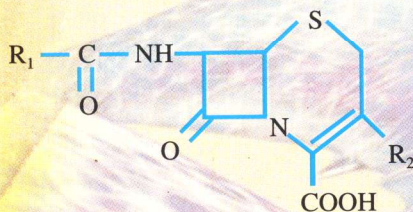


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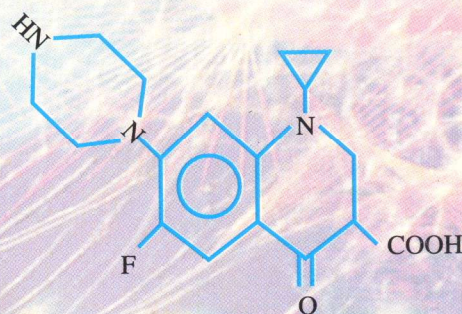
Medical Journal

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INAUGURAL
ISSUE



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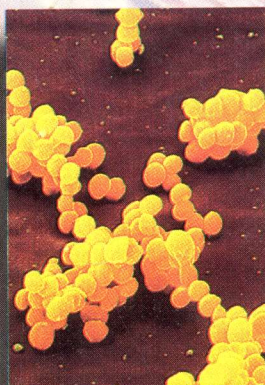
ANTIBIOTIC

a

BACTERIUM
SUSCEPTIBLE
TO ANTIBIOTICS

SOMEWHAT
INSENSITIVE
BACTERIUM

b



Staph aureus



E coli

SURVIVING
BACTERIUM

c

DEAD
BACTERIA

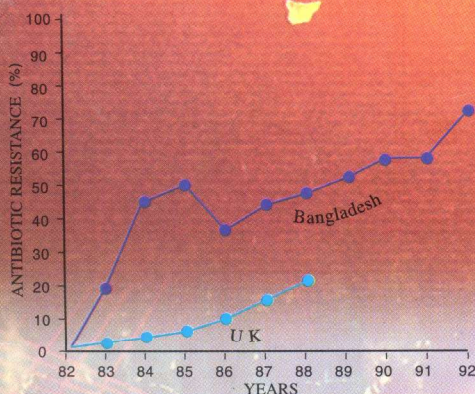
d

BACTERIUM
WITH INCREASED
RESISTANCE

e

HIGHLY
RESISTANT
POPULATION

f



The Growing Antibiotic Resistance:
A Crisis Needs Rational Use of Antibiotics



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F e v a c

Paracetamol (Tablet/Suspension)

F e v a c

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Chief Editor

Dr ATM Azizur Rahman, MBBS

Executive Editor

Dr James Jacob Ribero, MBBS

Editors

Dr Adnan Karim, MBBS

Dr Md Mahmud Hasan, MBBS

Dr Md Javed Sobhan, MBBS

Cover illustration: antibiotic molecules vs resistant pathogens, emergence of antimicrobial resistance and a graphical presentation of antibiotic resistance with time on a background of cellular microarchitecture

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EDITORIAL

This is the maiden issue of "The ORION", the quarterly medical journal of *MEDICAL SERVICES DEPARTMENT* of ORION LABORATORIES LTD. (OLL). The main purpose of the journal is to approach our fraternity in medical profession with the latest developments in the fields of medical practice and research. We offer our best compliments to the esteemed readers. It is a matter of great pleasure for us to have been able to publish this journal against various odds. OLL, a prominent member of ORION group, is one of the fastest growing pharmaceutical companies in Bangladesh. ORION's motto is to provide our compatriots with quality medicine at an affordable price. To ensure the quality of products, it follows cGMP (Current Good Manufacturing Practice) and guidelines set by WHO. ORION is leaving no stone unturned to forge ahead. It is manned by technically qualified, experienced staff, and highly dedicated and skilled workers. ORION has been a regular supplier of medicine to the Government of Bangladesh for quite some time because of its excellent Quality Assurance System. It is going to be ISO 9001 certified very soon.

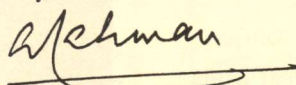
However, ORION has still a long way to go. It has recently set up a new department named *Medical Services Department* or *MSD*. This reflects its social commitment and keenness to operate in close association with physicians; ORION really cares for both doctors and patients. MSD aims at updating medical professionals with useful information on various subjects of medical interest, organizing and sponsoring clinical meetings from time to time, arranging video shows on acute medical emergencies and conducting clinical trials in health care centres and so forth.

In this inaugural issue, we are bringing into focus the problem of antibiotic resistance. Indiscriminate use of antibiotics and patients' non-compliance with dose schedule have given rise to this problem. Furthermore, the use of antibiotics for the purpose of increasing the production of meat in poultry and animal husbandry industries has made the problem all the more acute. Now-a-days the patients are also craving for taking powerful antibiotics with a view to gaining a quick recovery from diseases caused by various infections. Besides, the problem of antibiotic resistance has been further aggravated by the erroneous prescription of multiple and inappropriate antibiotics by non-qualified practitioners.

Let us think of tuberculosis, an endemic disease in Bangladesh. We often encounter this multidrug resistant disease in our clinical practice. Who knows, it may become an all-drug resistant disease some day as its antibiotic resistance grows further. The same thing may happen to other infectious diseases as well. This may render the physicians as well as the general mass hapless to the attack of microorganisms and take us back to pre-antibiotic era when man was absolutely at the mercy of nature.

We are confident that our attempt at highlighting this problem will alert all concerned. This being our first venture, may not be free from mistakes. We hope, all our mistakes would be graciously considered. Any suggestion or recommendation from our readers will be most welcome.

May all our readers be in the best of health and spirit.



Dr ATM Azizur Rahman
Manager
Medical Services Department



ORION LABORATORIES LTD. (OLL) HAS RECENTLY SET UP A NEW DEPARTMENT NAMED MEDICAL SERVICES DEPARTMENT (MSD). MSD STARTED ITS FUNCTION FROM APRIL 1998. MSD HAS IN ITS FOLD QUALIFIED DOCTORS HEADED BY A SENIOR MEDICAL PROFESSIONAL. THE ACTIVITIES OF MSD AS WELL AS THE FUTURE PLANS INCLUDE THE FOLLOWING:

1. Introductory and Orientation Meetings:

MSD has arranged a number of introductory and orientation meetings in different institutions, clinics and hospitals of Dhaka city with the participation of physicians. The participants appreciated these programmes and expressed their interest in the establishment of MSD in OLL.

2. Scientific Seminar:

MSD has started to organize various scientific seminars on current and burning medical topics. Already it has arranged a scientific seminar on Deep Vein Thrombosis at Women's Medical College and Hospital (WMCH), Uttara, Dhaka on June 27, 1998. Dr. Manjur Morshed, FCPS, MRCP, Asst. Prof. of Medicine, WMCH was the key note speaker in this seminar. Prof. MA Mojibul Haq, FRCP, MPhil, Principal of WMCH, Director of the Hospital, faculty members and other doctors were present in the seminar. The seminar was highly regarded by the audience and it helped enrich their medical knowledge.

3. Clinical Trials:

MSD has an ongoing plan of conducting clinical trials in different health care centres. The objective of this trial is to win the confidence of medical professionals in the quality and merit of the products of OLL.

4. Participation in Research Projects:

MSD will participate in research projects in Governmental and Non-governmental organizations of Bangladesh, providing fund and medicine. For this MSD is in contact with concerned physicians in the research projects of respective organizations.

5. Medical Resource Library:

MSD is building up a library consisting of both printed and audiovisual materials to provide recent advances and the latest technological development in various aspects of medical science for the physicians. Already MSD has procured the core books, journals, videocassettes, CD-ROMs etc. and is in the process of expanding the range of collection.

6. MSD and Information Technology

In this era of Information Technology where collection, archiving, retrieval and dissemination of huge informational databases and knowledge bases as well as communications are taking place through Internet ('the network of networks'), MSD is not lagging behind. MSD is already using the facilities of the Internet and is undergoing full computerization.





growing antibiotic resistance

A CRISIS NEEDS RATIONAL USE OF ANTIBIOTICS
Dr M Rahman, Dr ATM Azizur Rahman

Antimicrobial agents are among the most frequently prescribed medications in Bangladesh. Although antibiotic treatment has been of remarkable benefit to many patients, the widespread and inappropriate use of these agents are associated with allergic reactions, toxicities, superinfection and more importantly the development of antimicrobial resistance. Antibiotics are frequently prescribed inappropriately in terms of type, dose, duration and indication. In USA, a study on drug prescribing patterns of internal medicine residents for outpatients showed that 50% of antibiotic prescriptions are inappropriate. McManus *et al* found that antibiotics are inappropriately prescribed for 57-73% of upper respiratory tract infections in Australia. The excessive and inappropriate use of antibiotics add in an unnecessary economic burden to healthcare system and coincides with an increase in drug-resistant organisms, which has resulted in the use of more expensive and toxic drugs. It is known that patients infected with drug-resistant organisms are more likely to require hospitalization, have a longer hospital stay and die. Unnecessary costs of resistance in the USA have been estimated to range from US\$ 75 million to 7.5 billion annually. It is clear that antibiotic resistance is increasing worldwide and common pathogenic bacteria have become increasingly resistant to useful antimicrobials.

In Bangladesh, misuse and waste of antibiotics appear to be frequent. Over-the-counter availability of all types of antibiotics makes the situation worse. Antibiotic prescribing by the physicians appears to be less than ideal. The widespread and inappropriate use of antibiotic results in the development of a progressively antibiotic-resistant microbial ecosystem in Bangladesh. This is clearly indicated by the high prevalence of antibiotic resistance among community-acquired *Shigella*, *Salmonella*, *Vibrio cholerae*, *Escherichia coli*, *Neisseria gonorrhoe*, *Mycobacterium tuberculosis*, *Streptococcus pneumoniae* and *Haemophilus influenzae*

Dr M Rahman, MBBS, MSc, PhD
Dr ATM Azizur Rahman, MBBS, Manager (MSD)

infections in Bangladesh. For example, more than 98% of 243 recent isolates of *Shigella dysenteriae* type 1 in Bangladesh were simultaneously resistant to ampicillin, cotrimoxazole and nalidixic acid and 12% of them were also resistant to pivmecillinum. And more than 78% of *Salmonella typhimurium* isolates from faecal samples were also resistant to ampicillin, chloramphenicol, cotrimoxazole and ceftriaxone.

Antibiotic resistance is also frequent in human gut flora in Bangladesh. A study on children from a rural community of Bangladesh showed that 50% of children has enteric flora resistant to ampicillin, cotrimoxazole and streptomycin throughout the year.

A high prevalence of resistant gut flora in healthy human and probably in animals appears to be the source of antimicrobial resistance genes, the dissemination of which is enhanced by extensive use and misuse of antimicrobial agents and by environmental conditions such as crowding, poor sanitation or contamination of food.

Antibiotic resistant pathogens in Bangladesh

Salmonella typhi
S typhimurium
Shigella dysenteriae type 1
Neisseria gonorrhoeae
Staphylococcus species
Enterococcus species
Mycobacterium tuberculosis
Streptococcus pneumoniae
Plasmodium species
Nosocomial pathogens:
Pseudomonas spp.
Acinetobacter spp.
Klebsiella spp.

Emergence and Spread of Antibiotic Resistance

There are many factors that contribute to the emergence, persistence and spread of resistant bacteria. Selective pressure on microorganisms resulting from imprudent and indiscriminate use of antibiotics in humans and animals is the key factor for the emergence of antibiotic resistance gene among bacterial population. Mobile genetic elements such as plasmid or transposon carries and transports antibiotic resistance gene from one bacterium to

another bacterium of the same or different species or genus (Figure 1).

The intensive use of antibiotics, for treatment and prophylaxis, make hospital a prime site for the emergence, maintenance and spread of resistant pathogens. After discharge of patients from the hospital, resistant pathogens establish a niche in the community

and are transmitted from persons to persons or persons to household pets or vice versa (Figure 2). More than half of the total production of antimicrobials in the world is used in farm animals and in agriculture. All of these uses contribute significantly to the emergence, maintenance and spread of resistant pathogens in the community. Figure 2 illustrates potential interaction between community and healthcare settings in the transmission of resistant pathogens.

Detection of Antibiotic Resistance

Antibiotic resistance in bacteria is commonly detected as a part of standard clinical microbiological procedure for the identification of cause of infection and appropriate treatment. Detection depends on the collection of clinical samples from the patient, and on the isolation, identification and susceptibility testing of the pathogens in good Clinical Microbiology Laboratory by trained personnel in a cost-effective way. A good representative database on the current status of antibiotic resistance among common and important pathogens is essential for the proper treatment of infectious diseases in the country.

Containment of Antimicrobial Resistance

Energetic measures to slow down the emergence and spread of antimicrobial resistance should include programmes on surveillance, education and research on antimicrobial resistance, and regulation of use of antimicrobials in the hospitals and in the community. The efforts include:

- ▶ Detection and awareness of problem of antimicrobial resistance by microbiology laboratory and public media.
- ▶ Surveillance (local, regional and international) on antimicrobial resistance should be established in collaboration with WHO.
- ▶ Antibiotic use guidelines and committee should be developed for each country.
- ▶ Antibiotic use in hospitals should be regulated and rationalized.
- ▶ Detection and targeting the resistance
- ▶ Education on antibiotic resistance to manufacturers, prescribers, dispensers and consumers through continuing education and other means.
- ▶ Vaccines for preventing infectious diseases should be encouraged in all circumstances.
- ▶ Hygiene and sanitation should be improved and practised.
- ▶ Nutritional status should be maintained and improved.

