduardo Caianiello; on pattern perception by Igor Aleksander, John Stonham, and Bruce Wilkie in the UK; on the representation of speech by the Finnish pioneer Teuvo Kohonen; and on mathematical analysis of sound by John Taylor in the UK. In Japan, too, Shun-Ichi Amari of Tokyo University was developing elegant mathematical analyses from the 1970s onwards. This has flourished into a major Japanese research programme on cognition.

While the early models implemented broad engineering and mathematical concepts, the contemporary range of this approach now includes more detailed modelling of the way the brain generates cognitive behaviour. Notable in this context is the work of Edward Rolls of Oxford University, which, among other important models, indicates how the hippocampus area of the brain is involved in memory. A series of “adaptive resonance” models developed by Steve Grossberg and Gail Carpenter at Boston University have also served to elucidate many mechanisms of neural activity in linguistic and visual tasks, making particular inroads into issues of internal representation and attention.

COGNITION AND MENTAL HEALTH

In addition to the major ways of studying the normal nature of cognition discussed above, work has been done on brain function in order to better understand some of its abnormal conditions. Also, work done with brain-damaged patients has been invaluable in locating the mechanisms of cognition.

A Cognitive Neuropsychology

Cognitive neuropsychology is the study of the effect of brain damage on cognitive behaviour (see Cognitive Psychology). This approach needs to assume that behavioural deficits are clearly defined and may be traced to localized brain function. A factual and moving account of the way in which brain deficits affect the cognitive lives of sufferers is given by the British psychologist Oliver Sacks in his classic book, The Man who Mistook his Wife for a Hat.

B Cognitive Therapy

Difficult states of mind such as depression arguably occur because thought patterns enter a repeated negative spiral. Cognitive therapy, as advocated by the psychologist Aaron Beck, attempts to help sufferers by teaching them to recognize the thought pattern itself. It has been successful in instances where the patient becomes very depressed and even suicidal through a sequence of thought that could start with a simple
reflection on a minor mishap such as an admonition at work, followed by a generalization to “I can never get on with my superiors” to thoughts of inferiority and the fruitlessness of life. The therapy would attempt to teach the patient to recognize the thought pattern itself at an early stage and to break it by reflecting (say) on the true, specific causes of the admonition and breaking the link with a general negative train of thought.

LOCATION OF COGNITION IN THE BRAIN

Contemporary studies attempt to localize cognition with greater accuracy than the broad classifications into hemispheres and lobes. In particular, in the field of cognitive neuropsychology mentioned above, it is necessary to know how cognitive behaviour maps on to different regions of the physical brain. However, knowledge of this is partial and sometimes controversial. For example, in the United States, the British Nobel laureate Francis Crick and American psychologist Christoph Koch are developing a hypothesis regarding the localization of visual awareness. Contrary to earlier belief that the primary visual cortex might be the salient site, Crick and Koch refer to a deeper part of the brain called the extrastriate cortex. This is where neural signals of eye movement meet the visual pathways, explaining why awareness is that of a coherent world, despite being captured by moving eyes. Edmund Rolls has studied the localization of various forms of memory: part of the prefrontal cortex is involved in rapid learning and unlearning of vision and taste stimuli, while episodic memory may be traced to subcortical structures in the temporal lobes.

It should be remembered that while such localizations are possible, particularly with the use of scanning techniques, it is likely that cognitive phenomena such as attention and use of language could involve many functional modules of the brain. Understanding both the localization and the interaction between functional areas in the brain is now the goal for most neuroscientists.

A Brain Imaging Methods

Computers have made it possible to study brain activity by reconstructing the images generated by scanning machines. Early Computer Tomography (CT) scanners used X-rays. This was followed by Positron Emission Tomography (PET), which relies on the injection of a radioactive tracing compound into the brain. This illuminates areas of brain activity according to the distribution of the radioisotope. A further advance has been the use of Magnetic Resonance Imaging (MRI), which avoids the use of a radioisotope, is faster and more accurate, but requires very large electromagnetic equipment. This stimulates and measures the motion of molecules as if they were little magnets. Particularly important is functional MRI (fMRI), where changes in brain states can be highlighted by subtracting the contents of scans taken on different occasions. These methods are becoming central to research on cognition and the location of specific functions as they link brain activity to cognitive states as reported by the subject.

