Ann Natl Acad Med Sci (India), 34(4): 207-211, 1999

Detection of Japanese Encephalitis Virus Cell Associated Antigen in CSF by Indirect Immunoflourescence

PV Raghava and S Badrinath

Department of Microbiology,
Jawaharlal Institute of Postgraduate Medical Education
and Research, Pondicherry - 605 006.

ABSTRACT

Japanes encephalitis [JE] is a mosquito-transmitted virus disease. A large number of people with JE die during the early phase of illness. We carried out a study for rapid detection of cell-associated antigen in the cerebrospinal fluid [CSF] samples of patients clinically diagnosed to have viral encephalitis. One hundred twenty patients clinically diagnosed as viral encephalitis were included in the study. Fifty five patients with various other illness based on culture and serology were taken as controls. An indiect immunoflourescence test was employed to detect the cell-associated antigen in CSF cells. The cell associated antigen was detected in 53 of the 120 patients clinically diagnosed as viral encephalitis. The distinct advantage of cell-associated antigen detection test is that it could be completed in 2-3 hours. Although the diagnostic value of antigen detection is less than demonstration of IgM antibodies in CSF, it is useful during the first week of illness when IgM antibodies cannot be demonstrated in CSF.

Key words: Japanese encephalitis, cell-associated antigen, CSF, diagnosis

INTRODUCTION

Japanese encephalitis [JE] is the most common form of epidemic viral encephalitis in India and several South East Asian countries (1). Morbidity rate varies from 0.3 to 1.5 per 100,000 population with case fatality of 10%-60% (2). A rapid and definite laboratory test is necssary to identify JE among patients clinically diagnosed as viral encephalitis. Virus isolation and serology are time consuming. Immuno fluorescence assay is a rapid and specific test for virus identification (3). A study was carried out to demonstrate the cell-associated Japanese encephalitis virus [JEV antigen in the cerebrospinal [CSF] cells of patients clinically diagnosed to have viral encephalitis.

Correspondence: S Badrinath, Professor and Head, Department of Microbiology, Jawaharlal Institute of Posgraduate Medical Education and Research, Pondicherry - 605 006, India. Tel 91-413-372380-89, Extn 264/265; Fax: 0413-372067, e-mail: jipmer@ipmer.ren.nic.in

MATERIAL AND METHODS

Patients

One hundred twenty patients clinically diagnosed to have viral encephalitis, aged 2 years to 28 years, admitted to the Paediatrics and Medicine wards of Jawaharlal Institute of Postgraduate Medical Education and Research [JIPMER] hospital, Pondicherry during the period of one year [May '97-April '98] were included in the study. Patients were admitted with moderate to high grade fever, headache, altered sensorium, meningeal signs and convulsions. Altered sensorium was seen in 88 patients [73.3%]. Of these 88 patients, 36.4% of patients had Grade I sensorium, 40.9% patients had Grade II sensorium and 22.7% had Grade III sensorium.

In all the cases CSF was clear, sterile for bacterial and fungal culture. In 18.2% of patients CSF pleocytosis was observed, of which lymphocyte predominance was seen in 81.2% cases.

CSF glucose was mildly elevated [79-136 mg %] in 30.2% of cases, normal [45-72 mg %] in 48.3% of patients and decreased in 23.3% cases. In 59.3% of patients CSF protein was normal [range 15-40 mg %] and increased in 40.5% [range 48-152 mg %]. Signs of meningeal irritation [neck rigidity and Kerning's sign] were seen in 14.8% of the patients. Clinical diagnosis of viral encephalitis was made based upon these data.

Control Group

CSF was procured from 55 patients with various illness such as bacterial meningitis, tuberculous meningitis, herpes encephalitis and non-infectious neurological conditions who constituted the control group.

Cells

Vero cells infected with JEV [P 20778] and positive CSF sample were used as positive control in each batch of the test.

Mouse ascitic fluid

The lyophilised mouse immune peritoneal fluid [M 61107, 84151-1] was obtained from National Institute of Virology, Pune.

Immunofluorescent assay

Aseptically collected CSF samples were subjected to cytocentrifugation at 1000 rpm for 10 minutes. [Sakura Fine Technical Co. Ltd., Japan]. The cell smears were air-dried and fixed in cold acetone for 20 minutes. Indirect immunofluorescence technique was employed to detect the JEV antigen in cells (4).

Briefly, JEV specific immune peritoneal fluid was used at a dilution of [1:10] in phosphate buffered saline. The immunofluorescent antibody titre was determined by using JEV infected vero cells. Goat-anti mouse fluoroscene isothiocyanate [FITC] conjugate [Dakopatts, Netherlands] was used as secondary antibody [1:10 in PBS]. The smears were quenched with 1% Evan's blue to stain the cells to obtain a good background.

The smears were screened using a BHF Fluorescent Microscope [Olympus, Japan]. The smears were graded from [+] to [++++] based upon the percentage of cells showing fluorescence and amount of fluorescence emitted by the cells [Figure 1]. The cells sharing $\geq$ ++ were considered positive Non-specific reaction was ruled out by checking the antibody with normal CSF cells.

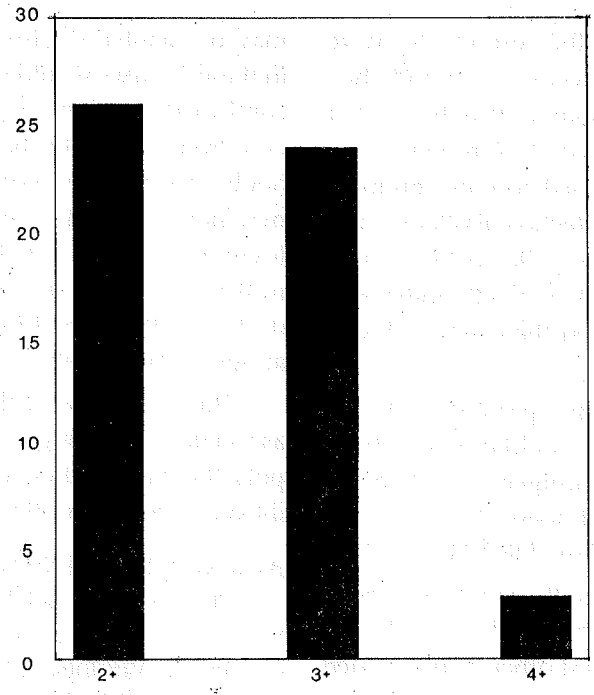

Figure 1. JEV cell-associated antigen grades in CSF cells

RESULTS

Out of 120 CSF sample tested for JEV cell-associated antigen, 53 samples were positive [44.2%] by indirect immuno-flourescence. The infected cells showed extranuclear apple green fluorescence which were clearly distinguished from the uninfected or control normal cells. The duration of fever on admission was available for 76 patients which was in the range of 3-5 days.

Of the 53 patients tested positive for cell-associated antigen in CSF, 10 expired [18.9%] during their hospital stay.

Ten patients [18.9%] were seriously ill during their hospital stay and were taken against medical advice [AMA]. Fourteen patients [26.1%] who recovered had neurological deficit at discharge.

DISCUSSION

Japanese encephalitis is prevalent in and around Pondicherry (5,6). The mortality in this disease varied from 20%-40% in different parts of India (7).

Immunoflouresence was introduced Coons et al in early 1940 (4). After the development of non-destructive conjugation of FITC to antibody, its use has considerably broadened in diagnostic virology (8).

In the present study we have used indirect immunoflouresence test to detect cell-associated JEV antigen in human CSF cells using polyclonal antibodies raised in mice. In 53 out of 120 cases [44.2%] JEV antigen could be detected in CSF, while in the remaining 67 [55.8%] which were clinically diagnosed as viral encephalitis were negative for JEV antigen.

In ten patients the test results were inconclusive [fluoroscence <++] and they were considered negative. It is likely that these are cases of secondary response i.e., they have been exposed to other group B viruses prior to the infection. Earlier studies have shown that West Nile and Dengue 2 viruses are prevalent in South India and these could have been the cause of broad antibody response (9).

The findings of the present study are comparable with those of Matur et al, 1990, where JEV specific antigen was detected by indirect immunofluoescence technique in 15 out of 31 patients [48.4%].

Negative test results could have been due to following reasons. Firstly, clinical presentation of several other diseases such as encephalitis caused by other viruses, cerebral malaria, tuberculous meningitis may reresemble JE (10) and the diagnosis in these 67 cases would have probably been confirmed if other diagnostic tests were employed. Secondly, the method used may not be sensitive. Secondly, the method used may not be sensitive enough to detect the level of antigen or JEV would have multiplied with in the CSF cells and destroyed them resulting in the absence of antigen bearing cells (11).

Thus, detection of the presence of cell-associated JEV antigen in CSF cells using polyclonal antibodies seems to be a rapid, inexpensive diagnostic procedure.

ACKNOWLEDGEMENT

The authors wish to thank Dr G Sridharan, Professor and Head, Department of Clinical Virology, CMC, Vellore for the help rendered by him for carrying out this study.

REFERENCES

1. Umenai T, Krzysko R, Bektimirov TA and Assaad FA (1985). Japanese encephalitis: Current world wide status. *Bull World Health Organ* **63**:625-31.
2. Banerjee K (1988). Epidemiology of JE in India. In: Proceeding of the workshop on Japanese encephalitis, 18-22 January. New Delhi: National Institute of Communicable Diseases, 20-35.
3. Gardner PS and Mcquillin J (1980). Rapid virus diagnosis-application immuno-fluorescence, 2nd edition. London: Butterworths, 3.
4. Liv C (1956). Rapid diagnosis of human influenza infections from nasal smear by means of fluorescent labelled antibody Proc Soc Exp Med **50**:1743-52.
5. Lepeysonnic L and Gobalakichenin S (1958). Japanese B Encephalitis in Pondicherry. *J Indian Med Assoc* **29**:1-6.
6. Namachivayam V and Umayal K (1984). Profile of 1981 epidemic of encephalitis in South Arcot District of Tamil Nadu. Proceedings of National Conference on Japanese Encephalitis. New Delhi: Indian Council of Medical Research, 30-33.
7. Rodrigver FM (1984). Epidemiology of Japanese encephalitis in India. A brief overview. In: Proceedings of the National Conference on Japanese encephalitis. New Delhi: Indian Council of Medical Research, 1-9.
8. Riggs JL, Sciwald RJ, Burckhalter JH, Downs CM and Metcalf TG (1958). Isothiocyanate compound as fluorescent labelling agents for immune sera. *Am J Pathol* **23**:1081-1097.
9. Badrinath S and Sambasiva Rao R (1989). A serological study of Japanese encephalitis and related flaviviruses in and around Pondicherry, South India. *Natl Med J India* **2(3)**:122-125.

10. Gourie-Devi M (1984). Clinical aspects and experience in the management of Japanese encephalitis patients. In: Proceeding of the National Conference on Japanese encephalitis. New Delhi: Indian Council of Medical Research, 25-29.

11. Anita D, Chandramuki A, Gowri-Devi M, and Ravi V (1994). Detection of Japanese encephalitis virus antigen in the CSF using monoclonal antibodies. *Clin Diagn Virol* **2**:191-199.