Finally, an international collaboration, for prudent and rational use of antimicrobials in human and animals through more stringent regulations of marketing, sale, use and consumption of these drugs is essential for the prevention and control of antimicrobial resistance among microorganisms. And all efforts to contain the problem must include manufacturers, prescribers, dispensers and consumers of antimicrobial agents to work in a group.

GUIDELINES FOR USING ANTIBIOTICS

1. Diagnose infections first - whether community or nosocomial in nature
2. Isolate or predict infecting pathogen
3. Knowledge about antibiotic susceptibility of the pathogen in the locality, country and region.
4. Consult Clinical Microbiologist for opinion, if necessary
5. Select an appropriate *narrow spectrum*, low-cost, 1st-choice bactericidal drug
6. Prescribe for appropriate duration
7. Ensure adequate concentration at the site of infection
8. Inform patient about potential side-effects

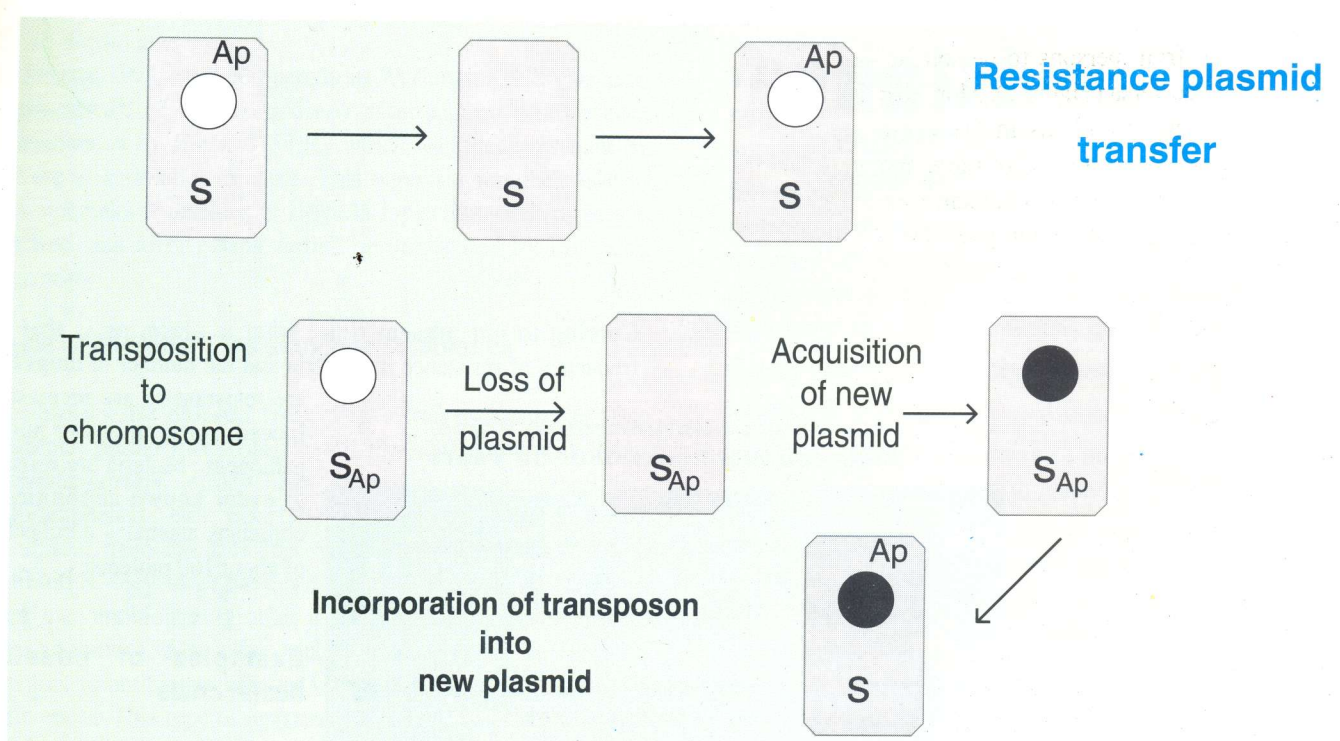


Fig: 1. Resistance spread by plasmids and transposons (*S* = chromosome, *Ap* = ampicillin resistance transposon).

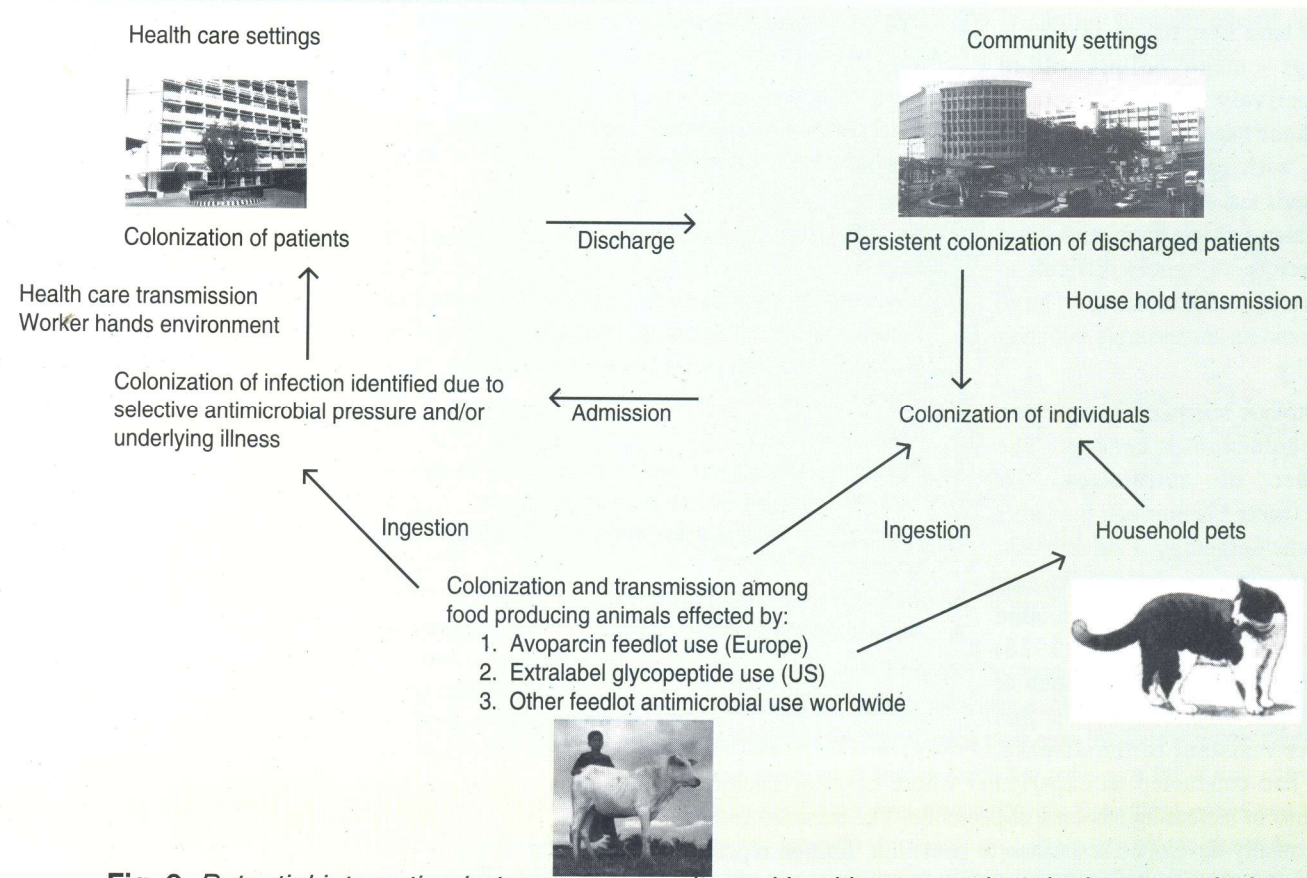


Fig. 2. Potential interaction between community and health-care settings in the transmission

resistance

A GLOBAL THREAT

Dr James Jacob Ribero

Antibiotic resistance is rapidly emerging as a public health issue throughout the world. Mankind has enjoyed about half a century of virtual complete control over pathogenic microorganisms thanks to antimicrobials (antibiotics and chemotherapeutic agents). Ever since their wide availability in 1940s, they have been hailed as miracle drugs – magic bullets able to selectively destroy bacteria without harming human tissue. Yet with each passing decade, bacteria that defy not only a single but also multiple antibiotics – and therefore extremely difficult to control and eradicate – have become an increasingly common reality.

Antibiotic resistance is not a new phenomenon or concept. The father of antibiotics, Sir Alexander Fleming and the father of chemotherapy, Paul Ehrlich, were aware of it. In 1945 Fleming warned that misuse of penicillin (discovered by him in 1928) could lead to the proliferation of mutagen forms of bacteria that were resistant to the disease.

He had conducted an experiment where he grew bacterial strains in increasing amounts of penicillin. The bacterial strains eventually developed resistance to penicillin. Ehrlich reported resistance to chemotherapeutic agents used against trypanosomiasis.

Dr James Jacob Ribero, MBBS, Executive, MSD

Coming to our present time, what is alarming is that the frequency of resistance in bacteria and the number of drugs they

are resistant to are increasing. Indeed, some strains of human pathogenic bacteria are resistant to every known antibiotics in clinicians arsenal – a collection of about 160 molecules.

Microbes vs Antimicrobial Drugs Selected Highlights Over 50 Years

1940s

1. Streptomycin was very effective against TB, but patients relapsed due to rapid emergence of resistance
2. PAS was effective for TB, but rapid emergence of resistance limited its usefulness

1950s

1. *Staphylococcus aureus*, which was usually (80%) sensitive to penicillin, changed to 80% resistance to penicillin via beta-lactamase production
2. Gram negative rods became resistant to streptomycin

1960s

1. Large proportion of meningococci became resistant to sulfonamides
2. Gram negative rods acquired resistance to kanamycin

1970s

1. *Hemophilus influenzae* resistance to ampicillin appeared
2. Pseudomembranous colitis (antibiotics associated) linked to *Clostridium difficile*
3. Some gram negative rods became resistant to gentamicin

1980s

1. Methicillin-resistant *Staphylococcus aureus* (MRSA) became a problem in some hospitals
2. Penicillin-resistant pneumococci became a problem in South Africa and Spain
3. Coagulase-negative staphylococci, half of which are inherently resistant to beta-lactams including nafcillin, became important organisms infecting plastic catheters in people

1990s

1. Penicillin-resistant pneumococci became common in USA; the eighth patient with meningitis due to cefotaxime-resistant pneumococci reported
2. Enterococci with high level of resistance to aminoglycosides and to vancomycin detected
3. Multidrug resistant TB found to be common in some populations
4. Varicella-zoster virus resistant to acyclovir emerged in immunocompromised patients

Examples of possible health crisis

A. *Staphylococcus* infections: In 1952, almost 100% of *Staphylococcus* infections were susceptible to penicillin. By 1982, fewer than 10% of *Staph* cases could be cured with penicillin. The resistance initially was due to one type of resistance mechanism, and alternative drugs were available for it. For example, in the late 1960s, physicians switched to methicillin for *Staph* infection. In the early 1980s, *Staphylococcus* strains were found that were resistant to penicillins, methicillin, nafcillin and cephalosporins. In 1992, roughly 15% of all *Staphylococcus* strains in USA were methicillin resistant. By 1993, only one sure-fire *Staphylococcus* killer remained: vancomycin. However, vancomycin-resistant strains of other bacteria being found, it

was feared that *Staphylococcus* strain would arise that is resistant to vancomycin. Indeed, in 1997 vancomycin-insensitive *S aureus* emerged in three geographically separate places. Fortunately in these cases, *S aureus* remained sensitive to other antibiotics and were eradicated.

B. *E. coli* infections

In January 1993, over 600 people in Washington, USA became seriously ill (3 children died) after eating hamburgers contaminated by *E. coli* 0157:H7 which was made resistant by the use of antibiotics in cattle. This organism was the cause of two outbreaks of diseases in 1996. In Japan thousands of people became sick after eating radish contaminated by the same organism.

Basis of Microbial Resistance to Antibiotics

Antibiotics are derived from certain microorganisms. For example: penicillins from *Penicillium*, cephalosporins from *Cephalosporium*, tetracyclines, aminoglycosides, macrolides, chloramphenicol etc. from *Streptomyces* spp., polymyxin and bacitracin from *Bacillus* spp. Since microorganisms produce antibiotics, they must have a way to protect themselves from their own antibiotics. In other words, they are *resistant* to their own antibiotics. Also other species of microorganisms may be resistant to antibiotics because of the physical and biochemical differences. This type of resistance is called *Inherent* or *Natural Resistance*. Bacteria can develop resistance to antibiotics i.e. bacteria population previously sensitive to antibiotics can become resistant. This is called *Acquired Resistance*. This type of resistance comes from changes in the bacterial genome. Acquired resistance is driven by two genetic processes in

bacteria: a. mutation and selection (*vertical evolution*) and b. exchange of genes between strains and species (*horizontal evolution*).

Vertical evolution is strictly a matter of Darwinian evolution driven by the principles of natural selection: a spontaneous mutation in the bacterial chromosome imparts resistance to a member of the bacterial population. In the selective environment of the antibiotic, the wild type (non-mutants) are killed and the resistant mutant grows and flourishes. The mutation rate for most bacterial genes is approximately 10^{-8} . This means that if a bacterial population doubles from 10^8 cells to 2×10^8 cells, there is likely to be a mutant present for any given gene. Since bacteria grow to reach population densities far in excess of 10^9 cells, such mutant could develop from a single generation during 30 minutes of growth (a typical doubling time for bacteria).