CONTROVERSIES: ANIMALS AND MACHINES

What kind of cognition is available to animals and how this compares to that of human beings is a controversy that will not easily be resolved. And the discussion which focuses on animals has many common factors with that resulting from applying the same consideration to machines. Neither animals nor machines use language in the same way as human beings and this, in the opinion of some, disqualifies both from being treated as
thinking organisms. Also thought, as it links to the idea of free will, has theological overtones that set human beings apart from all else. This leads some to regard animals and machines as not being worthy of possessing thought.

A Cognition in Animals

The fact that cognition in animals, if it exists, is a poor version of the human kind is rarely disputed. The central question is whether all animal behaviour is entirely innate and instinctive or whether there is any element due to an absorption and interpretation of experience. Against animal thought is the possibility that high levels of performance based on finely tuned perceptual and sensory properties and instincts could mistakenly be interpreted as “thought”. Positive evidence ranges from experiments where apes appear to have understood the meaning of numbers to the experience of blind owners of guide dogs who feel that their dogs plan and communicate. Closer attention is also being given to problem solving among many species—bees that use “mental maps” to return to sources of honey; ravens that use stones as tools; herons that use bread crumbs to lure fish; and the classic example of the ape that uses a stick to reach a banana.

A further area of debate concerns whether it is possible that while they may be conscious, animals may not be “self-conscious”. That is, they are not able to reflect on their mental state as human beings can do largely through the use of a sophisticated language. Whatever the case may be, this is a difficult area of scientific research that requires unprejudiced investigations to produce further results.

B Cognition in Machines

The old question of whether machines can think has become complicated because they clearly can nowadays be made to model cognitive behaviour (as seen above), build up experience, learn, and plan. The difference between machine behaviour and that of human beings is sometimes presented as merely a matter of scale: someday machines might be complex enough and powerful enough to think. A deeper consideration rests on the debate over whether machines could not only perform competently but also be conscious of what they do. Here, divisions of belief about the nature of consciousness come into play. Those who believe that consciousness is directly related to neural activity in the brain will more readily believe that such activity could be reproduced in machines to produce internal states that are equivalent to conscious states in a human being. However, those who believe that neural activity cannot account for the occurrence of first-person sensation or “qualia” (the personal quality of a sensation), the nature of which is often referred to as the “hard” question regarding consciousness, will not support the notion of a truly cognitive machine. Clarification might come from the work of several interdisciplinary teams that are coming into being in the United States, Europe, and Japan. Within these teams, philosophers, neuroscientists, and engineers can work together and attempt to agree on the nature of cognition by working both with living organisms and machines.

THE FUTURE

The 20th century has given birth to the study of cognition as a way of providing insight into the character of our mental life. It has also raised some vitally important questions that still require an answer. How does cognition evolve and develop? How does it depend on the mechanisms of the brain? How do cognitive defects arise? How unique is cognition to human beings? How does it shape societies of cognitive beings? These questions ensure that cognition will continue to be not only one of the most exciting pursuits in the 21st century, but also a most satisfying topic within which people with different backgrounds and skills can come together in order to further our understanding of our own selves.
Breast Pain

Breast pain (mastalgia) or tenderness is a common symptom and most frequently occurs as part of normal changes in the breast during the menstrual cycle.

Women aged 35 through menopause in particular often develop benign breast lumps or cysts in their breasts before their monthly menstrual periods. Diffuse and dull pain is common, with both breasts generally affected. Noncyclic pain (most often experienced by women with lumpy breasts) tends to occur in one breast only and can be sharp and stabbing. It generally occurs in women in their 40s. Women who have just started taking oral contraceptives or estrogen replacement therapy also sometimes experience breast pain, but this usually disappears within a few months.

In pregnant women breasts often become painful, tender, or tingly as early as a week or two after conception. In nursing mothers, breast pain can result from the engorgement with milk that sometimes occurs when the baby's need for milk is not coordinated with the mother's production. This often happens in the early stages of breastfeeding or during weaning. Nursing itself can produce cracked and sore nipples; often limiting lactation time or rubbing the breasts with lanolin can help relieve the pain. Blocked milk ducts can also produce red and tender lumps. These may be relieved by nursing the baby more frequently on the affected side. Occasionally a blocked milk gland will produce a painful cyst called a galactocele, which can be drained by a surgeon. Nursing mothers may also develop mastitis, a breast infection that occurs when bacteria from the baby's mouth or surrounding skin enters the breast through cracks in the nipple. Women with mastitis will generally have chills, fever, and malaise in addition to breast pain, and they can be treated with antibiotics. If there is also a palpable (easily felt) lump, however, the mastitis has probably produced an abscess (a collection of pus) under the skin, which will have to be drained by a surgeon. Lymph node enlargement can accompany mastitis and should not be confused with breast cancer. The enlargement should go away as soon as the infection is cured.