Ann Natl Acad Med Sci (India), **34(4)** : 213-223, 1998

Advanced Breast Cancer : Current Status in Management – a Personal Experience in Indian Scenario

Anand Kumar

Professor of General Surgery, Institute of Medical Sciences, Banaras Hindu University, Varanasi - 221 005.

INTRODUCTION

It is a privilege and honour to me to have been awarded this prestigious Glaxo Oration of the National Academy of Medical Sciences for the year 1997. I am grateful to the Governing body of the Academy for the confidence bestowed on me to deliver the oration on one of the common problems of the country as well as of the globe i.e., advanced breast cancer. I have been involved in the study of various aspects of this disease and would like to highlight on the following issues.

Advanced breast cancer - its definition, scenario of beast cancer in Indian population with emphasis on clinical presentation, its problems, management objectives, management options i.e., various protocols, extent of surgery and the results, management problems e.g., cost vs. benefit, newer drugs vs. conventional drug.

When to treat, how long to treat and how to treat or not to treat at all.

Personal experiences of treating locally advanced breast cancer, quality of life assessment, thrombasthenia, a new side effect of cancer chemotherapy and assessment of prognostic parameter in Indian patients.

Advanced breast cancer incorporates:

1. Locally advanced breast cancer [LABC]
2. Inflammatory breast cancer
3. Metastatic breast cancer
4. Recurrent breast cancer

Stage wise, it is IIIa-IIIb, inflammatory carcinoma and stage IV disease. The classification incorporates different therapies from such groups of advanced breast carcinoma with varying prognosis. Stage IV disease is referred to as metastatic breast cancer and has different management policy than LABC. Recurrent breast cancer may be grouped with metastatic breast cancer. Similarly, though inflammatory breast carcinoma has certain peculiarities with reference to diagnosis and prognosis, it has been grouped in LABC.

Glaxo Oration of the National Academy of Medical Sciences, 1997.
Correspondence: Prof Anand Kumar, MS, FAMS, Professor of General Surgery, Institute of Medical Sciences, Banaras Hindu University, Varanasi - 221 005.

EPIDEMOLOGY

Nearly 75-80% cases of breast carcinoma in developing countries are advanced at the time of presentation contrary to developed countries (1). The overall incidence of breast carcinoma is 30% of all female malignancies and it accounts for 10% of all cancer deaths in females. In western population, the observation that 1 in 9 women are likely to develop breast cancer during their life time, suggests the magnitude of the problem. Nearly 48% new cases are likely to occur in patients more than 65 year of age. Screening for breast cancer is associated with early detection and better prognosis. But according to NIH Survey [1992], 27% of elderly women in advanced countries did not have adequate screening. The patients denied screening are likely to develop breast cancer, of which 50% had either stage III or IV disease (2). Another remarkable fact in this reference has been that the relapse after adjuvant treatment is more aggressive and carry a poor prognosis (3).

Bloom et al (4) quoted the survival statistics of untreated patients. Mean survival is reported as 38.7 months. Fifty per cent of patients die by 2.7 years, 82% die by 5 years and 96% by 10 years. Nearly 75% of patient had ulcerated lesion at death and 25% had chest wall erosion. Early detection causes 40% reduction in advanced cases and 30% increase in survival.

Unfortunately statistics in our country are sparse and the age adjusted reported incidence is 28/100000 new cases per year (5). Seventy five per cent of these cases are either locally advanced or disseminated. In Banaras, the hospital statistics suggest that breast cancer accounts for 11-15/1000 admissions. The various factors for the cases to have advanced disease at presentation include ignorance, fear, denial, socio-economic factors and illiteracy. The worst factor has been the practice of various systems of medicine actively being practiced in the country. The myths and beliefs of practice of such medicine need to be addressed at all levels so as to bring down the incidence of advanced disease at presentation. Lack of screening programmes, health education are also accountable for such problems in the country.

Besides the epidemiological problems, the patients in this country face the overwhelming problem of adequate treatment even for those presenting at a relatively early stage. The concept of multimodal treatment though known to medical fraternity, is not being practiced or offered to patients for several reasons. One of the important factor has been non-availability of resources and the cost of the treatment. Neither the agencies involved in patients care nor the patients at large can afford the cost of adequate treatment, and are responsible for relapse, advanced disease and high mortality.

MANAGEMENT OBJECTIVES

Advanced breast cancer has a different objectives as regards its treatment. Broadly the objectives are classified as:

a. Palliation [*not cure*] including improvement in quality of life
b. Increased disease free survival
c. Balancing effect of treatment versus toxicity

The questions "whether to treat or not to treat at all", if "yes" how much and how long to treat? should also be addressed. The philosophy of treatment ought to be more subjective and should be more individualised than generalised in third world countries. The treatment should be directed towards comprehensive care and not towards terminal care. The phenomenon of comprehensive care demands contributions from family, fraternity [medical], friends and ignorance on anybody's part would lead to failure of management objectives.

Increase in disease free survival

Five-year survival in stage III disease before the concept of neoadjuvant therapy was only 30%. The break-up of disease free survival [DFS] with the advent of neoadjuvant chemotherapy has been shown in Table 1.

Table 1. *Break-up of disease free survival with the advent of neoadjuvant chemotherapy*

DFS	Stage IIIa	Stage IIIb
5-year DFS (%)	80	45
10-year DFS (%)	64	28

DFS = disease free survival

Let me address the philosophy of treatment in advanced breast cancer. Though multimodality treatment has been advocated using anthracycline based chemotherapy with above quoted response, in India, in my personal experience, only 10% of the patients could afford or accept the anthracycline based chemotherapy. The fate of the remaining 90% patients remains still gloomy. The aim is to treat as best as possible considering cost vs. effective therapy. In this regard CMF combination seems appropriate in the Indian setting, though response is nearly 10%-15% less than anthracycline based chemotherapy. The treatment is affordable, acceptable and has appropriate response.

Question of how much to treat is totally governed by several clinical and investigatory parameters and should be purely individualised. No strict general policy could be adopted in the Indian setting. The treatment with a rational approach which fulfills the objectives of management is advocated for Indian patients.

Palliation and not cure

Cure in breast cancer is only known for patients detected and treated in early stage. In advanced breast carcinoma the objective is not to cure the disease but to provide relief from symptoms, make the patient acceptable to society and rehabilitation. Palliation virtually is the major objective of management of advanced breast cancer. It is agreed that survival longevity without comforts and function would not be tenable. In order to have an effective palliation, the initial assessment of symptomatic sites of disease involvement is essental. Mangement of ulcers in LABC, local pain, painful or unstable weight bearing bones, hypercalcaemia, cord compression, neurological changes seen in metastatic breast disease are important aspects of management. The initial assessment of symptoms are supplemented with desired investigations which ultimately become the

monitoring parameters for the assessment of response. The common problems associated with breast cancer patients in India are fungation, foul smelling ulcer, anaemia, pleural effusion. These problem could be alleviated with systemic chemotherapy, local surgery, graded analgesics and intra-cavitary instillation of cytotoxics. Improvement in quality of life becoming increasingly important in the treatment of advanced cancer. The parameters accountable are [i] disease related symptoms and toxic effects of treatment; [ii] functional status; and [iii] psychological status. Psychological aspects assumes different dimension depending on local socio-cultural beliefs and economic factors.

Management options in Advanced Breast Cancer

Systemic therapy/chemotherapy/ hormone therapy/biologic therapy are the main stay of therapy for advanced breast cancer. Local treatment i.e., surgery and radiotherapy is always adjuvant to systemic therapy. Till 1970 only loco-regional therapy was advocated and 5-year and 10-year survival following radical mastectomy were 30%-45% and 20%-30% respectively. Similarly for stage IIIb the corresponding results was 2%-28% and 0%-10% respectively. Surgery if performed alone leads to 60% local treatment failure, hence is not the only treatment. The best ultimate results are achieved through combined modality treatment. Houston (6) observed 2 times more response in patients receiving adjuvant treatment for the first time than those who received treatment without adjuvant treatment.

Role of surgery

Role of surgery dates back to Hippocratic era [400 BC]. Anatole Francis quotes *"Let us not cast aside things that belongs to the past for only with the past can we weave the fabric of the future."* As early as 30 BC- 38 AD Celsus opposed surgery and cautery for advanced breast cancer. Galen [181-203 AD] stated that once a breast malignant mass grows to a noticeable size, no one has cured it with surgery alone. Rhazes [841-966 AD] warned not to incise and advised complete removal of the breast. Ambrose Pare [1510-1590] opposed all the philosophers of local excision for large ulcerative lesions of breast. These historical data holds true even today and the role of local surgery alone for advanced breast carcinoma is very limited.

Indications for surgery in advanced breast carcinoma has been in conjunction with chemotherapy/radiotherapy for specific indications like local, invasion, extensive axilliary disease, extensive bulky disease and inflammatory carcinoma (7-9).

Radiotherapy

This modality of treatment has been purely loco-regional. Five years survival for LABC varies from 10%-30% and local failure ranges from 25%-72%. Radiotherapy when compared to surgery alone as a method of treatment, was difficult to compare because of different inclusion criteria of patients in both the groups. Veronesi (10) in his series reported 42% 10-year survival following surgery and excluded T4, N2, supraclavicular lymph node [SCLN] cases. Pierquin (11) reported similar results following radiotherapy using

the same exclusion criteria. Most of the series edge towards less favourable outcomes after radiotherapy. Though there are reports of long time survival with radiotherapy in the treatment of LABC (11,12) considerable toxic and unacceptable long term side effects have been observed(13).

Next milestone in treatment of LABC has been combination of surgery with pre-operative or post-operative radiotherapy. This modality though has a better local control but did not add to survival benefits and systemic failure (14). Role of radiation has been significant in the management of localised bony metastasis, cerebral metastasis and spinal bone compression. It provides best palliation when used in conjunction with chemotherapy and surgery.

Systemic Therapy

Systemic therapy comprises of hormone therapy and chemotherapy (15). It has been employed in the management of breast cancer since 1970. Various factors are being analysed towards their use. These are age and menopausal status, stage of the disease, performance status, hormone receptor status, histology, tumour grade, oncogenes expression, aneuploidy and sites of metastases. These have a significant effect on disease-free survival (3,16). Use of systemic therapy has improved the overall prognosis in advanced breast carcinoma particularly LABC.

Hormone Therapy

Hormone therapy includes opherectomy, LHRH analogues, adrenalectomy, aromatase inhibitors, antiestrogen [tamoxifen] and progestins. It is used alone and in combination with local therapies for LABC. Used alone it has achieved objective regression in breast tumours [upto 56% in LABC] but without any added advantage as regards overall survival. When used as an adjuvant treatment after loco-regional treatment, it did not contribute towards overall survival. However synchronised chemo-hormone therapy achieved 82% response as compared to 43% for chemotherpy alone (17).

Hormone therapy options for advanced breast cancer are classified as *ablative* [oopherectomy, LHRH analogues or medical oopherectomy, adrenalectomy and aromatase inhibitors or medical adrenalectomy], *additive* [progestins, oestrogens and androgens]; *antagonistic* [antioestrogens and antiprogesterone]. These are best indicated in patients without visceral crisis and with either positive or unknown hormone status. Primary hormone therapy has been grouped as oopherectomy and LHRH analogues for pre-menopausal patients, antioestrogens for pre- and post-menopausal patients.

