

Non-Communicable Diseases

India is facing progressive onslaught of non-communicable diseases like cancer, cardiovascular diseases, psychiatric disorders, disability and accident related injuries with increase in developmental activities and industrialization. Changes in life-style resulting from improvement in socio-economic status is another factor leading to higher prevalence of non-communicable diseases. Average life-expectancy has increased thereby resulting in rise in ageing population and health problems in these people. The Council is carrying out research projects in major non-communicable diseases like cancer of the cervix, breast and stomach, hypertension, rheumatic heart disease, ophthalmic disorders and mental illnesses.

The Council's Institute of Cytology and Preventive Oncology (ICPO) at New Delhi continued its research and human resource developmental activities in the field of cancer of the uterine cervix, breast and stomach.

ONCOLOGY

In the field of oncology Cancer Registries continued to provide valuable data on cancer occurrence which has its utility in development of hypothesis as well as for evaluation of intervention projects. Project on cancer atlas tried to assess the magnitude of problem through 99 pathology laboratories in India. An operational research project on screening for common cancers has been initiated. Besides this studies are being conducted on various aspects of cervical and breast cancer.

NATIONAL CANCER REGISTRY PROGRAMME

The National Cancer Registry Programme (NCRP), initiated in 1981-82, continues to collect authentic data on cancer occurrence in the country. The report providing data till the year 1998 has been printed. The network of NCRP

has been expanded by initiation of six population based cancer registries in North-East India and one rural population based cancer registry at Ahmedabad district. These new registries are one each at Dibrugarh and Kamrup (Assam), West Imphal district (Manipur), Mizoram and Sikkim. The new registry at Silchar covers urban area only, while other five registries cover urban as well as rural areas under the district/state. Other existing population based cancer registries are located at Bangalore, Bhopal, rural Barshi, Chennai, Delhi, and Mumbai. Hospital based cancer registries are functioning at Bangalore, Chennai, Dibrugarh, Mumbai and Thiruvananthapuram. These registries aim at generation of reliable data on cancer occurrence, conducting epidemiological studies and developing human resource in the field of cancer epidemiology and registration. Monitoring and evaluation of the programme is being undertaken by a coordinating unit (Bangalore) under the guidance of a Steering Committee.

The crude incidence rate of cancer for 1999 in different urban population based cancer registry areas varied between 55.7 and 92.5 per 100,000 males and between 61.4 and 103.0 per 100,000 females. The crude incidence rate in the rural registry at Barshi (Maharashtra) was 46.1 per 100,000 males and 56.5 per 100,000 females. Hospital based cancer registries at Chennai, Thiruvananthapuram and Mumbai have initiated a project to study the patterns of care and survival in cancers of cervix, breast, and head and neck. Currently investigation is being done in patients diagnosed during 1997 and 1998.

The project on development of an atlas of cancer in India is collecting data from the departments of pathology of medical colleges and major cancer hospitals. About 99 centres are actively providing the data. So far, information on about 100,000 cases has been received. The minimum crude incidence rates for different districts have also been calculated.



CERVICAL CANCER

Multidisciplinary Study on Cervical Cancer

A multidisciplinary study on cervical cancer is ongoing at ICPO. The study involves cytomorphological, HPV, genetic and molecular approaches. During the year under report 5063 new smears were screened cytologically, thus bringing the total cumulative to 24,163. Of these smears a total of 5.6% epithelial abnormalities were observed. Atypical squamous cells of undetermined significance (ASCUS) were reported in 3.3%, low grade squamous epithelial lesions (LSIL) in 1.2%, high grade SIL in 0.4%, atypical glandular cells of undetermined significance (AGUS) in 0.2% and 0.5% were malignant/suspicious. Rest of the smears were inflammatory or negative. Cytologically detected and biopsy proven lesions form the basis of cohort recruitment for various studies on cervical cancer and its precursors.

Early Detection of Cervical Cancer

Research projects are ongoing for developing alternate methodologies for early detection of cervical cancer and its precursors since 1988. A programme involving magnivisualizer was launched to study the efficacy and feasibility of its use by para-medical workers and its delivery to gynaecologists for their suggestions on improving its suitability and specificity. It further envisages training of paramedical personnel for use in the peripheral sectors.