Women who suffer from breast pain may want to keep a record of symptoms and menstrual periods to see if the pain is cyclic or noncyclic, that is, to see if lumps and pain worsen at particular times in the menstrual cycle. If the problem is cyclic, hormonal therapy such as danazol, tamoxifen, and bromocriptine are sometimes helpful. There have been no convincing studies that eliminating caffeine intake helps relieve breast lumps or pain. Hormonal treatment is usually unnecessary for noncyclic breast pain because symptoms generally disappear with menopause. Mild analgesics such as acetaminophen or ibuprofen can help reduce discomfort, as can breast support from a good bra. If any breast pain is associated with a small lump that does not go away, a woman should be checked for malignancies. Usually a normal clinical examination and a mammogram will reassure a woman that her breast pain has some other cause: only 6 percent of all women with breast cancer have breast pain.
Antibiotic Sensitivity and Resistance Profile of the Microorganisms Responsible for Urinary Tract Infection Observed in Kashmir, India

S Manzoor Kadri, Bashir Gash, Asif Rukhsana

Urinary tract infection happens to be common and is generally treated empirically by general practitioners, for which they need to be aware of the locally prevalent strains and their sensitivity pattern. Since over the last few decades the resistance pattern of urinary isolates has been showing dramatic changes all over the world, it was felt useful to study the existing microbiological pattern of the urinary tract infections in Kashmir valley and to assess the sensitivity profile of the isolated organisms to the generally used antibiotics for empirical therapy in primary health care settings. The retrospective analysis of 324 such samples which were found positive for pathological bacteria by the microbiology laboratory of Government Medical College, Srinagar, Kashmir revealed that 90.12% of the isolates were E coli followed by klebsiella (7.72%) and staphylococcus (1.24%). Significantly 43.57% of the E coli exhibited resistance to the commonly used antibiotics, and the most effective in-vitro agents were found to be amikacin followed by gentamicin among the injectables and ciprofloxacin among the orally administered ones. Other useful oral antibiotics were nitrofurantoin, chloramphenicol and nalidixic acid. The organisms showed resistance to currently preferred urinary antibiotics and chemotherapeutic agents like co-trimoxazole, norfloxcacin, pefloxacin and cephalexin. Conclusion was that among the orally administered antibiotics ciprofloxacin remains the choice while other quinolones or derivatives have turned ineffective and among the injectables gentamicin is still effective.

Urinary tract infection (UTI) is a common ailment and had exceeded in frequency among ambulatory patients only by respiratory and gastro-intestinal infections. Bacterial infections of the urinary tract are the commonest cause of both community acquired and nosocomial infections in patients admitted to American hospitals\(^1\). UTI accounts for about 6% of new consultations in general practice in Europe and Scandinavia\(^2\). Women are especially prone; about 5-6% of all sexually active women have bacteriuria\(^3\), which in them is associated with increased mortality as assessed in life table analysis\(^4\). The cumulative prevalence of asymptomatic bacteriuria in female increases about 1% per decade throughout life\(^5\), why more women acquire bacteriuria with increasing age is not known. In addition to causing considerable discomfort and ill health UTI, overt as asymptomatic, can lead to complications within and outside the urinary tract. In the developing countries, particularly in rural settings, the problem is compounded by the fact that patients are late to seek treatment. At the same time, because of lack of facilities, vast majority of urinary infections are treated empirically and only a small minority can get pre-therapy testing.
The Study

With the objective to have a retrospective study aerobic culture of 1,281 urine samples was undertaken. The samples were received at the microbiology laboratory of the Government Medical College, Srinagar from the outpatients as well as inpatients departments of the SMHS Hospital during the year 1997-98. Subsequent sensitivity testing of the positive isolates was done. The results were recorded, tabulated and interpretation done as required.