Subsequent hormone therapy is required are antioestrogens, aromatase, inhibitors, progestins, oestrogens for post-menopausal women and LHRH analogues, progestins and antioestrogens for pre-menopausal patients.

Tamoxifen is the initial choice for hormone therapy. Ten mg twice a day for 5 years is the dose recommended for hormone responsive advanced breast cancer. Tamoxifen in addition to oopherectomy has beneficial effects (18). The side effects are

minimal and treatment is cost-effective. Response ranges from 30%-75% (19). Response varies according to site of metastasis, [soft tissue > bone > visceral and duration varies from >2 years > 1 year < 1 year respectively] and absoute value of hormone receptors. Tamoxifen has proven to be as effective as any other form of hormone therapy (3, 20). Another important aspect about initial hormone therapy is, it does not compromise any delay in chemotherapy (21). Major advantage of hormone therapy has been 25% reduction in death hazards in long term follow-up (14).

Magesrol acetate [progestins] is an alternative to tamoxifen with similar response. It is preferred as second line therapy particularly in the high doses. It is relatively more toxic and expensive than tamoxifen. Aminoglutethimide [aromatase inhibitor] is the third line choice of hormone therapy for metastatic breast cancer.

There are no reports of randomised clinical trials on this subject from India. However considering the availability, affordability, assessment of duration of response and non-availability of hormone receptor status, oopherectomy tamoxifen still is the most cost effective hormone therapy for advanced breast cancer for Indian patients [Figure 1 and Table 2].

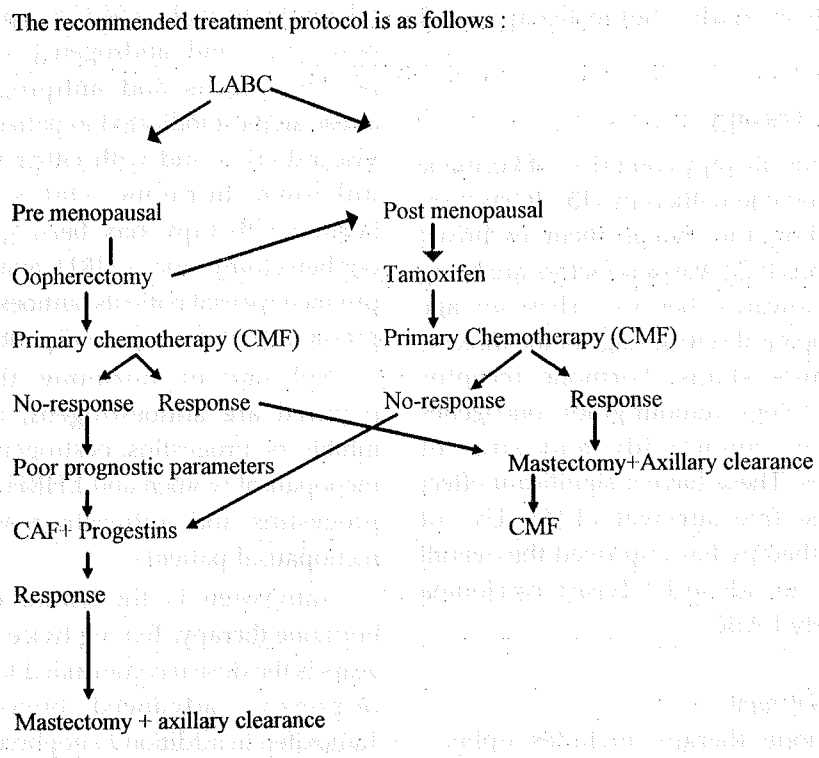

Figure 1. Recommended treatment protocol

Table 2. *Hormone therapy options for advanced breast cancer*

Therapy	Menopausal status	Treatment sequence		
Ablative				
Oopherectomy	Pre	+++	++	–
LHRH analogues	Pre	–	–	–
[Medical oopherectomy]				
Aromatase inhibitor [Medical	Post	+	++	+++
adrenalectomy]	Pre	–	+	++
Additive				
Progestins	Pre	–	+	++
Oestrogens	Post	++	+++	++
Androgens	Post	–	+	+
Antagonists				
Antioestrogens	Pre	++	+++	+++
	Post	+++	++	++
Antiprogestins	Pre	?	?	?
	Post	?	?	?

Chemotherapy

Before 1970 loco-regional treatment was the only treatment for advanced breast cancer and systemic therapy was added only if local recurrence or distant metastasis occurred. For a better overall survival and disease free survival the role of systemic chemotherapy was then recognised and introduction of adjuvant chemotherapy produced 60% response as compared to 25% by radiation alone (15). Chemotherapy was used in combination and various combinations were used. With the realisation of advantage of systemic chemotherapy over loco-regional treatment, chemotherapy was used as primary treatment for advanced breast cancer and 5-year and 10-year survival figures quoted for stage IIIa are 80% and 64%; and for IIIb are 45% and 28% respectively. This was in contrast to < 30% survival at 5 years without chemotherapy.

Table 3. *Use of chemotherapeutic protocols and their results*

Drugs	% Response	% CR	Duration response
CMF	40-70	8-15	6-10 months
CMF±V±P	30-80	7-25	6-14 months
CMFVP	46	11	9 months
CA	41-78	2-22	10-12 months
CAV	52-53	0-8	7-8 months

C = cyclophosphamide, M = methotrexate, F = 5-fluorouracil, V = vincristine, p = prednisone

The various chemotherapeutic protocols in use and their results are shown in Table 3. The mainstay of chemotherapy is still adriamycin and cyclophosphamide based regimens. Two common combinations are CAF and CMF. CAF has nearly 10%-15% advantage in terms of reponse than CMF but with added cost. When corrected for the prognostic factors there would appear to be only minor differences in the chemotherapeutic regimens at least as applied to advanced disease. There has been an explosion in new chemotherapeutic drugs [Table 4] which include traxol, navelbine, camptoghecin [CPT-II] with response around 35% when used alone and 25%-80% in combination.

Table 4. *Newer drug regimens and their response*

Drug regimens	% Response
AV	25
AM_{MC}	40
$FAVM_{MC}$	54
$VACL_{E}$	78

A = adriamycin, V = vincristine, M_{MC} = mitomycin C, F = 5-flurouracil, L_E = Leucovorine

Considering the response, there had been minimum variation, which raises certain ethical issues regarding the selection of combination chemotherapy regimes for advanced breast cancer. The issues involved are what should be an optimal regimen? [CMF vs. CAF vs. newer agents], dose of chemotherapy, duration of chemotherapy?

Tormey (22) and Aisner (23) compared the various combinations and concluded that adriamycin based combinations are better than any other combinations for the treatment of advanced breast cancer. There have been attempts to increase the response by several methods e.g.; dose intensification, use of GM-CSF and ABMT.

Honkoop (24) observed 82% response after dose intensification with GM-CSF and 83% response with 24% CR using a combination of adriamycin and paclitaxel. Bishop (25) compared the results following use of paclitaxel and CMFP [Table 5].

Table 5. *Comparison of results using CMFP and paclitaxel*

	CMFP	PACLITAXEL
Overall response (%)	35	31
Time to progression (months)	6.4	5.5
Neutropenia (%)	63	64
Mucositis (%)	27	13

Based on reference 26

The newer agents, though comparable and at times more effective, raise issues for Indian patients such as:

Are these cost effective and what is cost benefit ratio?

Henceforth the management of advanced breast cancer in Indian patients needs to be re-evaluated considering the applicability, affordability, availability and acceptability.

MANAGEMENT OF ADVANCED BREAST CANCER IN INDIAN SCENARIO-A PERSONAL EXPERIENCE

Considering the background of management of advanced breast cancer and the advances in chemotherapy, the

Indian patients have a few more ethical considerations. These are economy, cost vs. benefit in terms of quality and quantity of life, feasibility, evaluation of prognostic markers, drug related toxicity and follow-up. In a study conducted at the Institute of Medical Sciences, Banaras Hindu University, a combination of cyclophosphamide, methotrexate, 5-fluorouracil and prednisone was used to treat patients with advanced breast cancer. CMFP regimen has the advantage of being cost-effective, is well tolerated and results in 64% disease free survival for 18 months. The drugs used could be administered on domiciliary basis and nearly 90% patients did not need hospitalisation. Approximately 10% patient shaving dose limiting toxicity needed hospital admissions. This has been one of the major advantage of CMFP combination (26). Gastrointestinal, bone marrow toxicity and alopecia was observed in 44%, 12% and 14% cases respectively. In the same study it was highlighted that patients who received radiotherapy prior to chemotherapy had significant poor response [35% vs 70% respectively]. Patients with soft tissue metastasis responded better than visceral or osseous metastasis.

This study was extended to locally advanced breast carcinoma and fungating breast carcinoma in particular using CMFP (27). In this study, 26.7% patients had complete response and 33.3% cases had partial response. Nearly 83% patients were made operable using CMFP as primary chemotherapy for such cases [2 cycles preoperatiely and 7 cycles post-operatively. Advantage of primary chemotherapy had been the healing of malignant ulcer, mobility of lymph nodes and mobility of primary tumour making tumours operable. Mastectomy and axillary clearance which were not possible initially were only possible after primary chemotherapy. Clinical response was confirmed histologically in the form of tumour necrosis, smudging of cells, lymphocytic infiltration, stromal oedema and fibrosis. Major and minor toxicities were the same as reported earlier. The cases were followed up for 5 years and 16.6% cases were disease free while 28% had local failure and 52% had systemic failure. The results were comparable to current approaches for treatment of stage IIIb breast carcinoma (28).

The choice of current treatment for advanced breast cancer is based on study of prognostic indices e.g., receptor status, tumour grades, oncogenes, aneuploidy besides the clinical parameters of age, menopausal status, site of metastasis and lymph nodes. One of the current cost effective prognostic parameter studied has been argyrophilic nucleolar organizer regions [AgNOR].

AgNOR and their significance as prognostic parameter

AgNOR count determines the nuclear activity and a high count is associated with poor prognosis (29). These are loops of ribosomal DNA [rDNA] located on the short arm of the acrocentric chromosomes 13,14,15,21 and 22. These are identified by silver nitrate stains in paraffin section. High count is found in paients with advanced stage, > 4 metastatic nodes and distant metastasis. The clinical application of this study is, patients with higher AgNOR count

are prone to develop local and systemic failures and should be treated with aggressive combined modality for a favourable outcome. AgNOR count in benign breast disease and malignant breast tumors were 1.88 and 6.65 respectively [p<0.001]. The study suggests that any tumour with AgNOR>3 count is highly suggestive of malignancy. AgNOR count increases with increase in tumour size. The study sugests the value of AgNOR in predicting high risk patients and also an indicator of aggressiveness.