Further, a technical manual and a pictorial calendar has been prepared for use of visual inspection aids (VIA). These have already been circulated widely to the medical colleges and cancer hospitals. This manual is expected to go a long way in developing human resources for early detection of cancerous and precancerous lesions of the cervix.

Precancerous Lesions of Cervix

The ICPO continued its efforts for developing treatment modalities for precancerous lesions of cervix. ICPO has been recognized by International Agency for Research in Cancer as one of the centres for initiating a multinational

randomized trial to study the comparative efficacy of single vs double freeze technique of cryotherapy in controlling carcinoma-*in-situ* (CIN) lesions.

Biological Behaviour of HPV Infection

Various studies have been initiated at ICPO involving different aspects of human papilloma virus (HPV). One of these is the study of biological behaviour of HPV infection. During the year under report 580 women attending gynecologic OPD of a teaching hospital were tested for HPV DNA by PCR using L1 primer and 20.5% of them tested positive. Further typing for HPV high risk types (16 and 18) revealed rather low positivity, the reasons for which are being investigated.

Efforts are ongoing at ICPO for development of low cost easy HPV detection tests. Earlier it was shown by the Institute that HPV screening using hybrid capture technology has 75% sensitivity for detection of CIN 1 lesions and nearly 100% sensitivity for detection of high grade (CIN II+) lesions with a specificity of about 83%. Though the positive predictive value was rather low (6.7%), a very high negative predictive value of 99.2% makes it an ideal tool for Indian situation where frequent screening, as is being done in the western countries, is not possible. Once in a life time screening using HPV (high risk types) detection at 35 yr of age would confer an immunity for life in over 99% of the subjects. The only negative aspect of HPV screening is the prohibitive cost of more than Rs.500-700 per test. In order to resolve this issue, ICPO has initiated research for development of indigenous early detection tools involving multiplex PCR so that a single test can detect women harbouring high risk types of HPV. Another important aspect of HPV screening is the transport and storage of HPV samples from periphery to central PCR-based laboratories. A breakthrough made in developing a paper smear technology, wherein a dry smear can be stored and transported to the centralized laboratories without any risk of loss of DNA material is under patenting.

The ICPO is also engaged in molecular control of HPV infection by using synthetic and



herbal oxidants. In addition, phase III clinical trial of microbicidal polyherbal neem creams/tablets against HPV infection continued during the year.

The ICPO has been recognized by WHO for participating in the multinational programme for developing vaccine against HPV.

DNA Methylation Pattern and Differential Gene Expression in Cervical Cancer

Studies have been initiated to investigate DNA methylation pattern and expression level of methylase enzyme and differential gene expression in cervical and breast cancer. This study along with genetic instability in precancerous and cancerous lesions would increase the understanding of the molecular mechanism in the development of these cancers.

Telomerase Activity in Cancerous Lesions

In another study on cervical cancer, telomerase activity has been assessed in 150 samples comprising cancerous and precancerous lesions. In all the tumours and majority of dysplastic lesions around 68% were positive for telomerase activity which showed a positive correlation with hTERT expression. However, hTR expression was observed in all tumour lesions. This study further revealed that hTR and hTERT both are upregulated in the presence of HPV infection.

Genomic Instability and Genomic Deletion

Study on genetic instability, loss of heterozygosity (LOH) and β -catenin gene mutation continued during the year. Microsatellite instability was found to be an early event in the process of cervical carcinogenesis. Microsatellite instability (MSI) along with HPV infection appears to be a potential marker for detecting the disease in its early stage.

BREAST CANCER

Multidisciplinary Study

The ICPO has initiated a cohort study on breast cancer to study the clinical profile,

epidemiological risk factors, treatment patterns and survival of breast cancer patients. In addition, the prognostic factors including the role of sex hormones will be elucidated. One of the important parameters of the study would be identification of the disease susceptibility gene including genetical instability. A data bank and a bio-bank for storing biological samples from familial cases of breast cancer will be developed.