Horizontal evolution is the acquisition of genes for resistance from another organism. For example, a *Streptomyces* has a gene for resistance to streptomycin (its own antibiotic), but somehow that gene escapes and gets into *E. coli* or *Shigella*. Or, more likely, some bacterium develops genetic resistance through the process of mutation and selection and then donates these genes to some other bacterium through one of several processes for genetic exchange that exist in bacteria.

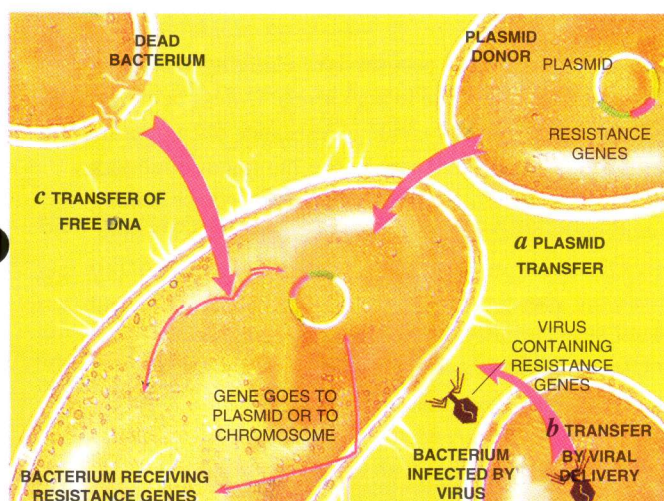


Fig 1. Bacteria pick up resistance genes from other bacterial cells in three main ways. Often they receive whole plasmids bearing one or more such genes from a donor cell (a). Other times, a virus will pick up a resistance gene from one bacterium and inject it into a different bacterial cell (b). Alternatively, bacteria sometimes scavenge gene-bearing snippets of DNA from dead cells in their vicinity (c). Genes obtained through viruses or from dead cells persist in their new owner if they become incorporated stably into the recipients chromosome or into a plasmid

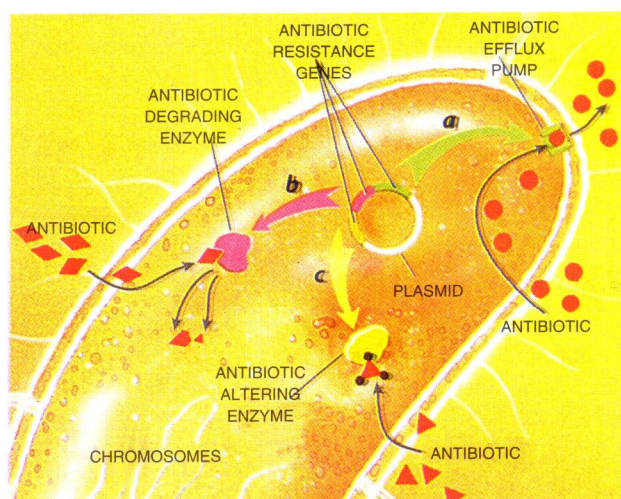


Fig 2. Antibiotic-Resistant bacteria owe their drug insensitivity to resistance genes. For example, such genes might code for "efflux" pumps that eject antibiotics from cells (a). Or the genes might give rise to enzymes that degrade the antibiotics (b) or that chemically alter—and inactivate—the drugs (c). Resistance genes can reside on the bacterial chromosome or, more typically, on plasmids. Some of the genes are inherited, some emerge through random mutations in bacterial DNA, and some are imported from other bacteria.

Bacteria are able to exchange genes in nature by three processes: *conjugation*, *transduction* and *transformation* (Fig 1). Conjugation involves cell-to-cell contact as DNA crosses a sex pilus from donor to recipient. During transduction, a virus transfers the genes between mating bacteria. In transformation, DNA is acquired directly from the environment, having been released from another cell. Genetic recombination can follow the transfer of DNA from one cell to another leading to the emergence of a new genotype (recombinant). It is common for DNA to be transferred as plasmids (a circular strand of DNA) between mating bacteria. Since bacteria usually develop their genes for drug resistance on plasmids (called resistance transfer factors, or RTFs), they are able to spread drug resistance to other strains and species during genetic exchange processes.

The combined effects of fast growth rates, high concentrations of cells, genetic processes of mutation and selection, and the ability to exchange genes, account for the extraordinary rates of adaptation and evolution that can be observed in the bacteria. For these reasons bacterial adaptation (resistance) to the antibiotic environment seems to take place very rapidly in evolutionary time.

Mechanisms of Antibiotic Resistance (Fig 2)

Antimicrobial drugs act at various sites in the microorganisms to inhibit or destroy them; resistance may therefore occur by several mechanisms or their combination. Most commonly these are:

The target site of action of antibiotics in the bacterium may be absent, lost or bypassed e.g. lack of activity of erythromycin or chloramphenicol against *P aeruginosa*; alteration or absence of penicillin binding protein (PBP), the receptor site for β -lactam antibiotics, can cause resistance etc.

Enzymatic inactivation is an important mechanism of drug resistance. It is best illustrated by resistance to β -lactam antibiotics (penicillins and cephalosporins) which are inactivated by β -lactamase, present in the extracellular space in Gram positive bacteria and in periplasmic space in Gram negative bacteria.

The drug may fail to reach its target site because of impaired permeability, enzymatic inactivation or substrate competition. In Gram positive bacteria, the outer membrane is penetrated by passive diffusion while in Gram negative bacteria penetration is facilitated by protein channels called porins. Alterations in porin channel may give rise to antibiotic resistance.

A more recently discovered and important mechanism of drug resistance is *efflux mechanism* in which the antibiotics (e.g. tetracycline, macrolides, norfloxacin) is extruded out from the cell by an energy dependent *efflux pump*.

Principles of Antibiotic Resistance

There are certain underlying principles of antibiotic resistance which will help us understand antibiotic resistance and devise strategy for overcoming it:

1. Given sufficient time and drug use, antibiotic resistance will emerge. There are no antibiotic to which resistance has not eventually appeared. The penicillin-resistant *S pneumoniae* took 25 years to become today's clinical problem. Fluoroquinolone resistant *E coli* took 10 years to emerge clinically. To these we can now add vancomycin-insensitive *Staph aureus* and erythromycin-resistant *Enterobacteriaceae*.
2. Antibiotic resistant pathogens are not more virulent than susceptible ones; the same numbers of resistant and susceptible bacterial cells are required to produce disease. However the resistant forms are harder to destroy. Those that are slightly insensitive to an antibiotic often can be eliminated by using higher doses of the drug; those that are highly resistant require other therapies.
3. Antibiotic resistance is progressive, evolving from low levels through intermediate to high levels. Unless acquired as a transferred genetic element resistance often appears in the form of small increases in the minimum inhibitory concentration (MIC). Fluoroquinolone resistance among *E coli* requires several sequential mutations to reach a high, clinically relevant level. Penicillin-resistant *Strep pneumoniae* emerged after a gradual progression from reduced susceptibility to high level of resistance. These examples reveal an important message: increasing MIC are a marker for future resistance. The few vancomycin-insensitive *Staph aureus* that have been detected are harbingers of future strains with full-blown resistance.
4. Organisms that are resistant to one drug are likely to become resistant to others. The first tetracycline-resistant gonococcus appeared among strains that were already resistant to penicillin. Fluoroquinolone resistance emerged among strains that were resistant to both tetracycline and penicillin. For *Staph aureus*, *Strep pneumoniae* and *Mycobacterium tuberculosis* resistance to any single agent can be used to predict the organisms that are more likely to become resistant to a second or third drug.

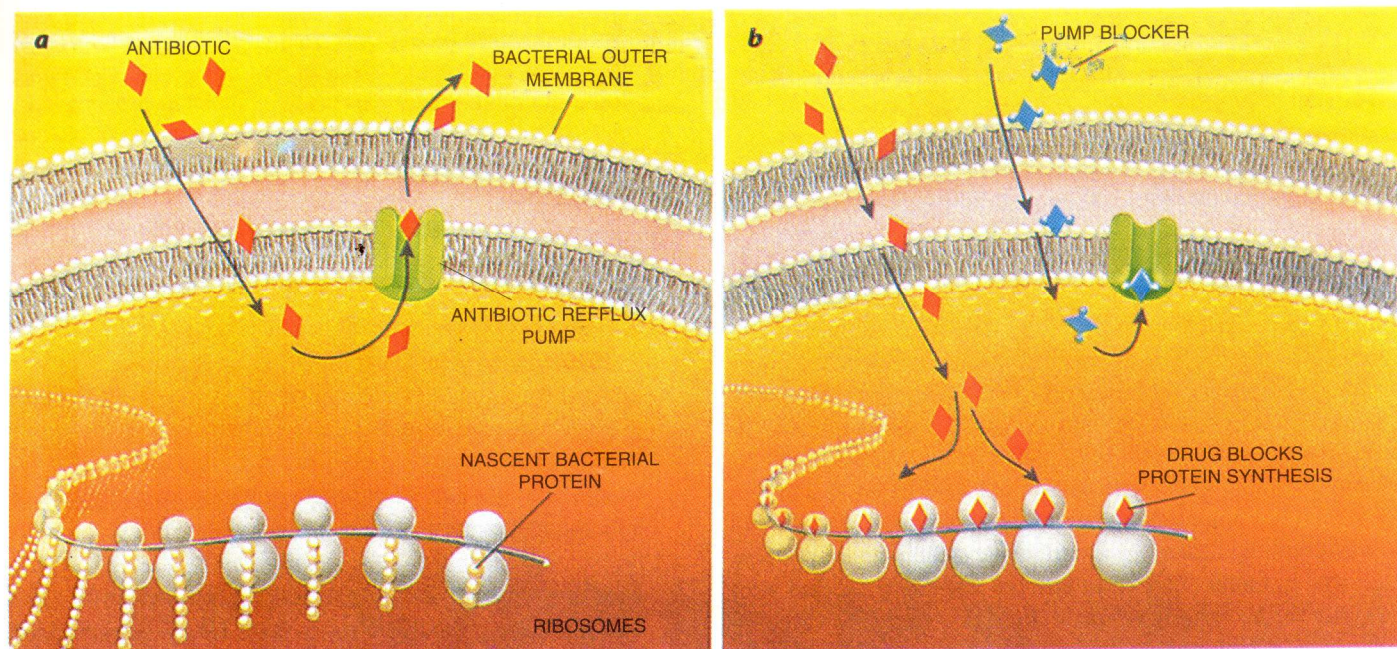


Fig 3. One pharmaceutical strategy for overcoming resistance capitalizes on the discovery that some bacteria defeat certain antibiotics, such as tetracycline, by pumping out the drugs (a). To combat that ploy, investigators are devising compounds that would jam the pumps (b), thereby freeing the antibiotics to function effectively. In the case of tetracycline, the antibiotic work by interfering with the ribosomes that manufacture bacterial proteins.

5. Once resistance appears, it is unlikely to decline slowly, if at all. There are no counterselective measures against resistant bacteria. The slow loss of resistance is linked to poorly reversible genetic and environmental factors.
6. The use of antibiotics by any one person affects others in the extended as well as the immediate environment. For example, housemates of patients treated with antibiotics for acne had large numbers of drug resistant flora on their skin.

New Antibiotics to Combat Antibiotic Resistance

Because of the concern about strains of bacteria that are resistant to all clinically available antibiotics, drug companies are attempting to develop new drugs. Some drugs showing encouraging results are (though most of the drugs will not be available for use until the 21st century):

1. Oxazolidinones

These compounds are structurally different from current antibiotics. They inhibit protein synthesis, but apparently at a different stage than current antibiotics.

2. Pump blockers (Fig 3)

As mentioned earlier, one mechanism of antibiotic resistance involves pumps that remove antibiotics from bacterial cells (e.g. this is the mechanism of resistance against tetracycline). To increase the effectiveness of tetracycline, it may be possible to administer a second drug, one that blocks the pumps so that the tetracycline remains inside the cells, thereby being able to kill them.

Antibiotic Resistance and the Global Community

Antibiotic resistance poses a global threat to humanity. To counteract it, united effort at the international scale is required. Fortunately, the process has already begun.

World Health Organisation (WHO) had from time to time issued various articles, press releases and directives to address the issue of antibiotic resistance. Under the auspices of its Antibiotic Resistance Monitoring (ARM) programme, a system of software called WHONET has been developed by Dr Thomas O'Brien, MD and Dr John Sterling, MD. WHONET is an integrated system for collaborative surveillance of bacterial resistance to antimicrobial agents at local, national and global levels. It allows a network of laboratories to analyse and share description and susceptibility test measurements of bacterial isolates.

Various international organisations such as Alliance for the Prudent Use of Antibiotics (APUA) have been founded to create awareness about the threat of antibiotic resistance among physicians and lay people. Internet has emerged as the media for rapid dissemination of information about antibiotic resistance. Resistance Web, WARN (World Antibiotic Resistance Network), WISARD (Web-based Interpretative System for Antibiotic Resistance Data) etc. are several web-based examples.