Quality of life assessment in Indian patients with advanced breast cancer

Quality of life [QoL] assessment is an important consideration in patients with cancer. The relevant measurement of quality of life can be established on the basis of expected impact of the treatment on quality of life, the expected impact of the treatment on survival and the health state of patients before initiation of treatment. In advanced breast cancer it is considered critical when it is one of the major objective of the treatment. Four domains of QoL, are ideal to study:

- The physical [symptoms/distress, activity leve/functional status]
- The psychological [symptoms/distress, or anxiety and depression and positive effect].
- The social [the quality of social interactions and relations]
- Financial concomitants of the disease and treatment

Considering the above domains of QoL patients with advanced breast cancer being treated with various therapeutic arms were evaluated. Following CMF therapy, patients with advanced breast cancer had improvement in their physical symptom score [73.68%, 90.93% and 81.8% over 6,9 and 12 months]. The improvement in physical symptoms are better than chemo-radiation group. Similarly daily functional status worsened in chemo-radiation group [80%] than in chemotherapy alone [36.6%] at 1 year. Job related social and overall functional status also had similar pattern of response. The study suggests that chemotherapy alone provide a better quality of life than chemo-radiation. Hormone therapy had the least deleterious effect on QoL. Eighty per cent patients in this group improved in their physical score.

Breast reconstruction has been reported to reduce the distress of mastectomy and to have a positive effect on life style, sexual and social relations. Cosmetic disfigurement by mastectomy causes less psychological concern to our patients than in western hemisphere. Since the dress and conservative life style managed to bypass these areas of cosmetic concern, their worries about the disease decreased from 84.2% to 57.9% during therapy and after treatment it declined to 39.5% [Unpublished data]. Worry about the cost of therapy and disruption of the economic structure of the family seen in 63.2% during treatment and 60.5% after treatment is an important consideration. This might rise if newer modalities of treatment are adopted. If financial concerns are addressed, the quality of life could be improved further if NGOs and consolidation of family resources support the patient. Counselling is an important aspect of patient management

with reference to QoL. This aspect has been lacking in this sub-continent.

One important aspect of CMF therapy has been study of toxicity. Though the major toxicity has been seen only 10% cases, the combinations of drugs were tolerated well. A new side effect with CMF combination was observed and reported i.e., aggregation defects in platelets responsible for clinical symptoms of mucositis and haemorrhage without thrombocytopenia (30-32). CMF or CMFP is a combination which has comparable toxic effect and with almost similar response is considered to be effective chemotherapy for advanced breast carcinoma in the Indian subcontinent.

REFERENCES

1. Rubens RD (1992). The management of locally advanced breast cancer. *Br J Cancer* **65**:145-147.
2. Roberts MM, Alexander FE, Anderson TJ, et al (1990). Edinburgh trial of screening for breast cancer: mortality at seven years. *Lancet* **335**:241-246.
3. Ruben, RD, Bajetta E, Bonneterre J, et al (1994). Treatment of relapse of breast cancer after adjuvant systemic therapy - review and guidelines for future research. *Eur J Cancer* **304**:104-111.
4. Bloom HJG, Richardson WW and Harries EJ (1962). Natural history of untreated breast cancer (1805-1933). *Br Med J* **1**:213-221.
5. Population based cancer registreis-an epidemiological study (1992). NCRP scientific publication, New Delhi: Indian Council of Medical Research.
6. Houston SJ, Richards MA, Bentley AE, et al (1993). The influence of adjuvant chemotherapy on outcome after relapse for patients with breast cancer. *Eur J Cancer* **29A**: 1513-1518.
7. Brun B, Otmezguine Y, Feuilhade, et al (1988). Treatment of inflammatory breast cancer with combination chemotherapy and mastectomy versus breast conservation. *Cancer* **61**:1096-1103.
8. Morris DM (1983). Mastectomy in the management of patients withinflammatory breast cancer. *J Surg Oncol* **23**:255-258.
9. Wiseman C, Jessup JM, Smith TL, et al. Inflammatory breast cancer treated with surgery, chemotherapy and allogenic tumor cell/BCG Immunotherapy. *Cancer* **49**:1266-1271.
10. Veronesi U (1987). Rational and indications for limited surgery in breast cancer: current data. *World J Surg* **7**: 231-239.
11. Pierquin B, Rynal M, Otmezguine Y, et al (1986). Le traitement conservateur des cancers du sein: resultata a 10 ans. *Presse Med* **15**:375-377.
12. Zucali R, Uslenghi C, Kends R and Bonadonna G (1976). Natural history and survival of nonoperable breast cancer treated with radiotherapy and radiotherapy followed by radical mastectomy. *Cancer* **37**: 422-1431.
13. Spanos WJ, Montagne ED and Fletcher FH (1980). Late complications of radiation only for advanced breast cancer. *Int J Radiat Oncol Biol Phys* **6**: 1473-1476.
14. Bartelink H, Rubens RD, Van der Schueren E and Sylvester R (1997). Hormonal therapy prolongs survival in irradiated locally advanced breast cancer: a European Organization for Research and Treatment of Cancer Randomized phase III trial. *J Clin Oncol* **15(1)**:207-15.
15. Rainer H (1993). Prospective randomized clinical trial of primary treatment in breast cancer stages $T_{3/4}N_{+}M_{0}$. Chemotherapy versus radiotherapy. *Anticancer Res* **13**:1917-1924.

16. Ruben RD, Bartelink H, Engelsman E, et al (1989). Locally advanced breast cancer: the contribution of cytotoxic and endocrine treatment to radiotherapy. *Eur J Cancer Clin Oncol* **25:** 667-678.

17. Sjovall MP and Malmstrom P (1997). Induction chemotherapy versus without hormonal synchronisation in locally advanced breast cancer. *Acta Oncol* **36(2):**207-212.

18. Bilimoria HM and Jordan VC (1996). Is it time to develop an optimal endocrine therapy for premenopausal patients with axillary node positive and negative breast cancer. *Semin Surg Oncol* **12(5):**339-45.

19. Rolski J, Pawlicki M, Zaamelka T and Pernal J (1996). Results of tamoxifen treatment in patients with advanced breast cancer. *Pol-Merkuriusz-Leks* **1(4):**271-3.

20. Robert NJ (1997). Clinical efficacy of tamoxifen. *Oncology-Huntingt* (2 suppl 1):15-20.

21. Wilsher PC, Robertson JF, Chan SY, Jackson L and Blamey RW (1997). Locally advanced breast cancer: early results of a radomised trial of multimodal therapy verus initial hormone therapy. *Eur J Cancer* **33(1):**45-9.

22. Tormey DC, Winberg V, Leone LA, et al (1984). A comparison of intermittent vs. continuus and of adriamycin vs methotrexate 5-drug chemotherapy for advanced breast cancer. *Am J Clin Oncol* **7:** 231-239.

23. Aisner J, Weinberg V, Perloff M, et al (1987). Chemotherapy vs. chemoimmuno-therapy (CAF v CAFVP v CMF, each + MER) for metastatic Carcinoma of the breast: a CALBG study. *J Clin Oncol* **5:**1523-33.

24. Honkoop AH, Hoekman K, Wagstaff J, et al (1996). Dose intensive chemotherapy with doxorubician, cyclophosphamide and GM-CSF fails to improve survival of metastatic breast cancer patients. *Ann Oncol* **7(1):**35-9.

25. Bishop JF, Dewar J, Toner GC, et al (1997). Paclitaxel as first line treament for metastatic breast cancer. The Taxol investigational trials group, Australia and New Zealand. *Oncology-Huntingt* (4 suppl 3):19-23.

26. Khanna N, Kumar A, Khanna S and Pant GC (1981). Chemotherapy in advanced breast cancer. *Indian J Cancer* **18:**59-62.

27. Kumar A, Shah LL, Khanna S and Khanna NN (1987). Preoperative chemotherapy for fungating breast cancer. *J Surg Oncol* **36:**295-298.

28. Kumar A and Harding KG (1992). Malignant ulcer-rationale of treatment (an experience with fungating breast cancer). Proceedings of 2nd European Conference on advances in wound management (UK), 61-63.

29. Kumar A, Kushwaha AK, Kumar M and Gupta S (1997). Argyrophillic nucleolar organiser regions: their value and correlation with clinical prognostic factors in breast carcionoma. *J Surg Oncol* **65(3):**201-204.

30. Kumar A, Chathurvedi P and Gupta YN (1966). Combination chemotherapy for breast carcinoma using a combination of cyclophosphamide, methotrexate and 5-flurouracil causes a platelet aggregation defect. *Int J Cancer* **66:**159-161.

31. Kumar A, Khanna NN, Khanna S and Gupta YN (1984). Qualitative platelets dysfunction following cancer chemotherapy. *J Surg Oncol* **25:**176-177.

32. Khanna AK, Saxena SK, Khanna S and Kumar A (1990). Histopathological changes following chemotherapy in advanced breast cancer. *Indian J Cancer* **27:** 109-115.

Ann Natl Acad Med Sci (India), **34(4)**: 225-229, 1998

Learning Medicine : a Pilgrims's Progress

KP Kochhar

Department of Physiology,
All India Institute of Medical Sciences, New Delhi - 110 029.

Entering the twenty first century is a time for rejoicing as well as reflection. Nostalgia permeates our attempts to redefine the doctor-patient relationship in the light of societal evolution and recent scientific developments. A longing for the lost ideals suggests dissatisfaction with the present and perhaps, a conviction that things used to be better. On the one hand so much has improved with respect to diagnosis, prevention and therapy, that practice has changed almost beyond recognition but on the other hand has brought in its wake 'a relegating of individual human values to a second order of priority'.

Popular culture views science as fundamentally independent of other fields of knowledge. Science is taken to be objective and certain, untainted by relatives and subjectivity to other disciplines. But medical science is not simply a cataloguing of hard facts, it is an enterprise permeated with supposition. Our calling is not a scientific one although it uses science as one of its instruments; doctors are not servants of nature but in the human race of life of the individual. In 1927 Francis Peabody wrote: "The secret of the care of the patient is in caring for the patient".

The patient's problem may stem from his inheritance, some organ dysfunction, from an excess for deficiency in the physical environment or even from a failure in human relationships. Thus each patient whether seen in the clinic, the home, the hospital bed and with whatever problem presents a diagnostic, therapeutic, preventive or promotive challenge which evokes all knowledge and skills learned about people in the arts, humanities and the sciences. If the student is to view the patient in this broad, social, cultural and biological perspective, his education should have made him aware of the nature and behavioural features of man-growth and development of the human being in relation to other human beings, the physical, biological and cultural factors of the world in which people live, become ill or disabled and the impelling spirit of man that sets him apart from other living creatures as well as aware of himself in relation to people and his own environment.

SHAPING PHYSICIAN IDENTITIES

Paradigms, language, metaphysics and cultural values all shape the conduct of medicine, as much as facts themselves.

Correspondence: Dr KP Kocchar, Associate Professor, Department of Physiology, All India Institute of Medical Sciences, New Delhi - 110 029.