Analysis

Pathological microbes were isolated from 324 samples (25.30%) which in the vast majority of cases (90.12%) were E coli, followed in order by klebsiella (7.72%) and staphylococcus (1.24%). Out of the total 201 females testing positive on culture, 94.03% exhibited E coli and 4.48% klebsiella, whereas among the culture positive males 83.75% revealed E coli with as many as 13% showing klebsiella. One case of pseudomonas and two cases of mixed infections (klebsiella and E coli) were detected in males only. About 79.9% (n=259) samples came from the outpatients departments while only 20% (n=65) were sent from the medical and surgical wards of the SMHS Hospital. Majority of E coli and klebsiella isolates had thus come from the outpatients' clinics (Table 1). Of the E coli isolates 43.57% showed resistance to the commonly used antibiotics (Table 2). The highest sensitivity was shown to amikacin followed among the injectables were the gentamicin and among the orally administered antibiotics chloramphenicol, ciprofloxacin, nalidixic acid and nitrofurantoin. In comparison to ciprofloxacin, pefloxacin had a dismal in-vitro performance and the isolates of E coli showed resistance to cephalexin, tetracycline, streptomycin and co-trimoxazole. No strain was sensitive of cephazoline and norfloxacin. Such isolates from the wards and from the females followed the same general pattern while as those from the OPD and male patients, most likely to be complicated, revealed much having sensitivity to antibiotics (Table 3). Of the klebsiella isolates only 37.97% proved sensitive to generally used antibiotics while, as 62.1% were either borderline sensitive or resistant. High degree of sensitivity was shown to amikacin followed by gentamicin, nalidixic acid, ciprofloxacin and pefloxacin. Widespread resistance was evident to all other generally used antibiotics for empirical therapy. Comparative susceptibility of klebsilla is depicted in Table 4.
Table 1  Distribution of cases according to the Organisms Isolated, Sex of Patient and Venue of Referral (n=324)

<table>
<thead>
<tr>
<th>Organisms Isolated</th>
<th>Total</th>
<th>Sex</th>
<th>Venue of Referral</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total</td>
<td>Females</td>
<td>Males</td>
</tr>
<tr>
<td>E coli</td>
<td>292(90.12%)</td>
<td>189(94.03%)</td>
<td>103(83.75%)</td>
</tr>
<tr>
<td>Klebsiella</td>
<td>25 (7.72%)</td>
<td>9(4.48%)</td>
<td>16(13%)</td>
</tr>
<tr>
<td>Staphylococcus</td>
<td>4(1.24%)</td>
<td>3(1.49%)</td>
<td>1(0.81%)</td>
</tr>
<tr>
<td>Pseudomonus</td>
<td>1(0.31%)</td>
<td>0</td>
<td>1(0.81%)</td>
</tr>
<tr>
<td>Mixed (E coli and Klebsiella)</td>
<td>2(0.61%)</td>
<td>0</td>
<td>2(1.63%)</td>
</tr>
<tr>
<td>Total</td>
<td>324(100%)</td>
<td>201(100%)</td>
<td>123(100%)</td>
</tr>
</tbody>
</table>

Table 2  Sensitivity Profile of E coli* and Klebsiella** Isolates to Commonly Used Antibiotics

<table>
<thead>
<tr>
<th>Antibiotic tested</th>
<th>No of sensitive isolates (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>E coli</td>
</tr>
<tr>
<td>Amikacin</td>
<td>141 (163.33%)</td>
</tr>
<tr>
<td>Gentamicin</td>
<td>83 (9.61%)</td>
</tr>
<tr>
<td>Chloramphenicol</td>
<td>58 (6.72%)</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>51 (5.9%)</td>
</tr>
<tr>
<td>Nalidixic acid</td>
<td>49(5.68%)</td>
</tr>
<tr>
<td>Nitrofurantoin</td>
<td>48 (5.56%)</td>
</tr>
<tr>
<td>Pefloxacin</td>
<td>28 (3.25%)</td>
</tr>
<tr>
<td>Cephalexin</td>
<td>17(1.97%)</td>
</tr>
<tr>
<td>Tetracycline</td>
<td>6(0.7%)</td>
</tr>
<tr>
<td>Streptomycin</td>
<td>4 (0.46%)</td>
</tr>
<tr>
<td>Co-trimoxazole</td>
<td>2 (0.23%)</td>
</tr>
<tr>
<td>Cephazoline</td>
<td>-</td>
</tr>
<tr>
<td>Norfloxacin</td>
<td>-</td>
</tr>
<tr>
<td>Total</td>
<td>487 (56.43%)</td>
</tr>
</tbody>
</table>