Other Studies in Breast Cancer

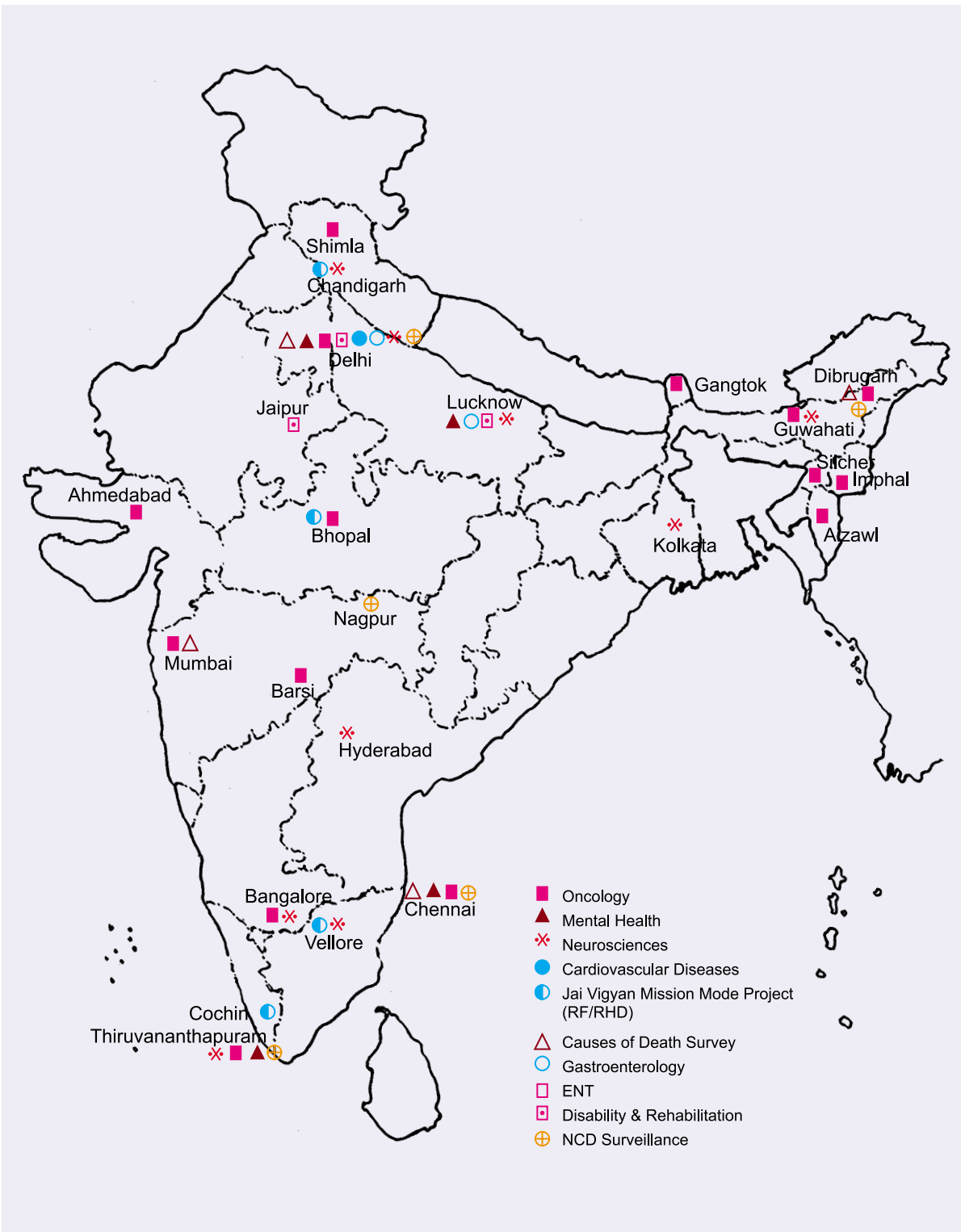
A study has been initiated to determine mutation of BRCA1, BRCA2 and P53 genes from tumour biopsies from 105 sporadic cases and blood samples from 28 familial breast cancer patients. All exons of BRCA1 and specific exons 2, 9, 11, 11a, 18 and 20 of BRCA2 which are frequently mutated in BRCA2 were analysed.

In sporadic breast cancer biopsy samples, only 4.8% mutations comprising 2% in exon 2 and 1% in exon 11 of BRCA1 and 2% in exon 2 of BRCA2 were detected by PCR-SSCP assay. Other exons of BRCA1 and BRCA2 showed no mutation. Out of 28 familial breast cancer samples analyzed, only 7% mutations could be detected in exon 2 of BRCA1 genes and no mutation in BRCA2 gene. In addition, 2.8% mutations were detected in exon 5 of p53 gene. Among 105 sporadic cases, no mutation was found in other exons. Out of 28 familial breast cancers analysed only one mutation could be detected in exon 4 of the p53 genes. In 60 samples expression of BRCA1 gene was found to be down-regulated and that of p53 gene was over-expressed. In almost all breast cancer cases, preliminary studies on levels of transcription factors, AP1 and NF κ B suggest possible downregulation.