Learning medicine should not reduce ecologies to taxonomies, qualities to quantities or a self conscious human being to a mass of biochemical interactions. Let not the patient's experience of illness be reduced to an anatomical lesion or a misspelled codon or the totality of pain experience to laws of neurochemistry. Learning to identify with the patient, what we call empathy is a natural endowment for most of us, but we tend to lose it along the way. As we know school students start out with much empathy, genuine love and a real desire to help other people. In medical school, however, they learn to mask their feelings or choose to deny them. Men cannot be subdivided endlessly; moreover the most critical tissues escape the scalpel; it is the entire organism which must be studied. Does not medical education change, rice kids into doctors playing 'God' who grab the chart, poke the patient and churn out case reports? Does not the roller coaster ride of a socially eroding five years in medical school sour the so called 'cream of bright youngsters'? It is recognized that most of the critical determinants of physician identities operate not within the formal medical school curriculum but in a more subtle, less officially recognized hidden curriculum of ethical training in corridors, canteens and campus life. An ethics curriculum might be more fruitfully structured to become a seamless part of the training process.

The doctors' and the patients' sense of identity and their sources of values and norms are conditioned by their way of life. The physician's behaviour is that of the subculture he represents. To a medical student his education should impart self knowledge of his own biological and psychological nature, of his gifts and limitations, values and aspirations. It should also encompass a knowledge of others - a comprehension of the roots of human behaviour as revealed both in modern scientific studies and in historical and literary sources. Along with it for universality it is important to have a knowledge of the physical and biological world for global understanding, a knowledge of his own and other cultures; a historical view of man's social, cultural and artistic achievements and for spiritual consonance a knowledge of his religious and philosophical heritage.

MEDICAL EDUCATION IS UNIQUE

There is no student in higher learning more privileged or penanced than the medical student. Except when in the laboratory unravelling the mysteries of physical and biological sciences, he is dealing with people in whom the particular disease or disability represents a pause or break in the human life process. Both endogenous and exogenous factors have been noted in our loss of humaneness and altruism whether at the personal or historical level . These factors are linked to societal changes, managed care, a proclivity to litigation, and increasing cost of medical education. Perhaps people now feel a more urgent need for immediate gratification because any other goal seems increasingly evanescent. Obsessed with miracles of modern medicine and technology, hypnotized by their own hype that medicine can cure all, physicians have much less patience and time for the patient who does not respond who cannot or 'will not' be cured.

While learning medicine a lot of social taboos are broken. A child of four years is told to cover his body, to shun excreta, keep away from infection but in a medical school these very children are taught to seek out the deviant, the deformed and the dying, to probe the body's orifices and examine effluvia. A study of the student's emotional and social growth as he assumes new relationships with people, merit a concern equal to the present teacher concern with his intellectual advancement. We also need to see how the student can retain his intellectual goals and social aspirations while adjusting to training requirements and come out of medical school as one whole with his humanity enhanced.

DISABILITY AND MEANING

Our most basic concepts influence out work as medical scientists and clinicians. Consider disability: is it an unfortunate aberration, a non-essential plague to be eliminated in some future utopia, or can illness be ever integral to the biology of health-compensatory, necessary, reflective of an unrecognized process. Are diseases entities that attract from outside, challenging us to wage war? Are they inner betrayals of tucked away genes or submerged unconscious complex. Or are they aspects or self, ordained manifestations or personal destiny? Does the reality of disease exist exist independently or culture? Do we recognise an ailment only when it violates out sentiments about convenience, pleasure or beauty? Does a condition become a disease because it can be influenced pharmaceutically? Real answers to many of these questions about sickness can never be experimentally proven by medical science. Nevertheless, prepared answers are incorporated into the very structure of medical sciences.

THE IMPORTANCE OF MEDICAL EDUCATION

During the past fifty centuries of its recorded and unrecorded history India has always been conscious of the fact that "The health education of today shall determine the pattern of health care of tomorrow". Societal, political and economic compulsions have shifted emphasis from Gurukuls to governing bodies. Medical schools have been turning away from their principal vocation of being nurseries for good doctors. The tragedy today is that medical education to many a faculty member has become a distraction or just a by-product of the principal business of research and hospital care. The specific charge of a medical teacher is to foster in his student open mindedness, critical thinking, value analysis and self reflection as well as scope for handling diversity and ambiguity in outcomes A medical teaching institute is a responsible social unit in a society undergoing rapid change. It is therefore imperative for all of us, medical teachers, researchers and practitioners in the pursuit of common objective of improving the lot of men to prevent social erosion and attrition of ethical values in budding doctors.

THE DOCTORS' IMAGE OF HIS PATIENT

The main question has to do with the students' perception and understanding of his education. The graduate has been

diligently examined by each medical school department with weightage accorded to grades or accomplishments following hierarchical orders of specialities and super-specialities and he has been variously characterized with respect to cognitive and procedural core competencies and finally because of his age, if for no other reason, he is generally judged to be mature, however one defines maturity. There is a crying need to reinforce the values of justice, fairness, beneficence, non-maleficence, and autonomy to the patient. A new dimension should be added to the meaning of a degree in medicine by typing to assess what is 'The doctor's image of his patient'. It would include all that a physician and a patient learn about each other in brief or prolonged periods of time through verbal, visual, auditory or tactile means, and how they react to each other, and hopefully would pave the way for physician's acceptance of the patient and also patient's acceptance of the physician. Issues of equity and economics as well as institutional and professional goal actualization should be inherently part of this set up.

Medical student's should be sensitized to faith, prayer positive conditioning and alternative medicine. A grounding in humanities, arts and literature are not just accoutrements or embellishments for a doctor to indulge in name dropping during evening parties or social dos but are legitimate accompaniments of a total education. Incidentally the word doctor means a teacher or one who indoctrinates. The turn of the century beckons a revisiting and reliving of the credo that familiarity with literature, art and humanities goes a long way in improving healing outcomes. What does he know of medicine who only medicine knows? Medicine is a co-operative art just like theology and farming. It should be pursued as an emblem of glory and an article of faith. The doctor's life is a pilgrim's progress, both a privilege and penance. The medical teacher is charged with a commitment to his diverse student constituencies and an obligation to pursue teaching of 'Medicine is that medicine does' in good faith.

Quantum leaps in technology should not be associated with descent in the quality of human endeavour. The need of the hour is a contextual and consensual approach, a comprehensive, composite and care provider concept of health, a congruence of objectives and convergence of services for optimising the functional output and have a sustainable health care delivery system. Caring has to become a mindset, a way of life, a given in this vocation.

SCIENTIFIC TO SALUTARY CONCEPT OF HEALTH

The methodological breakthroughs and molecular biological advances of the 20th century have built the scaffolding on which the structure of integrative holistic health providing systems would emerge in the coming century. There is no obvious way to measure achievement in this but in some settings the atmosphere is more conducive to this than it others. For all time to come, medical education should provide a moral compass to seek direction while navigating the seas of sickness and to land on the shores of health in body, mind and spirit. Perhaps the only true measure of accomplishment will lie in the heart and mind of the student who will have learned

something of the nature of man and of himself and to have reached sufficient sublimity and maturity to know what it takes, intellectually and spiritually, to lead another person, through the highways and byways of health and disability. So that in whatever situation organizational, economic or social the doctor finds himself, his decisions and actions would be eternally in favour of the patient.

Ann Natl Acad Med Sci (India), **34(4)**: 231-234, 1998

Risk Factors for HIV Seropositivity among First Time Blood Donors in Delhi

Geeta Tiwary, DS Rawat and AB Dutta

Department of Blood Bank and Transfusion Medicine,
Safdarjung Hospital, New Delhi - 110 029.

ABSTRACT

We studied the factors associated with increased likelihood of human immunodeficiency virus [HIV] infection among newly recruited blood donors and assessed their feasibility as criteria for exclusion from donation. Of the 20,000 subjects tested, 0.8% were HIV positive. Factors significantly associated with HIV seropositivity included recruitment venue, age, marital status, donor residence, residence of primary partner, occupation, history of sexually transmitted disease. An exclusion strategy based on these would exclude a large proportion of HIV infected donors without substantial loss of uninfected donors. So exclusion of donors who are likely to be infected with HIV is a sound policy for improving blood safety and reducing operating costs.

Key words: HIV seropositivity, blood donors

INTRODUCTION

According to recent studies in some parts of India, 1% of Indians are infected with human immunodeficiency virus [HIV] (1). The WHO has warned that if infection rate in general population reaches 1% the virus spreads very fast.

At present, three effective strategies to prevent transfusion associated HIV transmission are avoidance of unnecessary use of blood, HIV antibody screening and selection of donors at low risk of infection with HIV (2,3).

The objective of present study was to identify risk factors for HIV infection that could serve as criteria for the exclusion of high risk first time blood donor.

MATERIAL AND METHODS

The procedure described in this study are in accordance with guidelines for blood donor recruitment and selection.

Study subjects

Adults volunteering for blood donation for the first time at the Safdarjung Hospital, New Delhi were included in the study. Risks and reasons associated with blood donations were explained to the donor. Persons previously testing positive for HIV, syphilis, hepatitis B and hepatitis C were deferred.

Correspondence: Dr Geeta Tiwary, 130, Masjid Moth Doctors Hostel, AIIMS, New Delhi-1100049.

Survey design and method

Questions about putative risk factor for HIV seropositivity were based on the risk factors previously described. The questionnaires began with a series of demographic characteristics including age, marital status, residence of primary partner, residence of donor and type of employment. In addition, the history of sexually transmitted disease in the last 5 years was examined. After the pilot testing of the survey among first time donors, minor changes were made to the working and the formatting of the questionnaire.

The present study thus attempts to find self-reported information, that can identify donors, who are likely to be HIV seropositive at the time of initial interview.

Laboratory methods

Usual laboratory testing protocols were followed. Donations were initially screened for HIV antibodies by using third generation ELISA [HIV1/HIV2]. Specimens that tested positive were confirmed by retesting with another third generation ELISA test. Only specimens that reacted according to the manufacturer's specifications for both tests were considered positive.

The potential impact of the risk factors on donor selection was estimated by comparing the proportion of HIV positive donors excluded and the proportion of HIV negative donors retained if each risk factor was use as a criteria for deferral. A desirable deferral criteria maximises the number of HIV positive donors excluded, while retaining the maximum number of HIV negative donors.

RESULTS

Of the 20000 blood donors completing the survey, 160 [0.8%] tested positive for HIV antibodies by two ELISA tests. Donors recruited at worksite had higher HIV seroprevalance. Demographic variables associated with increased HIV seroprevalance included greater age, being or having been married, having a primary sex partner who does not reside with the donor, living in high density urban area and work as security guard or driver. Gender was not associated in the sample. Age cut-off of 22 years most successfully, discriminated between donors with high and low HIV seroprevalance. Reporting sexually transmitted diseases [STD] in the last 5 years were associated with high seroprevalance.

Table 1 summarizes the usefulness of various HIV risk factors as criteria for deferral from blood donations by examining the percentage of HIV positive donors excluded and percentage of HIV negative donors retained. Risk factors that performed well included working as driver, STD in previous 5 years, residence of primary partner away from the donor. The proportion of HIV negative donors rejected on the basis of these risk factors was less than the proportion of HIV positive donors excluded for the same risk factors.