* E coli isolates tested were 863
** Klebsiella isolates tested were 79
Table 3  Comparative Susceptibility (in Per cent) of E coli in various Groups

<table>
<thead>
<tr>
<th>Antibiotic tested</th>
<th>Overall</th>
<th>Venue of referral</th>
<th>Sexwise comparison</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>sensitivity</td>
<td>OPD</td>
<td>IPD</td>
</tr>
<tr>
<td>Amikacin</td>
<td>28.37</td>
<td>26.77</td>
<td>33.62</td>
</tr>
<tr>
<td>Gentamicin</td>
<td>16.7</td>
<td>18.9</td>
<td>15.52</td>
</tr>
<tr>
<td>Chloramphenicol</td>
<td>11.67</td>
<td>12.86</td>
<td>7.76</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>10.26</td>
<td>10.5</td>
<td>9.49</td>
</tr>
<tr>
<td>Nalidixic acid</td>
<td>9.86</td>
<td>9.71</td>
<td>12.93</td>
</tr>
<tr>
<td>Nitrofurantoin</td>
<td>9.65</td>
<td>9.45</td>
<td>10.35</td>
</tr>
<tr>
<td>Total</td>
<td>487(100%)</td>
<td>373(100%)</td>
<td>114(100%)</td>
</tr>
</tbody>
</table>

Table 4  Comparative Susceptibility (in Per cent) of Klebsiella in various Groups

<table>
<thead>
<tr>
<th>Antibiotic tested</th>
<th>Overall</th>
<th>Venue of referral</th>
<th>Sexwise comparison</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>sensitivity</td>
<td>OPD</td>
<td>IPD</td>
</tr>
<tr>
<td>Amikacin</td>
<td>30</td>
<td>34.61</td>
<td>75</td>
</tr>
<tr>
<td>Gentamicin</td>
<td>20</td>
<td>23.08</td>
<td></td>
</tr>
<tr>
<td>Nalidixic acid</td>
<td>13.33</td>
<td>15.38</td>
<td></td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>10</td>
<td>7.69</td>
<td>25</td>
</tr>
<tr>
<td>Pefloxacin</td>
<td>10</td>
<td>7.69</td>
<td>7.69</td>
</tr>
<tr>
<td>Total</td>
<td>30(100%)</td>
<td>26(100%)</td>
<td>4(100%)</td>
</tr>
</tbody>
</table>

Comments :