Resistance & UTI

Dr Md Firoz Khan

Resistance to antibiotics is a problem that confronts all of us. In the treatment of inpatients and outpatients the frequency of resistance in bacteria and the number of drugs to which they are resistant are increasing. Multidrug resistance marks this decade. Two major factors contribute to antibiotic resistance - the antibiotic itself and the type of resistance traits being selected for. As a further complication, these traits can spread among different bacteria. 14 years ago, a multidrug resistant strain of *Salmonella enteritidis* serotype *newport* associated with hamburger was traced to a farm using antibiotics to promote growth in cattle. This issue has become most relevant with respect to the fluoroquinolones. An expert panel convened by the Food & Drug Administration, USA, recommended caution in the approval of quinolones for use in animals because of the potential consequences for people. These were good reasons for concern. Soon after fluoroquinolones were given to animals in Netherlands, fluoroquinolones resistant appeared in another zoonotic organism *Campylobacter*. With the introduction of quinolones for use in poultry, resistant strains of *Campylobacter* are now appearing in the United States. More importantly *S typhimurium* that is resistant to fluoroquinolones has emerged in Europe. Antibiotic resistance, initially a problem in hospitals in developing countries, today affects the world at large. Some strains of disease-causing bacteria in the United States may now be untreatable, such as the vancomycin resistant *enterococcus*, *Mycobacterium tuberculosis* & *Pseudomonas aeruginosa*. The current antibiotic resistance crisis differs from those of the past because several different organisms are involved and because there are no immediate solutions on the horizon.

The consequences of resistance include higher mortality and greater morbidity, such as neurologic damage in children in whom meningitis is caused by a *pneumococcus* not recognized as resistant. Infections with organisms resistant to antimicrobial agents lead to longer hospitalization and greater expense. For example, the need for valve replacement in patients with enterococcal endocarditis or long resection in those with pulmonary tuberculosis. If an even more virulent organism such as methicillin resistant *Staphylococcus aureus* (MRSA) acquires resistance to vancomycin the consequence will be still more devastating because the alternatives are few or non-existent.

Although the emergence of resistance may be an inevitable result of the use of antimicrobial agents, there is clear evidence

that it did not occur to the degree that it now does. The rates of resistance to antimicrobial drugs are higher for community-acquired *Escherichia coli* in developing countries. Antibiotic resistance in the community is also a growing threat particularly in developing countries and in high risk setting in the developed world. Prolonged, repetitive courses of antibiotics for colds and even otitis media should be discouraged. In addition, there is an urgent need for new antimicrobial agents for use in patients infected with already resistant organism.

New drugs should avoid cross resistance with known agents. The 1990s have brought a world wide resurgence of bacterial and viral disease. An important factor in this phenomenon is the acquisition of antibiotic resistance genes by virtually all major bacterial pathogens. Disturbance of ecosystem has lead to the tremendous increase in the size of population at high risk because of immunocompromise and due to the increased frequency of invasive medical interventions and the prolonged survival of many patients with chronic debilitating disease which thus amplified the problem to one of global dimensions. Recently bacterial strains resistant to all available antibacterial age were identified among clinical isolates of some bacterial species.

During the past decade Gram-positive bacteria have gradually emerged as the most frequent causes of nosocomial disease. These pathogens are specially difficult to treat because of their high frequency of drug resistant traits. Methicillin resistant strains now is up to 60-90% of all isolates of coagulase negative *Staphylococcus*. The most frequent cause of infections by methicillin resistant strain is related to intravascular catheters and prosthetic devices. In large hospital the proportion of methicillin resistant *Staphylococcus aureus* among nosocomial isolates increased from 8% in 1986 to 40% in 1992. The majority of methicillin resistant *Staph aureus* isolates are also resistant to most other antibiotics, necessitating the use of the vancomycin. In 1993, 14% of *Enterococci* isolates from patients in intensive care unit were resistant to vancomycin and 88% of other strain were also resistant to β -lactamase antibiotic, aminoglycoside and fluoroquinolones.

Community acquired pathogens e.g. *Neisseria gonorrhoeae*, *Salmonella*, *Shigella* are emerging as multiple antibiotic resistant. According to WHO, about one third of the world's population is infected with *Mycobacterium*. Each year this disease attacks about 8 million people, 3 million die of it.

Dr Md Firoz Khan, MBBS, MD, Assist. Professor, Dept. of Nephrology, DMCH

Although infection due to the usual strains of tuberculosis have high rates of cure, multidrug resistant strains have emerged in several countries, including USA, with fatality rates of 40-60% with normal immunity and over 80% in immuno-compromised patients. In one particular strain (*W strain*) that is resistant to the most frequently used antitubercular agent, outbreak of multi-drug resistant tuberculosis has been reported.

The transmission of resistant pathogens can be effectively curtailed in a hospital by means of intensive infection control measures, provided these effort include the control of antibiotic use. Special efforts should be made to bring the issue of antibiotic resistance to the attention of clinical microbiologists, government health authorities and physicians. Investment in basic research should be substantially increased. The emergence and spread of resistance pathogens is an environmental problem analogous to other problems in the human environment that threaten health at the end of the 20th century. The frequent misuse of antibacterial agents in clinical practice both in the third world and in the developed nations, and the release of enormous quantities of antibiotic agents in agriculture, fisheries and animal husbandaries, continue to provide favourable conditions for the spread of resistant bacteria. There is need for both more prudent use of antimicrobials and revolution in marketing policies. To bring these problems under control will require international agreement and strengthened alliance among the research, medical and pharmaceutical communities. People should also realize that although antibiotics are needed to control bacterial infections, they can have broad undesirable effects on microbial ecology. They can produce long lasting change in the kinds and proportion of bacteria. The compounds should thus be used only when they are truly needed and they should not be administered for viral infections over which they have no power. Notably many physicians acquiesce to misguided patients who demand antibiotics to treat cold and viral infections. Researchers at the Center for Disease Control and Prevention (CDC), USA have estimated that some 50 million of the 150 million outpatients prescriptions for antibiotics every year are unneeded. Patients often fail to finish the full course of treatment. They then stockpile the left over doses and medicate themselves or their family and friends, in less than therapeutic amounts. In both circumstances the improper dosing will fail to eliminate the disease agent completely and will furthermore encourage growth of the most resistant strains, which may be later difficult to treat.

Resistance can be reversed by a number of corrective measures:

- 1 The public should wash raw fruits and vegetables thoroughly to clear off both resistant bacteria and possible bacterial residence.
- 2 People should maintain improved hygiene.
- 3 Farmers should be helped to find inexpensive alternative for animal growth.
- 4 When the patients receive prescriptions for antibiotics they should be notified to complete the full course of therapy.

- 5 People also should be educated to refrain from demanding antibiotics for colds and other viral infections.
- 6 Physicians, when possible, should try to identify the causative pathogen and drug sensitivity before beginning therapy.
- 7 Physicians should also wash hands after seeing each patient.
- 8 To avoid spreading multidrug resistant infection between hospitalized patients, the affected patient should be placed in separate rooms. Health workers as well as visitors must use gowns and gloves whenever they visit the affected person.
- 9 An international forum should make cooperation among countries around the globe. The forum should also make concerted efforts to educate the world's population about drug resistance and the impact of improper use of antibiotics.

Drug resistance can endanger the life of any patient either acute or chronic infection. Above mentioned recommendations are very much essential for all nephrologists, particularly when dealing with a patient of UTI and renal transplant. UTI is a completely curable disease, if in right time the right antibiotic is used. So it is very much essential to have urine culture & sensitivity report. Incompletely treated UTI will have infection with resistant organism. Acute infection may lead to chronic urinary tract infection and then chronic renal failure. Two decades before, in Bangladesh chronic pyelonephritis was the second common cause of End Stage Renal Failure (ESRF). At present chronic pyelonephritis is down at the bottom of the list. This was probably due to lack of knowledge and awareness of the patient as well as the doctor. Even today many patient occasionally ignore the importance of laboratory support for confirmation of diagnosis and to identify the organism in UTI. All renal transplant patients are immunosuppressed and vulnerable to opportunistic infection. So all nephrologists must be very careful when treating the infection of renal transplant patient. Any resistant organism may lead to either acute or chronic rejection of the graft, thus endanger the life of the graft recipient and destroys all the tenacious effort given by the graft recipient. Resistant tubercular organism is coming forward to a immunocompromised patient. About 20% of renal transplant patient developed tuberculosis in their life, so a bulk of patient may have resistant tuberculosis. Vancomycin resistant peritonitis have been reported in at least 15% of the CAPD (Continuous Ambulatory Peritoneal Dialysis) patients. A variety of other regimens for initial therapy for CAPD peritonitis have been advocated. One regimen is to give a single daily dose of cefuroxime and aztreonam but again this regimen is abandoned due to development of resistant organism peritonitis in follow up cases. All nephrologists dealing with UTI, dialysis related peritonitis and any infection in transplant patient must have culture and sensitivity test and treat with proper dose and duration to avoid drug resistance and thus save the life of patient.

in antimicrobial prescribing

PERSPECTIVE: DRUG RESISTANCE

Dr Md Mahmud Hasan

When one compares the challenges clinicians faced a decade ago in prescribing antimicrobial agents with those of today, many of those same challenges still exist. One of the primary concerns a decade ago was the fear that the widespread use of antimicrobials would lead to the development of resistant bacterial strains. In part, the prediction has come true. Worldwide susceptibility patterns indicate an increasing trend

towards antimicrobial resistant, particularly among Gm(-)ve bacteria. As the spectrum of antimicrobial agents has expanded, the inherent differences in their spectrum now overlap to the point at which numerous agent can be considered equally efficacious for a number of clinical situations. The "drug of first choice" has become the "drug of choice". The consequences of overuse of antimicrobial agents are more than just problematic, since the development of resistance erodes the effectiveness of these agents and since few drugs in development appear to show clinical promise as their replacement. In addition, inappropriate use of antimicrobials can expose patient to unnecessary toxicities and contribute to higher medical costs. Clearly the judicious use of broad spectrum

Table 1
COMMON ADVERSE EFFECTS OF ANTIMICROBIAL AGENTS

<i>Specific Agent/Class</i>	<i>General for Class</i>	<i>Specific for Drug</i>
Antipseudomonal penicillins Carbenicillin, piperacillin, mezlocillin Beta-lactamase inhibitor combinations Ampicillin/amoxicillin/piperacillin	Hypersensitivity reactions: rash - maculopapular, urticarial Diarrhoea	Coagulation defects - inhibit platelete aggregation
Cephalosporins (3rd generation) Cefotaxime, ceftizoxime, ceftriaxone, ceftazidime	Diarrhoea & colitis Allergic reactions	Coagulation defects: Hypoprothrombinaemia
Carbapenems Imipenem/cilastin		Allergic reaction Diarrhoea/colitis
Aminoglycosides Gentamicin, tobramycin, amikacin	Nephrotoxicity Ototoxicity: vestibular auditory	
Tetracyclines (2nd generation) Doxycycline, minocycline	Teeth & bone discolouration Gastrointestinal intolerance Superinfection	Vertigo
Macrolides Azithromycin, Clarithromycin	Gastrointestinal intolerance Diarrhoea	
Vancomycin		Red man syndrom, Phlebitis
Metronidazole		Gastrointestinal intolerance Metallic taste Peripheral neuropathy
Quinolones Ciprofloxacin, ofloxacin, lomefloxacin	Gastrointestinal intolerance Central nervous system effect: Haedache insomnia, agitation, convulsion.	

Dr Md Mahmud Hasan, MBBS, Executive, MSD

antimicrobials is required to preserve long term effectiveness of these agents.

Top priority should be given to the selection of most efficacious agent (the concentration of the drug must reach the site of infection, the concentration at the site of infection should be at least equal or greater than the minimal inhibitory concentration (MIC) of the infecting organism) with secondary concern for the avoidance of toxicity and minimization of costs. The culture and sensitivity results should guide the clinician to continue or alter the empiric drug regimen.

ADVERSE DRUG REACTION

With the increasing use of drugs to promote health and life, there is also an increasing incidence of adverse drug reactions. This increase has occurred because every drug has the potential to produce an adverse response in the patient being treated. Most drugs produce a spectrum of effects that range from the desired and routinely expected response to the unexplained and potentially life-threatening reaction. In all drug therapy, the clinician must weigh the drug's therapeutic effects against its potential adverse reactions.

Antimicrobials may cause a wide spectrum of adverse effect ranging from anaphylaxis with penicillin, aplastic anaemia with chloramphenicol and nephrotoxicity and ototoxicity with the aminoglycosides. It is important for physicians to have knowledge about specific adverse reactions associated with different antimicrobial drug classes, to observe for early signs and symptoms of adverse effect and to take step to prevent or to minimize these undesirable reactions. Table 1 summarizes the major adverse reactions of the specific antimicrobial agents/classes based on frequency or severity.

COMPLIANCE

Failure on the part of the patient to comply with a therapeutic regimen remains the single most important factor in treatment failure. It has been estimated that 125,000 deaths each year are attributed directly to illness caused by patients failing to comply with their prescribed medication regimens. Noncompliance can be manifested by a number of different behaviors, including complete absence of dosing, occasionally missing a dose, systemic deviation in dose taking (e.g., taking a medication once daily instead of twice daily), systemic deviation in timing of a dose (e.g. alternating 14 and 10 hrs intervals for a 12 hrs interval), or occasionally taking an extra dose. Patient compliance with antimicrobial regimens has taken on increasing importance as more patients are discharged early while still requiring antimicrobial therapy.

To maximize compliance, convenient or short course therapies are often recommended. It is a common perception that compliance is inversely correlated with the complexity of a medication regimen. In studies comparing complexity of dosage regimens, compliance generally drops off when medications have to be taken more than once or twice a day. In a study comparing trimethoprim 200 mg prescribed twice daily versus cephalexin 250 mg prescribed 4 times daily for the treatment of urinary tract infection, cure rates were found to be significantly highest in trimethoprim group (93%) than in the cephalexin group (67%) even though the causative agent is sensitive to both. So, clinicians must consider compliance in antimicrobial prescribing.