DISCUSSION

The exclusion of donors who are likely to be HIV positive serves several purposes, even when all donations are screened for HIV antibodies. Because no test is perfect, the greater the number of HIV infected units

Table 1. *Estimated performance of risk factors for HIV seropositivity in screening adult donors*

Risk factor studied	HIV positive donors deferred (%)	HIV negative donors deferred (%)
Worksite recruited	58.3	4.3
Small town address	7.2	3.7
High density urban neighbourhood	74.4	60.8
Work as driver or security guard	6	1
STD in previous 5 years	9	3
Partner resides away from donor	20	9
Multiple risk factor	38	10

STD- sexually transmitted disease

screened, the greater the chances that units that test false-negative in the laboratory will be released for transfusions (4-6). Moreover the handling of large number of HIV infected units of blood increases the likelihood of human errors that will result in transfusion of contaminated blood or the exposure of blood bank and hospital staff to contaminated blood. In addition, the collection of HIV positive donations result in considerable waste of resources, as these units will ultimately be discarded. To some extent, the exclusion of donors who are likely to be HIV infected, but in the window period, may be helpful.

There is also association between HIV infection and socioeconomic condition. Socioeconomic conditions have fastened a system of seasonal, internal migration from rural to urban areas. As individuals [mainly men] seek employment in the cities, their spouses remain behind in rural areas. These conditions may in turn encourage high risk sexual behaviour. The relationship between these factors provide a plausible explanation for the increased seroprevalance observed among donors recruited from worksite, who don't reside with their primary partners, donors providing address in small town and donors residing in high density urban neighbourhood. The association between HIV seropositively and employment as driver is also consistent with the high prevalence of HIV described among truck drivers. History of STD has been confirmed as a risk factor for HIV infection in multiple studies and is thought to be market for engaging in unprotected sex, as well as co-factor facilitating HIV transmission.

Evidence from present study and experience in the field indicate that a large proportion of HIV positive donors could be excluded without overall dramatic loss of donors overall. Survey questions were deliberately selected and were based on the knowledge of the local epidemiology of HIV infection. Demographic questions such as age, residence, employment, marital status, residence of spouse are likely to be answered more accurately than questions of sexual behaviour, that are widely known to be associated with HIV infection.

Association with HIV infection and screening performance must be confirmed under local conditions. Risk factors that serve as the most efficient donor defining criteria

may also change over time as HIV epidemic evolves. Exclusion by HIV risk factor should be considered as an important part of a multifactorial strategy to maximize blood safety that also includes universal HIV antibody survey and sound transfusion practice.

REFERENCES

1. Kimball AM, Berkeley S, Ngugi E and Gayle H (1995). International aspects of the AIDS/HIV epidemic. *Annu Rev Public Health* **16**:253-82.
2. McFarland W, Mvere D, Shandera W and Reingold A (1997). Epidemiology and prevention of transfusion-associated human immuno-deficiency virus transmission in sub-Saharan Africa. *Vox Sang* **72**:85-92.
3. Zimbabwe National Blood Transfusion Service. Annual report for year ending June 1994. Harare, Zimbabwe National Blood Transfusion Service (Infotech publication), 1994.
4. Bassett MT, Latif AS, Katzenstein DA and Emmanuel JC (1992). Sexual behaviour and risk factors for HIV infection in a group of male factory workers who donated blood in Harare, Zimbabwe. *J Acquir Immune Defic Syndr* **5**:566-9.
5. Lackritz, Satten GA, Aberle-Grasse J, et al (1995). Estimated risk of transmission of the human immunodeficiency virus by screened blood in the United States. *N Engl J Med* **333**:1721-5.
6. Sitas F, Fleming AF and Morris J (1994). Residual risk of transmission of HIV through blood transfusion in South Africa. *S Afr Med J* **84**:142-4.

Ann Natl Acad Med Sci (India), **34(4)**: 235-248, 1998

Emergent Infection : a Global Health Threat

Syed Amin Tabish

SK Institute of Medical Sciences, PO Box 826, GPO, Srinagar - 190 001.

ABSTRACT

The world today is in a state of turbulence and rapid change. We are facing an alarming proliferation of emerging and re-emerging infectious diseases which is but one manifestation of instability and stress in the system. Many social, economic and political factors are contributing to the global spread of infectious disease. Changes in ecology and climate, the evolution of microbes and antimicrobial resistance also contribute to disease emergence. No nation can be complacent regarding human vulnerability to the microorganisms with which we share our environment. Emerging infections transmitted by contaminated foods and public water supplies place entire communities at risk. Emerging infections contribute substantially to the ongoing burden of infectious diseases on the public worldwide, resulting in economic losses and days of disability. Current public health systems are poorly prepared or inadequate to confront the present and future challenges of emerging infections. Meeting the broad challenge of emerging infections requires interaction, co-operation, and co-ordination among a wide range of public and private organisations. Multi-disciplinary approach to tackle the problem, approaching the problem at system level, investing in surveillance, information systems and research, capacity building, EID funding pool and emergency preparedness are worthy of top policy attention.

Key words: Emergent infection, microorganism, surveillance, infrastructure, capacity building, evolutionary potential, funding pool, emergency preparedness

Fatal interchange of disease between animal and human being is the story of civilization itself. Disease is a social development no less than the medicine that combats it. It is the price we have paid and are still paying for development. Societies shape patterns of disease-in part create diseases they experience.

The world today is in a state of turbulence and rapid change. The emergence of infections in many geographical areas is but one manifestation of instability and stress in the system. Infectious diseases remain the most common single cause of death in the world today. Once thought to be on the verge of being eliminated as a public health problem, infectious diseases are responsible for worsening the living conditions of many millions of people around the world. Infectious diseases thwart the economic development of the world's poorest countries and strain

Correspondence: Syed Amin Tabish, SK Institute of Medical Sciences, PO Box 826, GPO, Srinagar - 190 001.

already overburdened health care infrastructures.

In 1991, Cholera in Peru affected 300,000 people resulting in 3,000 deaths and amounting to $700,000 in expenses. Estimates are that in 1994, plague in India resulted in a loss of $2 billion due to the reluctance to report and lack of preparedness (1). Food borne pathogens such as *E.Coli* in the United States were linked to under cooked meats. While many infectious disease outbreaks have resulted in substantial economic and human loss, others have been better managed. For example. Zaire dodged a "bullet" in 1995 when the Ebola outbreak occurred.

Patterns of infectious disease are changing globally and on a massive scale (2). Emerging infectious diseases [EID] have been reported in all regions of the world. Three general forces can affect the burden of infectious diseases in humans: change in abundance; virulence, or transmissibility of microbes; an increase in probability of exposure of humans to infection and to the consequences of infection. A wide range of biological, physicochemical, behavioural, and social factors influence one are more of these forces. Many are interrelated, and multiple synergies exist (3).

The spectrum of infectious diseases is changing rapidly in conjuction with dramatic changes in our society and environment. Worldwide there is explosive population growth with expanding poverty and urban migration. Technology is rapidly changing: international travel and commerce is increasing all of which affect our risks to exposure to the infectious agents with which we share our environment. Other causative factors include: the emergence of new diseases, the re-emergence of old threats , inappropriate use of prescription drugs, human behaviour, economic development and change in land use, breakdown in public health infrastructure and microbial adaptation and selection. With the global population growing from 2.5 to 5.8 billion over the last 25 years, large urban centers throughout the developing countries are overcrowded and have inadequate sanitation, a setting ideal for the emergence of infectious diseases. By 2025, the global population will reach 8.6 billion. In developing world this represents an 84% increase, which will intensify overcrowding in these areas. In industrialized countries, an ageing population base, the advent of immuno-suppressive medications, and the emergence of human immunodeficiency virus [HIV] infection and acquired imunodeficiency syndrome [AIDS] are combining to increase the risk for opportunistic infections. Moreover, with increased travel, clinicians see increasing member of patients with exotic diseases acquired abroad. The emergence of multidrug-resistant tuberculosis [MDR-TB] in the United States and elsewhere, and recent migration of epidemic diphtheria from the former Soviet Union to Europe are but two examples of infections resulting from international travel (4).

WHY ARE THEY EMERGING NOW?

Many factors, can contribute to disease emergence. Newly emergent infectious diseases may result from changes or evolution of existing organisms; known diseases may spread to new geographic area

or new human populations; or previously unrecognized infections may appear in persons living in areas undergoing ecological changes, such as deforestation or reforestation, that increase their exposure to insects, animals, or environmental sources that may harbour new or unusual infectious agents (5-7).

Re-emergence of infectious diseases may occur because of the development of antimicrobial resistance in existing agents [e.g., malaria] or break down in public health measures for previously controlled infections [e.g. cholera, tuberculosis].

The process of emergence and re-emergence of infectious diseases is a co-evolutionary one. No genomes are more plastic than those of viral predators: even within a single infected individual, genomic change plays a large role in the pathogenesis of HIV, as well as in malaria or trypanosomiasis. Larger bacterial populations have exhibited dramatic shifts in antibiotic resistance. These resistant bacteria can then display promiscuous genetic exchange and resuffering through conjugal plasmid transfer (8). Accommodation by compensatory evolution is too costly to contemplate Human gene frequencies would diverge only after drastic natural selections, the sacrifice of a substantial past of the susceptible herd (8). Human genomic change is not the answer for this feasible future. Extensive cross-species contact among humans and certain domestic animals can dictate antigenic shifts in influenza viruses. The likelihood of emergence of a new influenza virus in the near future increases with the growth of the frog populations in China. The emergence of new viruses such as HIV and filoviruses, indicates the virtually unlimited capacity of pathogenic organisms to mutate and rapidly adopt to environmental changes and selective pressures.

Tens of millions of cases of dengue and hundreds of thousands of cases of dengue haemorrhagic fever are reported annually, and more than 2.5 million people are at risk for infection (4). Factors contributing to the emergence of dengue include unplanned and uncontrolled population growth associated with urbanisation in tropical regions; lack of effective mosquito control, deteriorating water systems that increase densities of *Aedies aegypti*, and viral migration among tropical urban centres due to international travel.

The exponential increase in ecologic change, both environmental and behavioural, is the major driving force for the increasing human risk for viral infection. Travel of infected humans and international transport of microbes and vectors help provide the maximum possible microbial evolutionary opportunities in the minimum amount of time.

In prior illnesses such as Creutzfeldt-Jakob disease, risk factors and iatrogenic factors are important. The illness is thought to be linked to Bovine spongiform encephalopathy [BSE]. Mathematical modelling suggests that 75,000 to 80,000 cases will occur in the foreseeable future.

Poverty, changing immigration patterns, and the emergence of HIV contribute to rate of increased incidence of tuberculosis. Poorly managed tuberculosis control programs, suboptimal access to

health care, an inadequate doctor knowledge base, and poor patient compliance have combined to increase the incidence of tuberculosis and especially MDR-TB. Sensitivity testing is critical in the management of resistant TB. Effective control of TB will require social, political, and cultural change as well as medical innovation (4).

General approach to antibiotic resistance include [i] source control, particularly hand washing, and the need to wear gloves during contacts with all patients; [ii] improved antibiotic use and control; [iii] improved infection control devices; and [iv] better use of pathology and immunologic modulation.

EVOLUTIONARY POTENTIAL OF MICROBES

We face an ever-evolving adversary: microbes a billion fold more numerous than ourselves, vested with high intrinsic mutability and replication times measured in minutes, not years. Within every infected person, we see a Darwinian struggle mobilizing the genetic diversity of our immune cells to respond to the efficiency of that machinery. But many microbes have learned their own trick of jamming or coming in under the radar scan, masking their antigens or simply multiplying faster than our immune system can respond for these, a strategy of mutual attrition, or evolutionary competition, is doomed. Pitted against microbial genes, we have mainly our wits (9).