UTI in adults is mostly confined to the lower urinary tract and is ascending in nature. E coli has been the predominant organism isolated and no significant change has occurred in this picture over the last so many decades. The researchers who assessed the microbiological pattern of the urinary isolates in the 70s and 80s found that E coli remained the most prominent isolate in acute UTI with an isolation frequency of more than 70% every year. In chronic UTI also E coli remained the most frequent species with isolation rates of 17-37%. During the same two decades some change was seen in frequency patterns of other organisms including staphylococcus, proteus, klebsiella and enterobacterium. Worldwide studies have revealed a preponderance of E coli in urinary isolates in the 70s and 80s and 90s ie, 65.3% in Japan, 69% in Italy, 74% in Sweden, 75% in England and up to 90% in USA. Recent studies in some countries again have indicated that E coli
still remains the most common isolated organism from the uncomplicated UTI ranging from 41.6% in Italy \textsuperscript{12}, 60% in Caudad \textsuperscript{13}, 90% in England \textsuperscript{14} to as high as 94% in Israel \textsuperscript{15}. E coli was the most frequently isolated organism in community infections in England and Ireland \textsuperscript{16} and Zagrab \textsuperscript{17}. A recent American study \textsuperscript{18} showed that the proposition of E coli in the current decade has risen significantly; it accounted for 69% of positive cultures in 1991, which increased to 75% in 1994 and 81% in 1997. In Harare 88.5% of outpatient urinary tract infections showed Gram-negative organisms out of which 40.5% were E coli \textsuperscript{19}. The present study revealed an isolation frequency of 90.12% for E coli, which is not different from that seen in England, Isreal and USA. Because of absence of clinical details it could not be ascertained the proportion of outpatients belonging to complicated UTI nor could it be found the number of uncomplicated UTI sent from the wards. Sexwise break up revealed that E coli was commoner isolate (94.03%) among females as compared to 83.75% from males. Obi et al \textsuperscript{19} in Harare also reports that E coli is more common in females than males. On the contrary klebsiella has been 3 times more commoner in urine of males (13.0%;4.48%) in the present study. Klebsiella has been the second most frequent organism isolated in this study as has been the case elsewhere \textsuperscript{7,8,19}. Many studies \textsuperscript{7,20,21}, in South-east Asia have shown klebsiella to be the most frequent isolate in hospital urinary infections but in this series E coli remained the most frequently isolated organism from the hospital acquired infections also. The results show that in this part of the country the urinary infection is primarily caused by E coli whether in the community (general practice) or within the hospitals. Although the spectrum of pathological bacteria isolated from the urine of patients across the globe remained largely unchanged over the past few decades there have been dramatic changes in the resistance pattern and sensitivity profile in most countries. Fukatsu et al \textsuperscript{14} in Japan who followed sensitivity patterns of the uncomplicated UTI from January, 1988 till December, 1991 found that E coli was sensitive to all drugs except ampicillin, and that klebsiella was highly sensitive to norfloxacin. A similar pattern had been seen by Doi et al \textsuperscript{6} earlier who followed emerging resistance patterns from 1977 to 1984; a decrease in sensitivity of E coli to ampicillin in UTI had been reported by them. Grunneberg \textsuperscript{7} monitoring resistance patterns from 1973-1984 found that sensitivity continued to fall to ampicillin/amoxicillin, nalidixic acid and cephaloridine. Ferry et al \textsuperscript{10} in Sweden observed increasing drug resistance in the isolated strains of E coli strains even to drugs not used for therapy of UTI generally. Schito et al \textsuperscript{12} observed that amoxicillin and norfloxacin were the least active compounds against E coli. Villar et al \textsuperscript{13} reported a widespread resistance of E coli to most common agents used in general practice, and among them quinolones and nitrofurantoin were more prominent. Obi et al \textsuperscript{19} in Harare found that E coli as well as klebsiella were resistant to ampicillin, nitrofurantoin, co-trimoxazole and tetracycline. Finkelstein et al \textsuperscript{15} found high rates of resistance to ampicillin, cephalazolin, cefuroxime, co-trimoxazole as well as the amoxicillin elavulanate combination while the organisms were still sensitive to quinolones and
nitrofurantoin. In the 70s and 80s when almost all antibiotics including penicillin, penicillin combinations, cephalosporins, old and new quinolones, aminoglycosides, co-trimoxazole were effective in uncomplicated UTI\textsuperscript{22} and the general consensus was that all these could be used for empirical or calculated therapy (if a rate of resistance of 10% was acceptable) currently the opinion is that widespread emergence of resistance makes it difficult to suggest empiric treatment of UTI\textsuperscript{15}. This is advisable in places where microbiological pre-therapy analysis is possible at the primary health centre level as in the USA, Europe and Scandinavia. In places like ours where such facilities are available, only inadequately and insufficiently, at the teaching hospitals only, the large majority of the physicians will have to restore to empirical therapy. Singh et al\textsuperscript{23} in North Indian studies found that most of the isolates (63.2%) were resistant to one or more drugs, of which 41% were multidrug resistant. Most were resistant to ampicillin, tetracyclines and trimethoprim. The researchers conclude that there is a high frequency of multidrug resistant strains of E coli in Northern India. And the present study has revealed that our valley shares this resistance pattern. Other than the parenterally administered amikacin and gentamicin, oral ciprofloxacin, presently considered the drug of choice of UTI caused by Gram-positive as well as Gram-negative organisms in Germany\textsuperscript{7}, Harare\textsuperscript{19}, Japan\textsuperscript{14} and Sweden\textsuperscript{22} as the most effective agent. Other useful orally administered drugs could be nitrofurantoin, nalidixic acid and chloramphenicol. It is to mention that organism isolated have shown widespread resistance to amoxicillin/ampicillin, co-trimoxazole and norfloxacin, which evidently cannot be recommended for empirical therapy in the valley. Practitioners need to be kept of the emerging resistance patterns of infectious diseases in a community.