STRATEGIES FOR IMPROVING COST-EFFECTIVE PRESCRIBING

For economic purposes, the units of cost-benefit are expressed in monetary terms. Cost-effectiveness analysis is used to compare costs and consequences of choices having similar outcomes but not necessarily identical. Costs are measured in monetary terms but outcomes are not. Therefore, in cost-benefit and cost-effectiveness studies, a judgment needs to be rendered regarding the monetary worth of therapeutic outcome differences. Various strategies aimed to achieve cost-effective antimicrobial therapy have been used by hospitals. Some have been used with greater success than others, but each institution has to adopt a program suitable to its needs and available resources.

Early switch to oral agents

Intravenous antimicrobial is inherently more expensive than oral therapy. With the availability of new oral antimicrobial agents that achieve comparable serum concentration, conversion to oral antimicrobials while the patient is still hospitalized is definitely more cost-effective. The clinician should remember that oral antimicrobial agents are generally less expensive than parenteral drugs, are much easier to administer, and can be given as outpatient therapy, thereby decreasing the length of hospital stay.

Alternative Dosing Schemes

The goal of alternative dosing schemes is to improve or maintain efficacy, minimize toxicities, and reduce the cost.

Once daily oral Administration: Once daily oral administration of antimicrobials can improve patient's compliance and reduce the cost of therapy. An antimicrobial agent must have excellent bioavailability to be considered for once daily dosing. Other considerations include the type and site of infection. Oral antimicrobial drugs that can be administered once daily include azithromycin, cefixime, doxycycline and lomefloxacin.

Table No 2
ANTIMICROBIALS WITH GOOD BIOAVAILABILITY

Drug	% of Absorption
Amoxicillin	60
Chloramphenicol	80
Ciprofloxacin	70
Doxycycline	93
Fluconazole	90
Metronidazole	90
Ofloxacin	98
Trimethoprim/Sulfamethoxazole	90-100

Once daily dosing of Aminoglycosides: once daily dosing of aminoglycosides has thought to reduce the emergence of gm (-)ve bacterial resistance as well as decrease the incidence of nephrotoxicity & ototoxicity. Researchers believe that the dose of aminoglycoside rather than the dosing interval determines the efficacy of these drugs. In a large clinical trial, once-daily dosing of amikacin was compared with multiple daily administration of the same total dose of amikacin in treatment of cancer patients with granulocytopenia. The authors reported that the incidence of nephrotoxicity and ototoxicity was comparable and concluded that once-daily aminoglycosides dosing can reduce patient inconvenience and effect cost-savings.

Dose dependent Pharmacokinetics of Antipseudomonal penicillins : Traditionally, these broad-spectrum penicillins have been administered every 4 to 6 hrs apart. At one teaching hospital, a program was instituted to replace the usual 3-4gm dose of mezlocillin every 4 hrs with a 5gm dose every 8hrs, which was later replaced by either 3 or 4gm of piperacillin given every 8 hrs owing to piperacillin's greater activity against *Klebsiella* species. The results showed that 4gm of piperacillin every 8hrs was more effective than 3gm of piperacillin or 5gm of mezlocillin given every 8 hrs. The authors concluded that such modification in dosing can result insignificant cost saving.

Appropriate length of Treatment: Optimal use of antimicrobial agents requires consideration of a number of important factors, including the appropriate length of therapy. Prolonged therapy is not only costly, but also can predispose the patient to unnecessary adverse effects, such as antibiotic-associated colitis. With broad-spectrum antimicrobial drugs, furthermore, inappropriate use of antimicrobial agents may be associated with the emergence of bacterial resistance, which limits the use of certain antimicrobial agents otherwise known as "drugs of 1st choice". Patients infected with resistant microorganisms have been associated with more morbidity, mortality, and cost than patients infected with susceptible strains. The clinician should remember that placing a patient on a prolonged course of antimicrobial therapy is not improving his or her clinical outcome. Instead, it may have a detrimental effect.

Timely use of Culture and Sensitivity Data : Selecting an antimicrobial regimen to treat a patient's infection depends on the clinician's clinical assessment, knowledge of the antimicrobial drugs' pharmacokinetics, and the in vitro activity of the suspected pathogens. Culture & susceptibility tests have been used to substantiate the appropriateness of empiric therapy or to direct the physician to more specific therapy for patient. It is more important that the infecting microorganism be rapidly and accurately isolated and its susceptibility to the various antimicrobial agents be determined. Once the pathogen is identified and its susceptibility known, a suitable narrow-spectrum antimicrobial drug can be used. Changing from a broad-spectrum empiric regimen to a narrow-spectrum antimicrobial drug can result in less potential adverse reactions, more cost-effective therapy, and less chance for selection of bacterial resistance.

ANTIMICROBIAL CONTROL PROGRAMS

The most common method to control the inappropriate use of antimicrobials in hospitalized patients is through formulary control. A formulary is a compilation of pharmaceuticals that reflect the clinical judgement of the medical staff. A formulary is a living document that changes with time. Constant revision is necessary to add new drugs and delete old ones that no longer used. A formulary should minimize duplication of the same basic type of drugs. Only one antipseudomonal penicillin, one first generation cephalosporin and one extended-spectrum third-generation cephalosporin would suffice for formulary inclusion. The status of an antimicrobial should be classified as follows: uncontrolled, monitored and restricted. An uncontrolled antimicrobial is available for use by all physicians, whereas a monitored one is closely scrutinized through the mechanism of drug usage evaluation even though all physicians can prescribe it. A restricted antimicrobial agent is available for use by certain physicians or after consultation with an infectious disease specialist. These drugs are restricted because of unique indications, significant toxicities or costs. The goals of a formulary system are to encourage cost-effective prescribing by physicians and improve the overall quality of medical care for patient.

SUMMARY

Soon after antimicrobial drugs became available, it was recognized that they were being overused and misused. Reasons for concern about the inappropriate use of antimicrobials include the emergence of resistant nosocomial bacteria, which have been identified in every hospital worldwide. The presence of resistance nosocomial bacteria presents the physician with a clinical problem and increases the cost of therapy. It is clear that methods need to be implemented to help physicians improve prescribing of antimicrobial agents.

As health care practitioners in all fields strive to make patient care more cost effective, one observation has become evident: the successfully treated patient consumes fewer resources and subsequently costs the hospital less than an otherwise similar, unsuccessfully treated patient. The goal of year 2000 is to provide optimal, cost-effective care for patients without compromising quality. This goal can be achieved by collaborative efforts of physicians, pharmacists, and microbiologists working together as a team to promote quality patient care.

of Septicaemia in newborns in Dhaka Shishu Hospital

Dr AK Azad Chowdhury, Dr M Mizanur Rahman, Dr AQM Rezaul Karim

Summary

Fifty four blood culture positive septicaemic neonates were studied in the special care baby unit of Dhaka Shishu Hospital. The aim was to find out the predisposing factors, aetiological agents, clinical features of neonatal septicaemia and its outcome.

Poor socio-economic conditions, maternal infections, inappropriate management of labor and lack of care of the umbilical stump appear to be the principal predisposing factors for the development of septicaemia in new born babies. Reluctance to feed, lethargy, apnoeic spells, jaundice, temperature instability, umbilical discharge were the main presenting features. *E Coli* was found in 39% cases, *Staph aureus* in 20.37%, *Pseudomonas* in 14.8% and others in 25.0%.

Improved antenatal care, adequate health education, hygienic baby care practices, early diagnosis and referral, uses of appropriate antibiotics, blood transfusion, and positive change in socio-economic condition of general people can significantly reduce the incidence, mortality and morbidity of neonatal septicaemia.

Introduction

Septicaemia in the new born babies is one of the leading causes of morbidity & mortality in this age. It is more common in the pre-term babies. Socio-economic, demographic and medical significance of this problem is relevant to the under-developed countries like ours. There have been few published reports of neonatal septicaemia

Dr AK Azad Chowdhury, DCH(UK), MRCP (UK), MRCP (IRE), FRCP, Assoc. Prof., Bangladesh Institute of Child Health, Dhaka

Dr M Mizanur Rahman, MD, PhD, Registrar, Dhaka Shishu Hospital

Dr AQM Rezaul Karim, MBBS, Medical Officer, Dhaka Shishu Hospital

in our country. We planned to look into the matter and studied the predisposing factors, aetiological agents, clinical features and outcome of treatment of the septicaemic cases admitted in the special care baby unit of Dhaka Shishu Hospital.

Materials & methods

This study was undertaken in the special care baby unit of Dhaka Shishu Hospital. A total number of 54 cases of septicaemia, confirmed by blood culture, were brought under the study.

Detailed history was obtained from mother or relative accompanying the baby. They were asked to answer a questionnaire which included detailed information about pregnancy, antenatal care, place & mode of delivery, cutting & care of the umbilical cord, first feed, the socio-economic condition of parents and their ages.

Upon admission investigations such as routine blood examination, surface swabs (umbilical, rectal, throat), pus and blood cultures were sent.

Skiagram of the chest was done for cases with respiratory symptoms.

Gestational ages were determined on the basis of mother's last menstrual period and was confirmed by Dubowitz & Parkin scoring system and by the graph of Lubchenko.

Results

Out of 54 babies with septicaemia, 42 (77%) were male and 12 (23%) were female. Twenty three were term and 31 were pre-term (GI-12, GII-13, GIII-6) which is shown in the Table no. 1.

Anamnestic data showing the different unfavourable factors influencing the development of septicaemia in most of the newborn babies are presented in Table no 2.

Laboratory findings: X-ray of the chest shows broncho-pneumonia in 24% babies, anaemia in 31.48%, leucocytosis in 78% with shift to the left in 57.4%, neutropenia in 9 (16.66%) babies.

Table 1

Distribution of Patients with Neonatal sepsis according to sex and age

Babies	Sex	Age at the time of admission in hospital				Total
Gest. ages	M/F	1-7 days	8-14 days	13-21 days	22 days	
(>37 Weeks)	M	9	3	-	2	14
	F	9	-	-	-	9
(35-36 Weeks)	M	6	5	1	-	12
	F	-	-	-	-	-
(32-35 Weeks)	M	5	5	1	-	11
	F	1	-	1	-	2
(<31 Weeks)	M	1	-	4	-	5
	F	1	-	-	-	1
Total		32	13	7	2	54(42/12)

Table No. 2

Different Social, Maternal and Neonatal Factors

Occupation of Parents	:	a. Manual labour / extreme low income group	-	55%
		b. Low income group	-	30%
		c. Moderate & high income group	-	15%
Family size (sibling)	:	a. Large (> 5 sibling)	-	70%
		b. Medium (2, but < 5 sibling)	-	25%
		c. Small (2 sibling)	-	5%
Mother's age	:	a. < 18 years	-	45%
		b. > 30 years	-	11%
Antenatal care	:	a. No care at all	-	35%
		b. Partial care	-	40%
		c. Complete check-up	-	25%
Maternal immunization	:	a. No immunization	-	30%
		b. Partial immunization	-	25%
		c. Complete immunization	-	45%
Maternal illness	:	a. Eclampsia, pre-eclampsia etc.	-	25%
Prolonged rupture of membrane			-	35%
Prolonged 2nd stage			-	50%
Forceps delivery			-	3.7%
Delivery by LUCS			-	3.7%
Twin babies			-	5.55%
Breech delivery			-	5.55%

Table - 3

Presenting Clinical Features	%
Reluctance to feed	- 95%
Temperature instability	-
a. Hypothermia	- 33%
b. Hyperthermia	- 66%
Apnoeic attack with cyanotic spells	- 18.5%
Jaundice	- 37%
Lethargy / Listlessness	- 77%
Skin septic spot	- 11.1%
Respiratory distress	- 14.8%
Convulsion	- 14.8%
Abdominal distension	- 74%
Sclermea	- 14.8%

Table - 4
Bacteriogram

Sl. No.	Organism	% of Cases	No of cases
1.	<i>E coli</i>		39.0% (22)
2.	<i>Staph. aureus</i>	20.37%	(11)
3.	<i>Pseudomonas</i>	14.8%	(8)
4.	<i>Proteus</i>	7.8%	(4)
5.	<i>Flavobacterium</i>	7.7%	(4)
6.	<i>Klebsiella</i>	5.55%	(3)
7.	<i>Strept. epidermis</i>	3.7%	(2)

Escherichia coli, *Staph aureus* and *Pseudomonas* were the predominant organisms in blood culture isolates. Summary of bacteriological findings is shown in the Table no. 4.

Before getting the results of bacteriogram, we used the combination of two broad spectrum antibiotics like ampicillin and gentamicin covering both gram negative & gram positive micro-organisms. After getting results we revised it accordingly. Blood transfusion was given in majority of the cases.

At the moment of admission in DSH the general condition of most of the babies (92.60%) were bad. The first sign of pyo-septic disease appeared in the first week of life in 32 (56%) babies, and in the rest of the babies in the second and third weeks of life.

Reluctance to feed, umbilical discharge, temperature instability, apnoeic attacks, cyanotic spells, jaundice, lethargy, abdominal distension etc. were found to be the cardinal features of neonatal septicaemia. Major clinical features with their incidence is shown in Table-3.

The artificially fed babies had higher mortality than the breast fed ones. The type of feeding is given in Table-5.

The average hospital stay for a septicaemic neonate was about 10 days. The preterm ones had longer stay. Full term breast-fed babies with septicaemia had quicker recovery and stayed in hospital for shorter period suggesting the positive role of breast-feeding.