Our ability to develop method to counter infectious agents so far have not matched the myriad strategies employed by the sea of microbes that surround us. Their sheer numbers and the rate at which they can evolve are daunting. Although new vaccines, new antibiotics, improved global communication and new modalities for treating and preventing infections will be developed, pathogenic microbes will continue to develop new strategies of their own, presenting us with an unending and dynamic challenge. (10)

ANTIMICROBIAL RESISTANCE

Evolution of resistant bacterial strains threaten to outpace development of new drugs and the ability of public health professionals to protect the community. Antimicrobial resistance comes of age. Diseases are fighting back.

Wide use of antimicrobials has led to high rates of resistance among many bacteria (11). Modern medical techniques applied with inadequate training and resources have had disastrous consequences, as shown by dramatic outbreaks of nosocomial lassa fever in Nigeria and Ebola disease in Zaire (12). Transmission of Virus resulted from exposure to contaminated needles and from lack of adequate barriers during surgery. Mass processing and distribution of food has resulted in occasional massive outbreaks of infections such as Salmonellosis and *E. Coli* 0157:H7. Changes in climate lead to creation of new habitats that are energy expensive and provide new avenues for spread of infection (3). With over 250 systemically usable antibiotics available worldwide. We are certainly not on the verge of a post-antimicrobial era. Control of interaction

measures and agreed policies of restricted drug use can do much by way of mitigation. Wasteful prescribing is not merely money down the drain, it increasingly adds to selective pressure for microbial drug resistance. Bacteria possess endless resources to ensure their revival. We have enough antimicrobial agents, but we must learn to use them more circumspectly. Governments should regulate, more effectively the use of antimicrobials. It is time for medical schools to introduce formal teaching of the principles of rational prescribing in infection. There is a need for continuing education and training of health professionals to bridge the gap between social behaviour, political structure and economic power. There is a need to reassess use of antibiotics in animal feed.

ERADICATION OR CONTROL

The advent of molecular biology, modern developments in newly available opportunities for earth-orbiting, satellite-based surveillance as a means of predicting certain regional epidemics, and the introduction of remarkable raw antibiotics which can cure some awesome problems would have astonished anyone only a few decades ago. Just the same, even with these laudable advances, malaria is still with us, tuberculosis, poliomyelitis and EID are growing worldwide problems.

Eradication may be considered an ultimate goal. Smallpox was a major human scourge that has now been eradicated. Eradication requires permanently breaking a link in the chain of events that maintain an infection. However, in most cases, control is the practical goal.

Narrowing the gap between discovery and production of new technologies and their practical deployment will be one of the cardinal challenges of public health in the 21st century.

There is an urgent need to integrate knowledge about infections diseases with knowledge of climate and environmental change, migration and population of growth, demography and the consequences of conflict.

GLOBAL RESPONSE

The global threat requires a global response. Tackling emergence of infectious disease is worthy of top level policy attention. The burden of protecting the people from emergent infection cannot and should not be shouldered solely by the medical community. If the public were aware of the dangers and of simple, common-sense strategies that can protect their families, many people could be spared from debilitating and even tragic illness.

Concerted global and domestic surveillance and diagnosis of disease outbreaks and endemic occurrence is needed. There is need for the installation of sophisticated laboratory capabilities at many centers. Vector management and monitoring and enforcement of safe water and food supplies should be ensured. Public and professional education need our attention. Scientific research on causes of disease, pathogenic mechanisms, bodily defenses, vaccines, and antibiotics should be a priority. Cultivating the technical fruits of such research with the full involvement

of the pharmaceutical industry, and a public understanding of the regulatory and incentive structures, are needed to optimise the outcomes (9). Investing in research activities and in health education to enhance the diagnosis, treatment, prevention of disease will go a long way to raise public awareness of the dangers such diseases pose and the measures we can take to protect ourselves.

Response to infectious disease outbreaks whenever and wherever they occur requires international preparations and planning. Each country must train medical workers and laboratory technicians and supply them with appropriate equipment and diagnostic resources. Several international elements must be in place to provide the wherewithal for effective and timely disease control and prevention efforts.

GLOBAL PARTNERSHIP

A worldwide partnership of countries, non-governmental organization, international organization, and individuals is required to respond to the threat of emerging disease by ensuring rapid detection and effective containment. There is a need to synergise global partnership by ensuring strong national disease surveillance and control programmes, global networks to monitor and alert the world to infectious diseases, rapid information exchange through electronic links, and rapid response to contain epidemics of international importance. Reliable and solvent information on diseases and outbreaks to the world community through media should be made available. This has to be supplemented with appropriate advice to people living in or going to affected areas. There is also a need to revise international health regulations to provide an internationally agreed code of practice and control of potentially dangerous infectious diseases, according to todays epidemiological and economic realities guidelines should be provided on the application of regulations to minimize the disruption of travel and trade.

Rapid communication is vital to the functioning of a global network of monitoring centers. Through the internet we can link clinical and health research facilities around the globe so that newly emerging diseases can be recognized early and dealt with rapidly. Within limited financial resources, a small network of strategically located sentinel centers may be the effective way to begin providing early warning of serious epidemics.

Historically strategies to control infectious diseases have included quaranies and barriers to international travel and immigration. There is a need to develop and agree upon more appropriate, medically sound and practical screening options. Such policies must respond to changing societies, the evolving epidemiology of disease, the rights of individuals, and the public health needs of the community (13).

SURVEILLANCE AND INFORMATION SYSTEM

Timely recognition of emerging infections requires early warning systems to detect these diseases, so that they can be quickly investigated and controlled before

they become major public health crisis. Prompt detection of these new threats requires careful monitoring by effective surveillance systems, a thorough understanding of trends in incidence and distributions of known infectious agents, and good communication among clinicians, medical laboratories,and public health systems.

The ability to detect what is new or re-emerging depends on the capacity to identify and track the routine as well as the unusual. Surveillance with appropriate laboratory support is critical to an effective defence against these diseases. They are the most important tools for determining which infectious diseases are emerging, causing serious public health problems, or receding. Effective surveillance also provides a basis for evaluating the outcome of both health and personal medical care programs.

In, addition to comprehensive and innovative surveillance systems, effective preparation for emerging infectious diseases requires sound foundations in professional expertise, laboratory support and research capability.

To be successful we must apprehend infectious diseases in their evolutionary and ecological context (3). The elements of a global network for disease surveillance already exist but need to be strengthened, linked, and co-ordinated (1).

The modern world is a very small place, where any city in the world is only a plane ride away from any other. Infectious microbes don't recognize national borders. Without preventive public health measures, uncontrolled outbreaks can grow into major epidemics. A global system for infectious disease surveillance and response will help protect the health of people throughout the world (1).

The direct and indirect costs of infectious disease are staggering. Clearly, public health measures that prevent infectious diseases can be extremely cost-effective.

Three steps involved in responding to a disease outbreak include surveillance, evaluation, and implementation of control measures. Surveillance begins with accurate diagnosis and requires open lines of communications among doctors, scientists, and government officials. Evaluation requires epidemiologic and laboratory based investigations. Disease control requires that public health infrastructures are in place and that resources are available to procure and distribute medical supplies, such as drugs and vaccines.

To avert the threat of emerging infectious diseases and prevent their spread, health officials must be aware when epidemics occur anywhere in the world. However, reliable information can only be secured through clinical and laboratory-based surveillance that links medical and public health workers into a cooperative world wide network.

Four strategic objectives are necessary to establish a global system for disease surveillance and response strengthen existing surveillance systems; determine which common disease should be diagnosed within a country and which uncommon ones should be referred to reference laboratories, diagnostic tests be made available through a regional laboratory referral and distribution system. Develop

simpler, more cost-effective procedures to determine the causes of disease; enhance the capabilities of government agencies and existing disease-specific networks to respond to recognized outbreaks identified through improved surveillance and interdisciplinary research to support control and prevention (1).

Each nation should be encouraged to report, as early as possible, new events or trends in human or animal disease that are affecting its own population. Collaborative research to determine the cause of epidemics, devise strategies for control and prevention, and identify environmental and climatic conditions that favour the emergence of pathogenic microbes should be encouraged. There is a need to identify regional and international resources that can provide diagnostic reagents for low incidence disease, and help identify rare and unusual diseases.

APPROPRIATE TECHNOLOGY

Government must do more to promote a healthier environment. Especially for the poor who face greatly increased risks from poor sanitation, insufficient and unsafe water, poor personal and food hygiene, inadequate garbage disposal, air pollution, and crowed and inferior housing. Collectively these risks are associated with 30% of global burden of disease.

Development of suitable technologies for utilization of wastes is essential to minimize adverse health and environmental consequences. In most of the developing countries, the collection, transport, and disposal of solid waste is unscientific and chaotic causing water pollution, methane emission and said degradations. An apathetic government and crumbling public health care systems create ideal conditions for the deadly miasma of diseases that rise from the clogged drains, rotten garbage heaps and stagnant pools of water. Spread rapidly by a host of vectors like rats, mosquitoes and scavenging animals. They will claim thousands of lives and incapacitate many more. It was only when the dengue epidemic was raging in Delhi (India) that the government seemed to realize that mosquitoes breed in open bodies of water.

Surveillance, applied research, and prevention activities are critical to maintaining a strong defence against infectious disease (14). There is a need to integrate laboratory science and epidemiology to optimise public health practice.

MULTIDISCIPLINARY APPROACH

To continue and sustain improvements in health. It is necessary to combine the knowledge and skills of the public health profession with the brilliance of the clinicians to create the maximum opportunity for all to enjoy lives of good health and longevity. Better understanding of infectious agents is needed as a basis for the development of new therapies.

Dramatic advances in molecular biology and genetic engineering techniques have provided a shaft of candidate vaccines that will simply immunization. Improve the performance of existing vaccines, and protect children against diseases for which no vaccine currently

exists. Vaccine development should be based on epidemiological realities rather than current market demand in order to be cost-effective and affordable.

New approaches have, to be found which are flexible and compatible with local needs. There is a need to switch the program focus away from coverage to disease to disease control. Emergency preparedness and response of humanitarian agencies to tackle epidemics and refugee emergencies is very important. It is essential to ensure 100% coverage of immunization. Poor performing regions must be targeted. Hepatitis B and Yellow fever vaccines should be added to Expanded Program of Immunizations. BCG should be replaced with tuberculosis vaccine.

CAPACITY BUILDING

There is a critical need for co-ordination and strategic planning to rethink and upgrade efforts for emergency preparedness for responding to disease outbreaks.

Forward looking, sustained efforts to control and ultimately prevent major disease threats form the essential foundations for any plan to successfully address emerging infectious diseases. The process of responding to international microbial threats encompasses a multitude of activities, including diagnosis of disease; research to understand its modes of transmission; research to develop adequate means to treat it or prevent its spread, and production and dissemination of the necessary drugs and vaccines. Effective response to outbreaks of infectious disease include both immediate response to disease emergencies and ongoing activities to develop and maintain the tools to contain outbreaks, or better yet, to predict and /or prevent them before they happen (1).