CARDIOVASCULAR DISEASES

The entire Southeast Asian region is threatened by the hidden epidemic of cardiovascular diseases (CVD). The number of deaths due to ischaemic diseases in this region is second to deaths caused by HIV in the younger age group of 5 to 59 yr; in the older age group of ≥ 60 yr ischaemic diseases accounted for maximum number of deaths. Identification of





MAJOR ICMR RESEARCH PROJECTS IN NON-COMMUNICABLE DISEASES

Non-Communicable Diseases



novel risk factors in Indian population using modern research tools will help in developing preventive strategies.

Hospital-based Study to identify Risk Factors for Acute Myocardial Infarction in Indians

The study is ongoing at New Delhi, Bangalore, Lucknow and Hyderabad and so far 2310 subjects have been enrolled.

Jai Vigyan Mission Mode Project

Community Control of Rheumatic Fever (RF)/Rheumatic Heart Disease (RHD)

This project was initiated under the Prime Minister's initiative as a mission mode project. Various components of the project-(i) to study the epidemiology of streptococcal sore throat; (ii) to establish registries for RF/RHD; (iii) vaccine development for streptococcal infections and (iv) conducting advanced studies on pathological aspects of RF/RHD - are interrelated and are providing a large data on disease prevalence in the northern and southern regions of the country, the types of group A streptococci (GAS) strains circulating in the community and the effectiveness of the secondary preventive measures in control of RF/RHD. The study is paving a way towards an indigenous vaccine against GAS. The epidemiology component undertaken at Chandigarh and Vellore has been completed. The *emm* typing data from both these centres show that the strains from Vellore are more heterogeneous than those from Chandigarh. The *emm* typing of 78 GAS strains from Chandigarh showed that 78% strains were homologous to M77, 81, 11, 71 and 69 *emm* types, rest were 18, 44, 65, 68, 75, 85, 87, 88, 92, 118, ST854 (Fig.1)

Under the Registry component, the three centres (Chandigarh, Vellore and Cochin) have registered 314, 274 and 142 confirmed cases of RF/RHD respectively after a thorough screening of suspected cases. Under the active surveillance component, screening of 23336, 26551 and 26341 school children by Chandigarh, Vellore and Cochin centres showed RF/RHD prevalence of 1.02, 1.46 and 0.228 per 1000 respectively. The

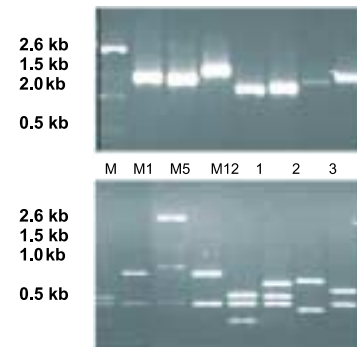


Fig. 1. (a) PCR amplification of *emm* gene and (b) RFLP pattern of the amplified product of *emm* gene. (lane 1-2 pharyngitis strains; lane 3-4 RF/RHD strains; M, M1, M5, M12 lanes show corresponding *emm* types).

three centres are also conducting training workshops for medical and para-medical staff for identifying and referring suspected cases of RF/RHD as well as community education programme in the selected districts.

Under the vaccine component 12 peptides corresponding to 20 amino acid of amino terminal of M protein have been synthesized. The tetanus toxoid conjugated peptides showed adequate protection of the immunized mice. Except for anti-peptide sera against N terminal peptides of one strain, all other 10 anti-peptide sera showed opsonic activity ranging from 43-95% against homologous strains. The results indicate that anti N terminal peptide sera mainly opsonize homologous strains with some exceptions. The cross protection is minimal.