References:


**Measles Vaccine: Over-inflated Coverage Targets:**

Exaggeration of vaccine targets is a common phenomenon in most of the developing world. Most of the government statistics forwarded to the World Health Organization is inflated. However, situation is probably the worst with measles-containing vaccines (as measles vaccine or MMR). Currently, the coverage for measles is the lowest, i.e., about 55%. A comparison of the government reported figures from India since 1985, when measles vaccine was introduced in the Universal Immunization Programme, with the WHO-Unicef evaluation figures is given below:

<table>
<thead>
<tr>
<th>Year</th>
<th>Figures reported in official statistics Of the Government of India (%)</th>
<th>The WHO-Unicef evaluation Figures (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1985</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>1986</td>
<td>68</td>
<td>10</td>
</tr>
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<tr>
<td>2000</td>
<td>89</td>
<td>56</td>
</tr>
<tr>
<td>2001</td>
<td>56</td>
<td>56</td>
</tr>
</tbody>
</table>

Even with universal coverage of measles vaccine, we expect periodic epidemics almost every 3-4 years because of accumulation of susceptible population. With a coverage as low as 55%, what can happen is anybody’s guess. Measles is a very dangerous infection in poor countries because of its direct relation with malnutrition. It affects the undernourished far more adversely. In turn, the infection exaggerates the effects of malnutrition and also exacerbates the condition thus further worsening undernutrition. Post-measles diarrhoea can even lead to blindness because of loss of vitamin A - a fat soluble vitamin lost in diarrheal stools.

Measles vaccine is a heat-sensitive vaccine, and needs to be stored and transported under strict cold chain precautions. There is no doubt that in most of the centres this vaccine is not stored in proper conditions. Once diluted with the solvent the vaccine has to be used within a few hours. Multidose vials especially can prove a big challenge in private since cost is high and no private practitioner is going to discard the diluted vaccine if leftover.

Measles vaccine was introduced in the National Immunization Schedule of the country in 1985. It is recommended to be given once in life at the age of 9 months. This is the time when the neutralizing effect of the transplacentally transferred antibodies has vanished and the infant is susceptible to get measles along with its detrimental consequences. Unlike chickenpox, measles is a serious infection and predisposes young children to diarrhoea, secondary bacterial infections and protein energy malnutrition. Practitioners should see that all children get measles vaccine – a measles-containing vaccine, as MMR – at proper time.

(Ed)

Louis Pasteur
A leaf from the history of medicine

Neelam Bashir

Pasteur was born to a tanner in Dôle on December 27, 1822, and grew up in the small town of Arbois. In 1847 he earned a doctorate at the École Normale in Paris, with a focus on both physics and chemistry.

Becoming an assistant to one of his teachers, he began research that led to a significant discovery. He found that a beam of polarized light was rotated to either the right or the left as it passed through a pure solution of naturally produced organic nutrients, whereas when such a beam was passed through a solution of artificially synthesized organic nutrients, no rotation took place. If, however, bacteria or other micro-organisms were placed in the latter solution, after a while it would also rotate light to the right or left.

Pasteur, Louis

(1822-1895), French chemist and biologist, who founded the science of microbiology, proved the germ theory of disease, invented the process of pasteurization, and developed vaccines for several diseases, including rabies

Pasteur concluded that organic molecules can exist in one of two forms, called isomers (that is, having the same structure and differing only in being mirror images of each other), which he referred to as “left-handed” and “right-handed” forms. When chemists synthesize an organic compound, these forms are produced in equal proportions, cancelling each other's optical effects. Living systems, however, which have a high degree of chemical specificity, can discriminate between the two forms, metabolizing one and leaving the other untouched and free to rotate light.

II WORK ON FERMENTATION

After spending several years of research and teaching at Dijon and Strasbourg, Pasteur moved in 1854 to the University of Lille, where he was named Professor of Chemistry and dean of the faculty of sciences. This faculty had been set up partly to serve as a means of applying science to the practical problems of the industries of the region, especially the manufacture of alcoholic drinks. Pasteur immediately devoted himself to research on the process of fermentation. Although his belief that yeast plays some kind of role in this process was not original, he was able to demonstrate, from his earlier work on chemical specificity, that the desired production of alcohol in fermentation is indeed due to yeast and that the undesired production of substances (such as lactic acid or acetic acid) that make wine sour is due to the presence of additional organisms, such as bacteria. The souring of wine and beer had been a major economic problem in France; Pasteur contributed to solving the problem by showing that bacteria can be eliminated by heating the initial sugar solutions to a high temperature.

Pasteur extended these studies to such other problems as the souring of milk, and he proposed a similar solution: heating the milk to a high temperature and pressure.
before bottling. This process is now called pasteurization.