The response component of a global infectious disease net work must rest on a complex foundation that includes skilled public health workers, national and regional laboratories for diagnosis and research, communications systems, and the commitment of national health ministries.

Disease prevention is an investment in the young people of the world and in our collective future. Prevention efforts immunisation, education to change unsafe human behaviours and other public health measures are the most cost-effective and beneficial of all measures that address the problem of infectious diseases (1).

Three ways to improve domestic surveillance of infectious diseases include: strengthen the national notifiable disease system; establish sentinel surveillance networks; and establish public health centers for emerging diseases to prevent future AIDS-like epidemics.

The effectiveness of a global disease surveillance and response system depends on each nations capacity to detect and control infectious diseases. In many developing countries, however, resources, are extremely scarce. A major objective of world bank, US AID, WHO, and developed economies should be the promotion of sustainable economic development around the globe. Helping other countries to help themselves -to improve the lives of their citizens, develop their economies, and find niches in the global economy should be a major guide for foreign assistance and aid.

All countries, should have the ability to provide laboratory diagnosis of "common" diseases endemic in their areas and the ability to refer specimens from "suspected" "uncommon" diseases to an appropriate reference laboratory. All the countries should have the epidemiologic capacity to investigate outbreaks, collect specimens, and analyse test results.

Capacity building in support of a national surveillance and response system encompasses a complex set of skills and resources. Many of which are readily available in industrialized nations but not in underdeveloped ones. The components of a public health infrastructure include human resources. Physical resources, systems for laboratory referral and information exchange and a favourable policy environment to encourage disease surveillance and permit disease reporting and cooperation with other countries. Recognizing, reporting, and responding to new disease threats involves each of these target areas (1).

Governments should encourage international communication among scientists and public health personnel regarding emerging infectious disease and request international assistance through WHO when disease outbreaks occurs or when unusual infections are suspected.

Epidemilogic and laboratory research are the essential foundation upon which a sound disease surveillance and response system is based. This is especially true in regard to emerging and unknown infectious diseases. To combat new diseases for which no treatments are known, it is essential to maintain an active community of epidemiologists and experimental scientists ready and able to seek new solutions for new disease threats. In addition, continued emphasis on effective social and behavioural science methods to enhance health promoting behaviour should be maintained. To meet the challenge of critical knowledge of the fundamental biology of infectious agents and the clinical disease processes they induce is essential. Scientific studies of infectious agents and the diseases they cause provide the fundamental knowledge base used to develop diagnostic tests to identify diseases, drugs to treat them, and vaccines to prevent them. In addition, the ability to intervene effectively in an outbreak or epidemic, or to implement a successful prevention strategy, requires a through understanding of the epidemiology of the disease (1). Maintaining diversity in infectious disease research will allow us to retain expertise on types of bacteria, viruses, and parasites that may emerge and or re-emerge unexpectedly. There is a need to encourage the development of tools to monitor, investigate and intervene in public health problems involving emerging or antibiotic resistant microbes. Interdisciplinary and interagency scientific exchanges and training programmes in the area of infectious diseases should be strengthened. Scientific research is also needed to guide public policy.

EMERGENCY PREPAREDNESS

Infectious diseases around the globe require serious attention from the world's policy makers. It is extremely important to prepare the world under united leadership

to address the dynamic threat to health amidst changing and mobile societies.

Policy efforts should focus on the preparation of an agreement which will lead to international legislation on EID that promotes collaboration. Establishing an infrastructure to address EID should be developed along the following lines; the protections of health and well being of people within all communities, preserving the basic human rights of individuals, balancing individual and community rights, as well as ensuring the socioeconomic stability of societies including national security, while observing and protecting the sovereignty of nations. Effective leadership should be a priority and include both the ability to anticipate change and envision a future state and the capacity to deploy and manage the implementation of an appropriate response. Leadership leaders at every level of society. Information technology for training in leadership development should be developed.

The management of EID requires a pro-active approach to ensure the appropriate prevention and control of disease by health authorities. Preparatory phase should include ongoing surveillance, routine reporting, clarity and definition of legal and ethical responsibilities, collecting and analyzing data and disseminating information about health and non-health indicators. This should be followed by investigations of possible outbreaks. Activities during the "alert" phase should include the detection, confirmation, and declaration of changes identified during preparatory phase. The "response" phase includes the ongoing assessment of information and the planning and implementation of an appropriate response which includes the co-ordination and mobilization of resources to support intervention activities.

A well planned systematic response is required which should include assessment of EID, an evaluation of existing resources capacity and the formulation of a strategic and operational plan to ensure a co-ordinated intersectoral global response. Capacity building should include strengthening global surveillance activities, strengthening infrastructure support, fostering applied research initiatives, and strengthening prevention and control efforts. Broadly defined strategic operation goals should focus on efficiency, equity, effectiveness and economy.

The development of information systems [the responsibility of the international community] includes addressing both the need for technology as well as ensuring the human capability to analyse and share information locally, and internationally. A comprehensive communication is required to ensure accurate and timely sharing of information. Technology for real time reporting of incidence of disease and feedback is needed. There should be regional sharing of information. Governments have to sit together for which willingness and understanding is needed. Communication to industry/corporate sector [who have a stake in it] is important. Communication should be strategically linked to other relevant issues. System of reporting [surveillance] requires good understanding of how other systems work. There is a need to establish national or

regional centers of excellence. Quality of information should be assured at all levels. Continued, on small network of strategically located sentinel centers may be the most effective way to begin providing early warning of serious epidemics.

Infrastructure and capacity building needs resources. There should be a "Funding pool" – International EID fund. This sustainable source of funding to support EID management initiatives will require innovative strategies for building public and private partnerships. Alternative mechanisms to pool public and private voluntary and commercial funds need to be explored. International travel associated with trade or leisure can be levied to enhance such funds. We must be aggressive in approaching commercial interests. There is also a need to reorganize and recapacitate present resources. Marketing campaign is required to create support that is needed to generate funds to strengthen public health services. Partnership with industry. pharmaceuticals and information technology organization is important. Cultural and institutional shifts are needed to create system to allocated scarce resource.

VISION FOR THE 21ST CENTURY

What is required is a world on the alert and able to contain communicable diseases through strong national disease surveillance and control programs; global networks of centers organizations and individuals to monitor disease: rapid information exchange through electronic links to guide policies, international collaboration, and rapid response to contain epidemics of international importance.

National and regional initiatives should include laboratory strengthening, provision of reagents, surveillance strengthening, epidemic response strengthening, and operational response should include epidemic response guidelines, surveillance case definition manual, surveillance assessment guidelines, vaccine and drug availability, epidemic response roster, research and development, and consensus meetings.

We have a responsibility to respond quickly when it is demanded. There is a need to develop a network, of multidisciplinary research centers firmly anchored in the countries around the world, especially in the tropics and near densely populated lower socioeconomic areas of third world countries. Without far better tools and a fa better understanding of disease, satisfactory disease control, let alone eradication is simply not in the cards.

Foundation has to be provided. National policies have to be devised to define specification of responsibilities: who is to do what? Quarantine needs firm guidelines, when it should be used and when it should not. Border policies should include repatriating carriers. Military should be trained to deal with refugees and quarantine measures. National activity should be supported to make things happen.

For responding to the challenge of EID, initiative has to be global and activity has to be local. We should ensure that future is better than the past.

People should share a belief that as a matter of birth. We are all entitled to basic human rights. People everywhere must

understand we are all born equal and that the border constructed between the self and others has to change. The world is continuing to move from independence to interdependence, nations must draw on strengths of other nations.

Nations need a new approach to identify, respond rapidly, and motivate translational actions. Disease and society are dynamic. Efforts to prevent and control the problem must begin with a search for a better understanding of the societal roots of disease, morbidity and mortality.

There is a need to assume a visionary perspective and to motivate change existing paradigms. Management policies are required to promote coordination of on-site operations and activities and to ensure responsiveness, preparedness and coordination.

The intervention activities may include needs assessment prioritization, the identification of barriers, contingency planning, communication strategies. Research and development of vacancies, drugs, and insect control intervention, among others.

Nations should assume responsibility for creating systems that support united leadership and which addresses the dynamic and rapidly changing social threats to health posed by EID. Effective leadership should include both the ability to anticipate change and envision a future state and the capacity to develop and manage the implementation of an appropriate response.

Development of successful communication strategy is a critical management issue during an infection outbreak. An approach to helping organizations prepare for the likely event of an outbreak and the need to manage the media is to conduct drills.

Individuals organization, and nations must manage the media proactively. Nations can identify the type of information needed or that will be needed by different audiences. Nations should be prepared to inform the media extensively.

For strategic surveillance and response capability. Addressing applied research priorities, improving prevention and control strategies, and strengthening the public infrastructure, effective partnerships are required with various agencies and organisations.

A well planned systematic response is required which should include assessment of EID. An evaluation of existing resource capacity building and the formulation of a strategic and operational plan to ensure a coordinated international global response. There is a need to pro-actively manage the global spread of EID.

REFERENCES

1. National Science and Technology Council. Infections Disease. A Global Health Threat. NSTC Committee on International Science, Engineering, and Technology working Group on EID. Centers for Disease Control and Prevention. 1995.
2. Wilson Me, Levins R, Speilman A (editors). Disease in evolution: global changes and emergence of infectious disease in

evolution: global changes and emergence of infectious disease. New York Academy of Sciences, 1994.

3. Wilson ME (1995). Infectious disease: an ecological perspective. *BMJ* **311**:1681-1684.
4. Greenberg RN, Reinberg JE and Pomeroy C (1998). The Hot Zone-1997: Conference on EID. *Emerging Infets Dis* **4(1):** 135-39.
5. Krause RM (1981). The Restless tide–the persistent challenge of the microbial world. Washington DC: The National foundation for Infectious Diseases.
6. Morse SS and Schuederberg A (1990). Emerging viruses: the evolution of virus and viral diseases. *J Infect Dis* **162**:1-7.
7. Epstein PR (1992). Commentary, pestilence and poverty-historical transition and the great pandemics *Am J Preventive Med* **18:**263-5.
8. Lederherg J, Shope RE, Oaks SC (1992) (editors). Emerging infectious microbical threats to health in the USA. Washington DC: National Academy Press.
9. Lederberg J (1996). Infectious disease-threat to global health and security. *JAMA* **276:**417-19.
10. Madoff LC and Kasper DL (1998). Introduction to infectious diseases: host-parasite interaction. In: Fauci AS, Braunwald E, Isselbacher KJ, Wilson JD, Martin JB, Kasper DL, et al. Harrison's principles of internal medicine. New York: McGraw-Hill, 749-54.
11. Neu HC (1992). The crisis in antibiotic resistance. *Science* **257**:1064-73.
12. Fisher-Hoch SP, Tomori O, Perez Oronoz GI, et al (1995). Review of cases of nosocomial lassa fever in Nigeria; the price of poor medical practice. *BMJ* **311:**857-60.
13. Weeker J and Herald S (1997). Is compulsory overseas medical screening of migrants justifiable? Public Health Rep **112:**396-402.
14. CDC (1994). Addressing emerging infection disease control & prevention strategy for the USA. Centers for Disease Control and Prevention, Atlanta USA: 1994, 1-6.