OPHTHALMOLOGY

Prevalence of Glaucoma

Glaucoma has been identified as one of the main causes of preventable blindness all over the world. In India there is a lack of data on prevalence of glaucoma in the population. The ICMR has conducted a population based study to determine the glaucoma prevalence in Angamaly district of Kerala. A total of 17706 individuals aged > 35 yr were screened of which 358 had confirmed glaucoma and 223 were glaucoma suspects. Out of the 358 cases 231 had primary open angle glaucoma, 74 primary angle closure glaucoma, 31 secondary glaucoma and the rest had other types of glaucoma. Prevalence





of glaucoma was the highest (2.91%) in the 55-64 yr age group. The age-specific rates showed a different trend in males and females. In males the highest rate was in the 65-74 yr age group (3.46%) while in females 55-64 yr age group had the highest prevalence (31.4%). The overall prevalence of glaucoma was 2.0% in individuals aged >35 yr. Primary open angle glaucoma had a prevalence of 1.3% while primary angle closure glaucoma had a prevalence of 0.42%.

The prevalence of blindness in the study area was 1.52%. The blindness figures have shown a decline as compared to the earlier multicentric study conducted by ICMR in the 1970. The decline is even more prominent when the figures are compared to one of the centres (Madurai) which was similarly located geographically. (Fig. 2)

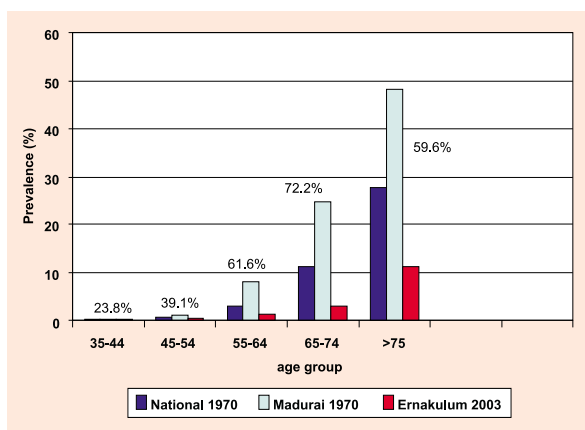


Fig. 2. Prevalence of blindness in Angamaly. Figures in red indicate the quantum of decline from the national average.

MENTAL HEALTH

According to World Bank study, mental health problems (including self inflicted injuries) are one of the largest causes of lost years of Quality of Life accounting for 8.1% of all such lost years. In adult population (15-44 yr), the neuropsychiatric disorders account for 12% of global burden of diseases. According to a World Bank report, psychiatric conditions measured in disability adjusted life years (DALYs) are five of the 10 leading causes of disability world wide. National and International statistics do not reflect the enormous toll of misery from mental disorders because these conditions are not the

immediate cause of death. The burden of DALYs due to mental health problems is projected to increase to 15% by the year 2020.

Urban Mental Health Problems and their Services Needs

Rapidly growing population in urban areas in India is causing various problems related to mental health. The rapid growth, without proper health services (especially those related to mental health aspects), stress, pollution, noise and overcrowding have a direct correlation with mental health.

The ICMR initiated a study on urban mental health problems at three centres viz. Delhi, Lucknow and Chennai with support from WHO. The study aims to collect and collate data related to existing mental health services-government, private and NGOs, in urban areas, through mapping of these services in the selected cities. The pilot phase of the project has been completed. The work was carried out as mapping of specialized mental health services, the assessment of diagnostic profile and pattern of utilization of services at five treatment centres, and the assessment of needs and services in community. Instruments were developed and pre-tested. Mapping of the specialized mental health services and NGOs was undertaken. In-depth interviews were held with patients, informants and service providers. Key informant interviews, free listing and focus group discussions were also undertaken with general practitioners and faith healers. As per the community perception, mental health problems were reported due to stress in majority and to medico-religious causes in a few patients. Interestingly most of the faith healers reported that mental health problems were due to illness of brain. The burden of psychological and psychiatric problems in community was reported to be 30% by general practitioners, 50% of whom felt that mental health services were satisfactory.

Suicide Behaviour

Suicide is a major public health problem and is among the top ten causes of death in most countries. Looking at the sociocultural diversity

of Indian population there is a need for well designed prospective study. A task force project on suicide behaviour was initiated at Delhi and Thiruvananthapuram with the objectives to adapt/develop and pretest study instruments, to work out field work logistics and referral system for community settings, to establish project work logistics for hospital based study and prepare guidelines for intervention and manuals for training of research staff. The study instruments have been translated, tested and adapted. Community surveys were conducted in metropolitan areas at both centres. Individual data from the families was collected. The qualitative study has indicated wide acceptability without any negative effect of the project in the community. Hospital arms of the project were also undertaken in both the cities. Preliminary results indicated that mean scores on all the instruments had increasing trend with the grade of suicidal ideation.