** III DISPROVING SPONTANEOUS GENERATION **

Fully aware of the presence of micro-organisms in nature, Pasteur undertook several experiments designed to address the question of where these “germs” came from. Were they spontaneously produced in substances themselves, or were they introduced into substances from the environment? Pasteur concluded that the latter was always the case. His findings resulted in a fierce debate with the French biologist Félix Pouchet—and later with the noted English bacteriologist Henry Bastion—who maintained that under appropriate conditions instances of spontaneous generation could be found. These debates, which lasted well into the 1870s, although a commission of the Academy of Sciences officially accepted Pasteur's results in 1864, gave great impetus to improving experimental techniques in microbiology.

** IV SILKWORM STUDIES **

In 1865 Pasteur was summoned from Paris, where he had become administrator and director of scientific studies at the École Normale, to come to the aid of the silk industry in southern France. The country's enormous production of silk had suddenly been curtailed because a disease of silkworms, known as pébrine, had reached epidemic proportions. Suspecting that certain microscopic objects found in the diseased silkworms (and in the moths and their eggs) were disease-producing organisms, Pasteur experimented with controlled breeding and proved that pébrine was not only contagious but also hereditary. He concluded that only in diseased and living eggs was the cause of the disease maintained; therefore, selection of disease-free eggs was the solution. By adopting this method of selection, the silk industry was saved from disaster.

** V GERM THEORY OF DISEASE **

Pasteur's work on fermentation and spontaneous generation had considerable implications for medicine, because he believed that the origin and development of disease are analogous to the origin and process of fermentation. That is, disease arises from germs attacking the body from outside, just as unwanted micro-organisms invade milk and cause fermentation. This concept, called the germ theory of disease, was strongly debated by doctors and scientists around the world. One of the main arguments against it was the contention that the role germs played during the course of disease was secondary and unimportant; the notion that tiny organisms could kill vastly larger ones seemed ridiculous to many people. Pasteur's studies convinced him that he was right, however, and in the course of his career he extended the germ theory to explain the causes of many diseases.

** VI ANTHRAX RESEARCH **

Pasteur also determined the natural history of anthrax, a fatal disease of cattle. He proved that anthrax is caused by a particular bacillus and suggested that animals could be given anthrax in a mild form by vaccinating them with attenuated bacilli, thus providing immunity from potentially fatal attacks. In order to prove his theory, Pasteur began by inoculating 25 sheep; a few days later he inoculated these and 25 more sheep with an especially strong inoculant, and he left 10 sheep untreated. He predicted that the second 25 sheep would all perish and concluded the experiment dramatically by showing, to a sceptical crowd, the carcasses of the 25 sheep lying side by side.

** VII RABIES VACCINE **

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Pasteur spent the rest of his life working on the causes of various diseases—including septicaemia, cholera, diphtheria, fowl cholera, tuberculosis, and smallpox—and their prevention by means of vaccination. He is best known for his investigations concerning the prevention of rabies. After experimenting with the saliva of animals suffering from this disease, Pasteur concluded that the disease rests in the nerve centres of the body; when an extract from the spinal column of a rabid dog was injected into the bodies of healthy animals, symptoms of rabies were produced. By studying the tissues of infected animals, particularly rabbits, Pasteur was able to develop an attenuated form of the virus that could be used for inoculation.

In 1885 a young boy and his mother arrived at Pasteur's laboratory; the boy had been bitten badly by a rabid dog, and Pasteur was urged to treat him with his new method. At the end of the treatment, which lasted ten days, the boy was being inoculated with the most potent rabies virus known; he recovered and remained healthy. Since that time, thousands of people have been saved from rabies by this treatment.

Pasteur's research on rabies resulted, in 1888, in the founding of a special institute in Paris for the treatment of the disease. This became known as the Institut Pasteur, and it was directed by Pasteur himself until he died. (The institute still flourishes and is one of the most important centres in the world for the study of infectious diseases and other subjects related to micro-organisms, including molecular genetics.) By the time of his death in St-Cloud on September 28, 1895, Pasteur had long been a national hero and had been honoured in many ways. He was given a state funeral at the cathedral of Notre Dame, and his body was placed in a permanent crypt in his institute.

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All letters to contributors and editors shall be got appropriately answered. The journal provides a forum to practising doctors to express their views. They form a resource of great experience which needs to be tapped. We welcome articles written by the doctor who is actually practising in the field. They can send us topics of their choice which they would like to see in their journal.