Fifteen (28%) babies died out of total 54 babies.

Discussion

The study results show that more than half of the babies came from slum areas, with no sanitary facilities. Deliveries conducted at home by untrained dais & relatives in unhygienic surroundings correlated well with the increased incidence of development of septicaemia.

From table No. 1 we can see that pre-term babies were more prone to septicaemia probably because of their immature immunological development. These deliveries were more

common in very young mothers and in complicated pregnancies like eclampsia, pre-eclampsia, maternal diabetes etc. Other important factors for development of neonatal septicaemia were prolonged rupture of membrane, difficult, deliveries, cutting and tying of umbilical cord with unsterile instruments.

Preterm and very low birth weight (VLBW) babies were in poor condition at the time of admission to DSH and they took more time for recovery.

Our result of higher survival rate of the breast fed babies comply with other reports.

The clinical patterns, morbidity mortality and therapy used are similar to these published in other parts of the world. Also aetiologically *E Coli* dominate the picture elsewhere in the world.

Thus the socio-economic condition of parents, maternal diseases, preterm labor and infections in the intrauterine, intranatal and post natal life appeared to be important factors in neonatal septicaemia, Gram negative bacilli and *Staph aureus* appeared to be most important causative organisms in neonatal septicaemia.

Conclusion

High degree of suspicion, use of appropriate antibiotics and repeated small blood transfusion can considerably reduce the mortality of neonatal septicaemia.

Improved antenatal care, better socio-economic condition and education of general population with early diagnosis and prompt treatment can significantly reduce the incidence of mortality due to septicaemia in newborn babies.

Table-5
Feeding Pattern

Sl. No.	Type of Feeding	No. of babies	%
1.	Breast	28	51.85
2.	Breast + Infant formula	22	40.74
3.	Infant formula	4	7.40





Abscess: Review of 24 Cases

AKM Eshaque, Nurun Nahar, M Safiullah

Abstract

Twenty four cases of ileopsoas abscess in children were studied. There were 5 cases of spinal tuberculosis with psoas abscess. One out of the 5 cases had bilateral psoas abscess with destruction of lumbar 3 and 4 vertebra with exposed spinal cord along with paresis of both lower limbs.

Nineteen cases had pyogenic psoas abscess. There were 8 cases of right sided and 6 cases had left sided flexion contracture of hip joint which were corrected by Buck's traction. The treatment and management of all the cases are discussed.

Introduction

Infection in psoas muscle is common in Bangladesh but uncommon in Western countries. Infection occurs due to specific and non-specific organisms. *Mycobacterium tuberculosis* is a common cause. *S aureus*, *E coli*, *S faecalis*, *Pseudomonas aeruginosa*, *Klebsiella oxytoca*, *Clostridium welchii*, *Pasturella multocida* and *Yersinia enterocolitica* are the other possible organisms. Again psoas muscle can also be infected by (1) Suppurative retroperitoneal lymphadenitis, (2) Direct extension of an abscess, (3) Haematogenous spread and (4) Secondary Infection of traumatic intramuscular haematoma. It is not difficult to diagnose the case when patient presented with high temperature, high leucocyte count, high ESR with reduced haemoglobin percentage. Sometimes there is confusion when presented with non-specific febrile illness with mild to moderate rise of leucocyte count. It is challenging when they co-exist with spinal disease. In some series there is increased morbidity and mortality rate especially in debilitated patients with pre-existing disease.

In this country a patient usually does not attend the hospital early. He attends the hospital only when there is complication. In this series most of the patients came from poor families. Early detection and prompt treatment is necessary to cure the patient as well as to avoid further complications. We discuss here the clinical presentation, treatment and management of children presenting with ileopsoas abscess.

Patients and Methods

Twenty four cases of ileopsoas abscess were studied for three years. There were 17 cases from Rehabilitation Institute & Hospital, 5 cases from Rangpur Medical College and 2 were from a private clinic in Rangpur. Age of the patients varied from 1 to 13 years and mean age was 7.45 years (Table-I). There were 21 (87.5%) male and 3 (12.5%) female patients.

After admission detailed history and clinical examination were done. Routine blood and urine investigation, plain X-ray of KUB region and Mantoux test were done in some cases. Culture was also done.

Results

24 cases of psoas abscess with hip contracture (14) were treated. 5 out of 24 cases had spinal tuberculosis and rest 19 cases had non-specific pyogenic infection.

Routine blood investigation revealed 5 cases showing relative lymphocytosis with high ESR (above 50mm/1st hour Westergren Method), 14 cases had high leucocyte count.

Plain X-ray revealed dense psoas shadow. There was destruction of dorsal vertebra 8-9, 9-10 with gibbus at the same level in two cases. One case showed destruction at L₃₋₄. Thirteen cases had right sided, ten cases had left sided & one had both sided ileopsoas abscess. Eight cases had right sided & 6 cases had left sided flexion contracture of hip joint, which varied from 15° to 30° with further range of movement.

Management

Twenty three cases needed surgical evacuation of pus. One case was treated conservatively i.e. with antitubercular drugs. The pus gradually absorbed and swelling subsided within 6 months. One out of 4 cases of spinal tuberculosis with psoas abscess needed extensive surgery i.e. evacuation of pus, curettage of lumbar vertebra with homogenous bone graft to stabilise spine. The patient was kept in body plaster for 3 months. All 5 cases of spinal tuberculosis with psoas abscess received full course of

Dr AKM Eshaque, D Ortho, MS Ortho, Professor of Orthopaedic Surgery, Rehabilitation Institute and Hospital for Disabled, Dhaka

Dr Nurun Nahar, MBBS, Lecturer, Dhaka Medical College, Dhaka

Dr Md Safiullah, FCPS (Med), Professor of Medicine, Dhaka Medical College, Dhaka

anti-TB drugs (Singapore Regimen). Rest 19 cases received broad spectrum antibiotics according to culture & sensitivity report. Wound healed by first intention, contractures were corrected by Buck's traction with gradual increase in weight (from 2 lbs to 5 lbs). High protein diet along with vitamins were provided. Recovery of non-tubercular patient was complete within 15 to 20 days while recovery from tubercular abscess was long, it took upto 10 months in some cases.

Discussion

In this series 24 cases were studied. All were children (21 boys & 3 girls). 5 out of 24 cases had spinal tuberculosis with psoas abscess. One out of five had spinal tuberculosis with bilateral psoas abscess with paresis in lower limbs who had extensive damage of lumbar 3-4 vertebra with exposed spinal cord. 4 cases had flexion contracture to hip joint. (2R, 2L). Ranges of flexion contracture varied from 20 degrees to 30 with further range of movement.

Table-I
Age Distribution

Sl. No.	Age	No.	%
1.	1-5 Years	8	33.3
2.	6-10 "	9	37.5
3.	11-13 "	7	29.16

Table-II
Causative Factor

No. of cases	Name of organism
5	<i>M tuberculosis</i>
14	<i>S aureus</i>
5	Mixed enteric organism

Table-III

No. of cases	Specific/ Non-specific	Psoas abscess	Side of hip contracture	Period of recovery
10	Non-specific	Yes	10 (6R+4L)	15 to 20 days
9	"	"	-	10 to 20 days
3	TB	"	3 (2R+1L)	6 to 7 months
1	"	"	1 (L)	10 months
1	"	"	-	6 months

L. Isabel studied 5 cases of pyogenic psoas abscess which were treated surgically. One out of 5 cases was a child of 12 years old female who had *S aureus* infection and other one had mixed enteric organism infection. The same pathogens were also found in other published series. In Isabel's series there was no flexion contracture of hip joint. 4 cases out of 5 who had tubercular infection were treated surgically and one case treated conservatively. Flexion contracture was corrected by Buck's traction with gradual increase of weight from 2 to 5 lbs.

All the five cases received full course of antitubercular drugs (Singapore Regimen). Blood count and ESR gradually returned to normal. Patients' appetite increased and they started feeling better with increase of body weight one month after getting antitubercular drugs. In this series one case needed evacuation of pus, curettage and homogeneous bone graft (from mother) to stabilize spine.

In Isabel's series one case needed bone graft. In this series one case also needed bone graft. Here body cast was also applied and kept for 3 months. In both cases bone grafts were incorporated. All 5 cases of this series had full recovery within 6 to 10 months. Contracture of hip joint also corrected within 10 to 20 days. 14 cases out of 24 had *S aureus* infection and 5 cases has psoas abscess due to mixed enteric organism. 10 cases of pyogenic psoas abscess had also flexion contracture of hip joint. (SR+4L). All 19 cases also treated by surgical drainage and contracture also corrected by Buck's traction. All the cases (19) of this series became well within 10-20 days. There was no death reported.

In 1881 Mynter studied two cases of pyogenic psoas abscess. He considered this as psoasitis. He drained the pus below inguinal ligament. However in this series 22 cases were drained through petitis triangle and another case through retroperitoneal approach. In 1911 Roger reported seven cases of psoas abscess that originated from lumbar lymphatics. In 1930 Behrman reported 4 cases and in 1950, Zadek reported 7 cases. All were apparently of primary origin. In 1961 Altemeier and Alexander reviewed series of retroperitoneal abscess and postulated direct extension to involve psoas muscle. In this series 5 cases had direct extension from spinal tuberculosis. In Isabel's series all cases presented with fever, leucocytosis and a very high ESR. Diagnosis was established by CT scan. But in one case it failed to identify the pathology.

In this series all cases had fever and high ESR. 5 cases of this series had relative lymphocytosis and the rest had high leucocyte count. All cases of this series got admission late with complications. Diagnosis was done mainly on clinical basis.

Several papers described the use of percutaneous route for drainage of psoas abscess with good result and it may well be a better approach to certain patients. In this series and also in Isabel's series cases were drained on emergency basis as soon as diagnosis was reached. Isabel used a grid iron incision which was used to approach extraperitoneal plane. In this series one case needed retroperitoneal approach and 22 cases needed incision through petitis triangle.

In this modern world major improvement has been established to perform early diagnosis as well as therapeutic facilities for treatment. In spite of these facilities in some series there had been reported mortality rate as high as 100%. Therefore early diagnosis and prompt measure are essential to avoid and to reduce morbidity and mortality rate in children.

BACK to nature

Dr Adnan Karim

The search for medicines from nature is an age-old affair. Many important drugs have been developed directly from nature's substances. For example, taxol and aspirin have come from extracts of bark of yew and willow respectively, and penicillin, cyclosporin and lovastatin from fungi.

In the early nineties, a new technology named combinatorial chemistry which allows diverse chemical groups to be bolted together in different concentrations resulting in the creation of thousands of chemical compounds, seemed to offer a better alternative. However, its success has proved short-lived, as its products have frequently failed to pass laboratory tests for the use of biological function.

Now-a-days, the use of biotechnology has opened new possibilities of extracting medicines from nature. Phytera, a Massachusetts, USA based biotechnology firm, along with few small companies is making the best use of the new tool. With a view to unlocking the biochemical diversity of plants fast enough to keep pace with modern drug development programme, this company is dealing with isolated plant cells in test tubes, preserved in cold glass vials in the laboratory instead of following the traditional and rather clumsy route of processing whole plants. If the growth of an interesting substance is noted, scientists may increasingly grow similar kind of cells from relevant species in a test tube.

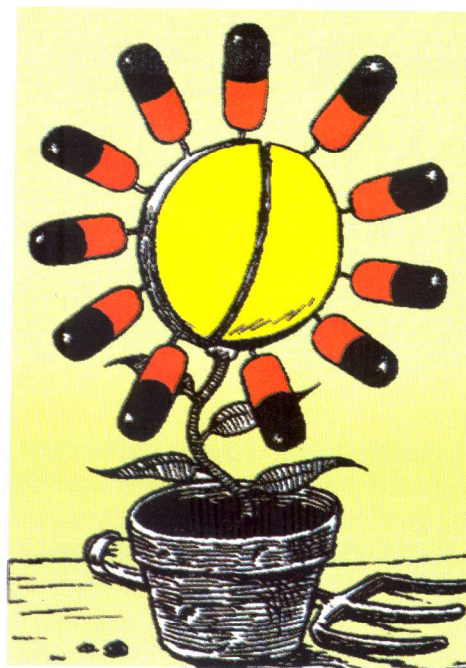
Plants have tremendous capacity to adapt themselves from the extremes of temperature, light or nutrient. Sometimes this happens by the production of important biochemicals. Plants are given vigorous treatment before chemicals are extracted. Suncillin is a newly discovered antifungal agent produced in Phytera's laboratory from cell culture of a plant. That unknown plant produces this agent only when it is

infected with *Candida* yeast and *Aspergillus* mould. The effectiveness of this agent is very encouraging. In one experiment on mice, the efficacy of suncillin superceded that of fluconazole. Another worth-mentioning discovery is Marinovar, an antiviral agent found in a bacterium residing in the seas surrounding California. It has the unique property to overcome drug-resistant viruses.

Apart from this, the numerous microorganisms under the sea and the soil may be very handy to obtain newer pharmaceutical molecules. One problem is that often the microbes resolutely refuse to reproduce.

TerraGen, a Vancouver based company has found a way to overcome the reproductive reluctance of microbes. They incorporated the DNAs of microorganisms into a strain of a bacterium called *Streptomyces* which is a free-growing bacterium acts as a microbial stand-ins, churning out biochemicals that are normally produced by the original soil species. About 20 potential antibiotics are thus isolated from the soils of British Columbia till now. They are also focusing on lichens where symbiosis between fungi and algae takes place. Diversa, a San Diego based company has also been able to find 100 new molecules.

Our flora are also quite rich. We should not also lag behind in the exploration of this exciting possibility.



Dr Adnan Karim, MBBS, Executive, MSD

INTERFERON

therapy in hepatitis C

Dr Md Javed Sobhan

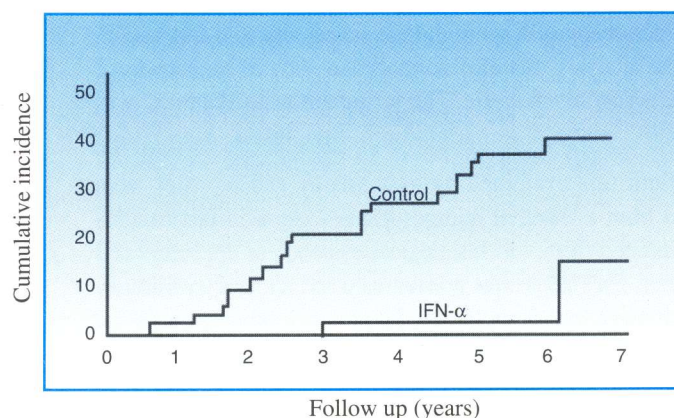
Hepatitis C virus (HCV) was discovered in 1989. Shortly after that, it became clear that HCV had a high prevalence and unusual ability to cause very long-lasting infection. Recently two studies have proposed modifications in the use of interferon in chronic hepatitis C and in patients with HCV cirrhosis.

Patients with chronic hepatitis C may inhibit virus replication, leading to long term remission and eradication of infection in sustained responders after administration of α -interferon. Unfortunately interferon is very expensive and causes serious side effects. However, the main drawback is the low rate of sustained response achieved with standard regimens. Administration of interferon in association with corticosteroids, ursodeoxycholic acid, non-steroidal anti-inflammatory agents and anti-virals (such as ribavarin) have all been enthusiastically explored and larger doses of interferon; the use of titrated doses increases the length of treatment. Chemello reports that administration of interferon for 12 months rather than 6 months reduces the risk of relapse after interferon withdrawals in responding patients. Most of the patients who develop a sustained response have a return to normal of aspartate aminotransferase and a negative HCV-RNA test within 4 to 8 weeks of therapy. Prolonging an expensive and often unpleasant treatment who are not responding does not seem reasonable. Association of ribavarin shows a promising improvement.

Attempts that are taken to differentiate bad from good responders to interferon show the HCV genotype 1b and a high level of viraemia are associated with a poor response. Other factors which are also associated with a poor response include older age, excess body weight, very long lasting infection, high gamma glutamyltransferase concentration,

high serum ferritin or liver iron content and severe hepatic fibrosis or cirrhosis. Therapy should be maintained for at least one year in responders and withdrawn after 3 to 4 months in non-responders. Disappearance of HCV-RNA from the liver in responders after several months of treatment would be the most reliable predictor of no relapse upon discontinuation of therapy. These reports seem against such a restrictive use of α -interferon in chronic HCV infection. Poynard reports that an 18 months administration of interferon produced significant improvement of liver lesions in comparison with shorter period of treatment. Histological improvement was not restricted to the patient with biochemical response. In this study, liver biopsies in 18 months treated group were done at the end of treatment and no information was provided on whether benefit would persist after interferon withdrawal. Terrault believes that this recommendation has many implications in clinical practice that confirmation of the results of this trial is mandatory.

Patients having HCV-induced cirrhosis are thought to be unrewarding candidates for interferon therapy. Nishiguchi observed a decreased incidence of primary liver cell carcinoma and an improvement in liver function in patients who received conventional doses of interferon for 12 to 24 weeks. From this study it has become clear that interferon should be given to patients who have HCV induced cirrhosis.



Cumulative incidence of hepatocellular carcinoma in α -interferon (IFN- α) treated and untreated patients with HCV induced cirrhosis.

Dr Md Javed Sobhan, MBBS, Executive, MSD

Tuberculosis of oesophagus : a rare condition

A 40 year-old man was admitted with progressive dysphagia and epigastric and retro-sternal pain without irradiation. He also suffered from odynophagia, nausea, diarrhoea, generalized weakness and an imprecise weight loss over the preceding months. There was moderate coughing with little sputum, and no other respiratory symptoms, no previous history of tuberculosis and no known contact with a tuberculous environment.

During the previous 15 years, the patient had been admitted to hospital twice: once for acute appendicitis and once because of non-infective diarrhoea. Apart from this, he was in good health.

There is no relevant physical findings at the time of admission, except for generalized weakness. The patient had no fever, a normal blood pressure and a normal pulse. Heart and lung stethoscopies were normal as well.

A radiograph of chest was normal, without enlarged mediastinal glands. Barium meals showed a normal oesophagus, stomach and small intestine. Urography was also normal and an ultra-sound scan of the pancreas, liver and biliary tract showed them to be normal.

Laboratory data showed normal ESR, Hb, WBC count, sodium, potassium, serum albumin and alkaline phosphatase.

Direct microscopy of sputum did not reveal any acid-fast bacilli. The urine analysis was also normal, and showed no growth of *Mycobacterium tuberculosis*. The tuberculin test (Mantoux) was positive.

The patient was examined by gastroscopy and biopsies were obtained from a lesion at mid-oesophagus. An acid-fast bacillus was found and there was histological evidence of epithelioid cell granuloma. The patient was re-examined and another gastroscopy was performed, which confirmed the presence of an ulcer on the anterior wall of the oesophagus merely 30cm from the incisors. The ulceration was described as a 15 x 20 mm irregular crater with a necrotic fibrin coated bottom and destroyed edges. Multiple biopsies were obtained which did not reveal further granulomatous processes, but Ziehl-Neelsen stains showed consistent presence of acid-fast bacilli, and no evidence of malignancy.

Positive growth of *Mycobacterium tuberculosis* was found in the material from the biopsies and also from the sputum. The patient was treated with isoniazid, rifampicin, ethambutol, pyrazinamide and pyridoxin. All the symptoms disappeared after 3 weeks of treatment, but the patient still complained of frequent stools.

The *Mycobacterium tuberculosis* appeared to be sensitive to all antituberculous drugs. Ethambutol was discontinued after 3 months without any evidence of eye lesion. Pyrazinamide was discontinued after 2 months, while the rest of the therapy was continued for approximately 6 months. After 1 year, a new endoscopy revealed a normal oesophagus, stomach and duodenum with a total cicatrization of the former oesophageal ulceration.

Seven years after the 1st diagnostic event, the patient shows no sign of relapse and biopsies from the scarred area show a normal epithelium.

DISCUSSION

Even among patients with cavitating TB, direct inoculation of the oesophagus is rare because of the oesophageal protective mechanisms, including the smooth stratified squamous epithelium, peristaltic cleaning, saliva and rapid transit, which tend to prevent the implantation of the bacilli. Pre-existing oesophageal disease, such as reflux oesophagitis, ulcerations, stricture or carcinoma are considered to be necessary conditions for bacillar implantation and no such condition was demonstrated in the above patient.

Localized TB of oesophagus means there is no evidence of the disease elsewhere. In this case the infection is assumed to arise from the swallowing of tuberculous bacillus.

The pathological types of oesophageal TB are distinct, consisting of either ulcerative or hyper-proliferative tumour-like forms, the ulcerative type being the most common. The diagnosis was supported by clinical suspicion based on patient history and symptoms, and it was verified on endoscopy with biopsies. The patient was completely cured by antituberculous chemotherapy and did not show any relapses during the 7 year follow-up period. Even if the most common manifestation of TB remains the pulmonary form, it is important to remember that rare manifestations also occurs as a localized infestation in other organs, for example in the oesophagus, as the case reported here.

DRUG induced side effects : Gastrointestinal System

Nausea/Vomiting

Digitalis	Theophylline
Opiate	Bromocriptine
Phenytoin	Tetracycline
Oestrogen	Quinidine
L-dopa	

Diarrhoea

<i>GIT Drugs</i>	<i>Chemotherapeutic Agents</i>
Mg-containing antacids	<i>Hypolipidaemic Agents</i>
Laxatives	Clofibrate
Misoprostol	Gemfibrozil
Olsalazine	Lovastatin
<i>Cardiac Drugs</i>	Probucol
Digitalis	<i>Neuropsychiatric Drugs</i>
Quinidine	Lithium
Procainamide	Fluxetine
Hydralazine	Valproic acid
β -blocker	Ethosuximide
ACE inhibitors	L-dopa
Diuretics	<i>Others</i>
<i>Antibiotics</i>	Theophylline
Ampicillin	Thyroid hormone
Cephalosporin	Colchicine
Clindamycin	NSAIDS
Erythromycin	

Constipation

<i>Anticholinergic properties:</i>	Sucralfate
Antidepressant	Iron supplement
Antipsychotic	Ca-channel blocker
Codeine phosphate	Ganglion blocker
Al/Ca-containing antacid	Cholestyramine

Oesophageal Ulceration

Doxycycline	Potassium chloride
Tetracycline	Ferrous sulphate
Clindamycin	Quinidine
Aspirin	Steroids & NSAIDS

Cholestasis

Methyl testosterone	Anabolic steroid
Erythromycin	Busulphan
Nitrofurantoin	Tamoxifen
Rifampicin	Cyclosporine
OCP (norethinordrel with mestranol)	Carbamazepine
Chlorpropamide	Nifedipine, verapamil
Chlorpromazine	Sulindac
	Methimazole

Fatty liver

Tetracycline	Zidovudine
Sodium valproate	Asparaginase
Amiodarone	Methotrexate

Hepatitis

Halothane	Indomethacin
Phenytoin	Diclofenac
Carbamazepine	Sulindac
Methyldopa	Ketoconazole
Captopril, Enalapril	Fluconazole, Atracozazole
Isoniazid	Zidovudine
Rifampicin	Nifedipine
Nitrofurantoin	Verapamil
Chlorthiazide	Diltiazem
Oxyphenisatin	Flutamide (anti-androgenic)
Amitriptyline	
Imipramine	
Ibuprofen	

Mixed Hepatitis/Cholestasis

Azathioprine	<i>Toxic (necrosis)</i>
Nicotinic acid	CCl ₄
Lovastatin	Yellow phosphorous
	Amanita phalloids
	Paracetamol

Granuloma (Liver)

Phenylbutazone	Quinidine
Sulphonamide	Carbamazepine
Allopurinol	

Pancreatitis

<i>Definite association</i>	<i>Probable association</i>
Sulphonamide	Paracetamol
Tetracycline	Nitrofurantoin
Pentamidine	Methyldopa
Thiazide diuretic	Erythromycin
Fruzemide	Salicylate
Oestrogen (OCP)	Metronidazole
Azathioprine	NSAIDS
6-mercaptopurine	ACE inhibitors
Valproic acid	

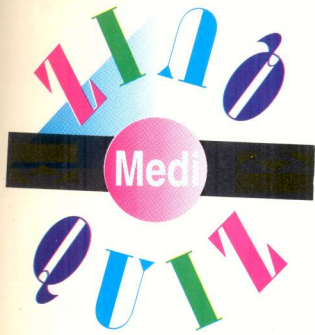
Assessment

INFECTIOUS DISEASE

1. In humans, the pathogenicity of *Hemophilus influenzae* correlates with the presence of:
 - A. A polysaccharide capsule
 - B. An endotoxin
 - C. An exotoxin
 - D. A neurotoxin
 - E. β -lactamase
2. Staphylococcal food poisoning:
 - A. Is synonymous with staphylococcal enterocolitis
 - B. Is produced by a heat-stable enterotoxin
 - C. Develops symptomatology after 48 hours
 - D. Is treated with penicillinase resistant penicillins
 - E. Is associated with high fever
3. Traveller's diarrhoea (turista, Montezuma's revenge) has been most commonly associated with:
 - A. A toxin of *Shigella dysenteriae*
 - B. An enterotoxin of *Vibrio cholerae*
 - C. The endotoxin of *Salmonella typhimurium*
 - D. A plasmid-associated toxin of *Escherichia coli*
 - E. A reovirus-like agent
4. A 14 year old American boy presents with a small scar on his left wrist, a moderate degree of lymphangitis of the left forearm and arm, and slightly tender lymph node in the left axilla. He is febrile and complains of severe arthralgia involving several joints. His hobby is raising small rodents and cats. The most likely diagnosis is:
 - A. Murine typhus
 - B. Cat-scratch disease
 - C. Rat-bite fever (etiology : *Spirillum minor*)
 - D. Ratbite fever (etiology : *Streptobacillus moniliformis*)
 - E. Tularaemia
5. The drugs now used most commonly for initial treatment of tuberculosis include all of the following except:
 - A. Rifampicin
 - B. Streptomycin
 - C. Ethambutol
 - D. PAS
 - E. INH
6. Which one of the following agents has proven effective in the prevention of influenza A?
 - A. Methisazone
 - B. Cytarabine
 - C. Clotrimazole
 - D. Amantadine
 - E. Idoxuridine
7. All of the following statements about botulism are correct except that:
 - A. Deep tendon reflexes are lost
 - B. Ptosis is present
 - C. Respiratory muscle paralysis often occurs
 - D. Symptoms appear 12 to 36 hours after ingestion of contaminated food
 - E. Dysarthria is a common finding

Self-Assessment Answers:

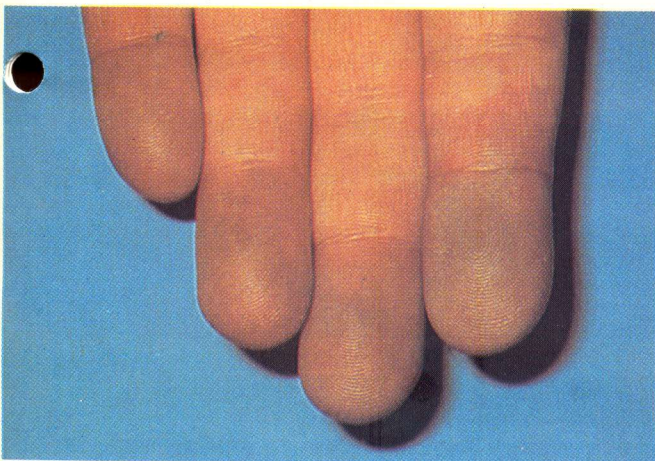
1. A) A polysaccharide capsule
2. B) Is produced by a heat-stable enterotoxin
3. D) A plasmid-associated toxin of *Escherichia coli*
4. D) Ratbite fever (etiology : *Streptobacillus moniliformis*)
5. D) PAS
6. D) Amantadine
7. A) Deep tendon reflexes are lost



1

This patient complains of discomfort in his neck and axillae after drinking alcohol. He has recently become aware of a change in the appearance of his skin.

- What name is given to the abnormal skin appearance?
- What is the most likely underlying disorder?



2

A smoker presented with cyanotic fingertips which later developed gangrene.

What is the diagnosis?



3

This patient's principal complaint is of pains across the shoulder girdle.

- What abnormalities are seen in
 - her hands?
 - her face?
- Suggest two possible diagnoses.



4

This 16-year-old girl presented at the casualty department with an epileptic attack due to failure of drug compliance.

- What is the cause of her epilepsy?
- What other features of this disorder should be looked for?

Please Use the Answer Sheet Opposite Page No. 28



Address

MRCP EXAMINATION

ROYAL COLLEGE OF PHYSICIANS OF EDINBURGH

9 Queen Street
Edinburgh EH2 1JQ
UK
Tel: 0131-225 7324

ROYAL COLLEGE OF PHYSICIANS AND SURGEONS OF GLASGOW

242 St. Vincent Street
Glasgow G2 5RJ
UK
Tel: 0141-221 6072

ROYAL COLLEGE OF PHYSICIANS OF LONDON

11 St. Andrews Place
Regent's Park
London NW1 4LE
UK
Tel: 0171-935 1174

PLAB TEST

Overseas Resistration Division
General Medical Council
178-202 Great Portland Street
London W1N 6JE
UK
Tell: 0171-580 7642

FOR IELTS EXAMINATION

THE BRITISH COUNCIL TEACHING CENTRE

754B Satmasjid Road
Dhaka -1205
BANGLADESH
Tell: 9116171, 9116545
Fax: 880-2-816554

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PATEST

Egerton Court
Parkgate Estate
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Cheshire WA16 7BR
UK
Email: pastest@dial.pipex.com
Tel: 0156-575 5226
Fax: 0156-565 0264

BPP

Medical Education
33 Flower Lane
Mill Hill
NW7 2JG
UK
Tel: 0181-959 7564

CONSULT- ED

Freeport (M28835)
Manchester M20 OPT
UK
E-mail: Grimmers@rapid.co.uk
Tel: 0161-445 5401
0161-434 4825
Fax: 0161-445 8155

FRCA EXAMINATION

ROYAL COLLEGE OF ANAESTHETISTS

48-49 Russell Square
London WC1B 4JY
UK
Tel: 0171-813 1880

MRCGP EXAMINATION

ROYAL COLLEGE OF GENERAL PRACTITIONERS

14 Princess Gate
Hyde Park
London SW7 1PU
Tel: 0171-581 3232



Medi News



ANTI-AIDS GENE THERAPY

A form of gene therapy tested in the best available animal model for human immunodeficiency virus (HIV) infection appears to reduce the pathogenicity of such viruses, report scientists at the National Institutes of Health, Bethesda, Maryland and the Johns Hopkins University School of Medicine, Baltimore, Maryland, USA.

The investigators tested the therapy in rhesus macaques, which develop an AIDS-like disease when infected with simian immunodeficiency virus (SIV). The experimental therapy targets retroviral RNA genes called *tat* and *rev* that code for 2 proteins needed for both HIV and SIV to reproduce in infected CD4 cells. The approach uses antisense RNA, a strand of nucleic acid that corresponds to and binds to genes – in this case, the *tat* and *rev* genes. The resulting double stranded RNA molecule encourages the degradation of SIV RNA and interferes with the ability of the retroviral RNA to direct the production of the 2 key proteins.

Macaques that were given engineered CD4 cell (cells, previously removed from the animals, into which researchers inserted antisense genes targeting *tat* and *rev*) and subsequently infected with SIV showed evidence of only limited SIV replication and less disease progression than was seen in control monkeys. The treated animals also had significantly fewer viruses in both their blood and lymph nodes and, unlike the controls, no decrease in number of CD4 cells.

"We've actually been able to show that in the best animal model for HIV infection, you can indeed stop viruses from replicating, and that can result in sustained CD4 cell counts," said Richard A. Morgan, PhD, who heads the gene transfer technology section at the National Human Genome Research Institute. "If you can maintain a number of CD4 cells that have normal function, if you're producing less virus, that may be of long-term benefit to people infected with HIV."



POTASSIUM AND BLOOD PRESSURE

Dietary potassium in the form of fruits and vegetables or supplements has been shown to lower blood pressure.

In a subset of 300 women in the Nurses' Health Study, potassium emerged as more effective than magnesium or calcium in lowering blood pressure. Women in the study had an average blood pressure of 116/73 mm Hg. Each received a supplement of potassium, magnesium, calcium, a combination of 3, or a placebo. The study authors reported that a daily potassium supplement of about 1600 mg lowered systolic blood pressure by 2 mm Hg and diastolic blood pressure by 1.7 mm Hg. Calcium and magnesium also lowered blood pressure, but the drop was not statistically significant.

Study author Frank M. Sacks, MD, professor of nutrition at the Harvard School of Public Health in Boston, Massachusetts, USA said nurses experienced a minimal effect from potassium because their blood pressures were normal. "But previous studies have shown that potassium in people with high blood pressure has a greater effect of lowering blood pressure from 4 to 5 mm Hg," he said. The study appeared in the January issue of Hypertension: Journal of the American Heart Association.



VITAMIN E AND PROSTATE CANCER

Moderate, daily doses of Vitamin E sharply reduced the risk of prostate cancer in male smokers and also lowered their chances of dying from the disease, according to the latest results from a large prevention trial conducted by the National Public Health Institute (NCI) and the National Public Health Institute of Finland.

In the α -tocopherol, β -carotene Cancer Prevention Study (ATBC study), 29133 Finnish male smokers 50-69 years of age were randomly assigned to receive a 50 mg daily dose of vitamin E (as α -tocopherol), a 20 mg daily doses of β -carotene, both supplements, or a placebo. The latest analysis of the study's findings found that the men who received the daily dose of 50 mg of vitamin E – about 3 times the recommended daily allowance – for 5 to 8 years (and a median of 6.1 years) had one third fewer prostate cancer diagnoses and 41% fewer prostate cancer deaths compared to men who did not receive vitamin E.

"These results give hope that a simple intervention may one day help reduce a man's chances of developing and dying from prostate cancer," said Demetrius Albanes, MD, of the NCI, one of the agency's lead investigators in the study. But other studies are needed to confirm vitamin E's beneficial effected in various groups of patients.

"What may be a beneficial supplement for some people may be harmful to others," he cautioned. Earlier results from the ATBC Study, for example found that men taking the β -carotene supplement had higher risk of developing lung cancer

and dying from the disease. In the current analysis, the investigators found that men taking β -carotene were more likely to develop prostate cancer, but the increase was not statistically significant and was limited to men who drank alcohol.

DRUG RESISTANCE DISCOVERED

Researchers in Canada and the United States have collaborated to discover how strains of ulcer-causing *Helicobacter pylori* have become resistant to the antibiotic metronidazole.

In genetic analyses, the researchers, from Dalhousie University Medical School in Halifax, Nova Scotia and Washington University of Medicine in St. Louis, Montana, USA tracked metronidazole resistance to a mutation in an *H pylori* gene called *rdxA*. The gene codes for a nitroreductase enzyme that allows the bacterium to break down organic nitrogen compounds. So when mutation inactivates the *rdxA* gene, *H pylori* cannot break down metronidazole and resistance occurs.

The researchers also reported that the enzyme for which the *rdxA* gene codes converts metronidazole to hydroxylamine, a mutagen and carcinogen. So if metronidazole is given alone, the resistant strains won't be eradicated and the sensitive strains could contribute to gastric cancer.

The researchers said that their study (in April 14 *Molecular Microbiology*) underscored the importance of combination therapy for *H pylori* infection.

DEAFNESS GENE IDENTIFIED

A team of researchers from Israel and the United States have identified a new gene that, when mutated, causes a form of progressive deafness (*Science* 1998; 279:1950-1954). The mutated gene, called *DFNA15*, was identified in several members of a large Israeli family affected by gradual hearing loss, beginning in their 20s and 30s.

The investigators mapped the newly discovered gene to a region of chromosome 5, near another gene recently found to cause progressive deafness. They found that affected family members, who usually experienced moderate to severe hearing loss by the time they reached their 50s, had a mutation in a gene known to cause progressive deafness in mice. Because the mutation doesn't interfere with normal auditory development and hearing is normal through early adulthood, the hearing loss resembles the age-related hearing loss that many people in the general population experience in their 70s and 80s.

"Discovery of this family offered an opportunity to identify a gene that is important for the maintenance of the auditory system" said Thomas B. Friedman, PhD, of the National

Institute of Deafness and Other Communication Disorders, one of the investigators who collaborated on the study.

NATURAL SELECTION

Genetic disorders have become an area of great interest to medical professionals. Incomplete penetrance, variable age of onset and expression, new mutations are their unique features. Sickle cell anaemia is an autosomal recessive haemoglobinopathy. The patients homozygous for this disease are susceptible to sickle cell crisis. However, heterozygous ones only express sickle cell trait. In sickle cell trait, the faulty haemoglobin somehow inhibits the growth of the protozoal parasite causing malaria – a fatal tropical disease. This protection outweighs the fatalities imposed by the anaemia. Thus sickle allele has been preserved in the population.

Interestingly enough, something similar is true in the case cystic fibrosis. According to the research carried out by Gerald Pies and his colleagues of Harvard Medical School, there is a relationship between *Salmonella typhi*, the bacterium causing typhoid fever and Cystic Fibrosis Transmembrane Conductor Regulator or CFTR, a defective protein responsible for cystic fibrosis. They demonstrated that *S typhi* uses the version of CFTR as an entry point to the infected gut cells. Moreover, they showed that a mixture of a normal and abnormal CFTR are much less likely to be infected.

CFTR sits on the outer membrane of a cell. It helps regulate the passage of chloride ions across the membrane. When it goes wrong the salt balance gets upset. As a result mucus becomes more and more viscous and builds up in gut, lungs and pancreas causing broncho-pulmonary infection, pancreatitis and steatorrhea. It is presumed that *S typhi* has a spot on its surface that binds to a part of CFTR. The anchor probably helps the bacterium penetrate cell membrane more easily. On the contrary changing the chemical composition of the anchor (which is what happens as a result of the faulty gene) prevents it from sticking to it.

To test their presumption, they first selected two sets of cells cultured from a cystic fibrosis patient – one contained only faulty protein while the other was a mixture of normal and defective CFTR. It was found that the mixture took up between two to ten times as many *S typhi* as those without the normal protein.

Afterwards to firm up their findings, they genetically engineered two strains of mice using the same principle mentioned before. The result revealed that those mice with a combination of two genes took 86% fewer bacteria than those who had only healthy genes.

It is really fascinating to note how natural selection has imposed one disease on humanity in order to protect it from another.

**10 SPECIAL
PRIZES FOR
ALL
CORRECT
ANSWERS**

Answer to MediQuiz (page no. 25)

1. a)

b)

2.

3. a) i.

ii.

4. a)

b)

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fold

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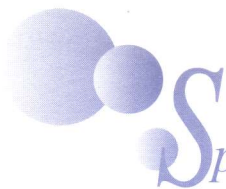
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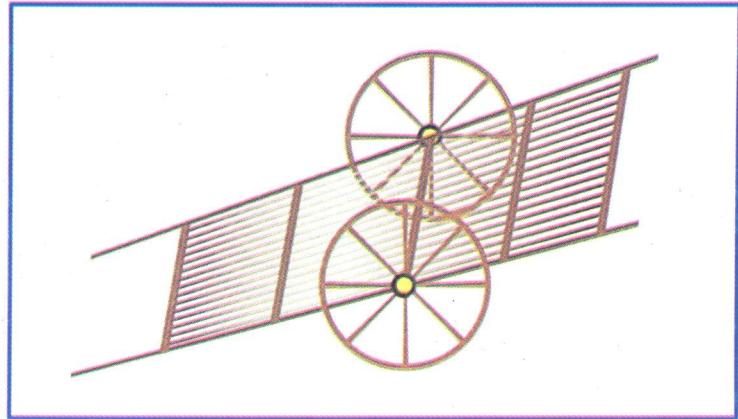
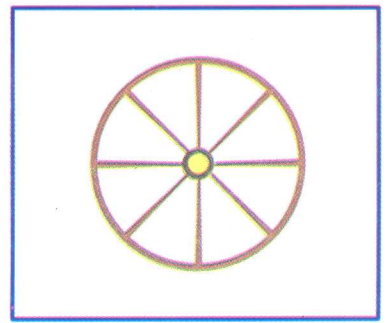
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