Mental Health Service Needs and Service Delivery Models in the Disaster (Earthquake) affected Population in Gujarat

Pilot study of the task force on mental health service needs and service delivery models in the disaster (earthquake) affected population in Gujarat was completed. The study highlighted the definitive need to focus on emotional and psychological needs of the disaster affected populations. It was observed that communities and populations can and do take care of their emotional and psychological needs with their own resources. Qualitative research methods have been finalized. The main study ongoing at 3 centres in Gujarat would focus on the long term psychological effects, psychiatric disorders, coping mechanisms and response pattern in disaster affected population.

NEUROLOGICAL DISORDERS

Epilepsy in Pregnant Women

Epilepsy is one of the most common neurological disorders and its prevalence in pregnant women is estimated to be around 0.5%-2%. A longitudinal prospective study was

initiated to assess the risk of malformations in newborn children of women with epilepsy at Safdarjung Hospital, New Delhi. So far, 170 women have been enrolled. The incidence of major malformations was found to be 6.8% in epileptic women compared to 2.87% in controls. The malformations were 12.1% in women with duration of epilepsy more than five years. Another project on Registry of Epilepsy in Pregnancy has been initiated in Thiruvananthapuram.

Other Studies

Studies have been initiated to detect Parkene gene mutations in Parkinson's disease and on prevalence of neurocysticercosis in Indian population.

GASTROENTEROLOGY

Interferon has been used as treatment for hepatitis C, either alone or in combination with other anti-viral agents. As this therapy is expensive and has to be taken for a very long duration, there is a need to identify some marker to predict the non-response and outcome. Though high baseline viral load and HCV genotype 1b has been reported to be influenced by therapy, there is scarcity of data to substantiate this claim in India.

A task force study to determine host and viral factors responsible for non-response to interferon therapy in patients with hepatitis C virus infection is ongoing at GB Pant Hospital, New Delhi. This project is also studying the genetic factors influencing the outcome of the therapy. The study population includes HCV RNA positive patients with histologically proven chronic hepatitis C with raised ALT. A total of 59 patients have completed 12 month follow up. Non-1 HCV genotype was detected in 43 patients, while standardization of the protocols for genotypes 2 and 3 are being undertaken. HLA typing has been completed in 16 patients. The CCR5 gene has been also studied and significant difference was found between the responders and non-responders of the therapy. Genotyping of 136 HCV patients has so far been completed. None of the CCR5 and TNF alpha allelic variants correlated with the disease severity and hepatic



inflammation. Based on univariate analysis, TNF- β A/A allele correlated significantly with hepatic inflammation. Amongst the VDR alleles, BB and tt were significantly associated with hepatic inflammation. VDR Aa were associated significantly with hepatic inflammation. TNF- β G/G and A/A, but not CCR5 δ 32 mutation, correlated with severity of hepatic fibrosis and liver disease. Among the VDR alleles, Bsm 1BB, bb Taq 1:TT and tt correlated significantly with the severity of liver disease.

CAUSES OF DEATH BY VERBAL AUTOPSY

A task force project on developing and testing the feasibility of utilizing the verbal autopsy technique to identify the underlying cause/s of death is ongoing since January 2001. The initial two years were utilized for developing and testing the study instruments and a pilot survey in two districts of Rajasthan and Chennai. Realizing the utility of this method to act as an adjunct to the existing system of death data collection in the country, the study was expanded to cover 5 representative states in the central, south, east, west and northeast regions of the country *viz.* Rajasthan, Tamil Nadu, Bihar, Maharashtra and Assam. Training programmes for the field staff were organized and the participating centres were Institute for Research in Medical Statistics (IRMS), Delhi, National Institute of Epidemiology (NIE), Chennai, NIRRH, Mumbai and RMRC, Dibrugarh. In each of these states the main study has taken off during the years 2003-2004. The first round of data collection has yielded information on more than 5000 deaths for a recall period of 6 months. More than 70% of these deaths constitute adult deaths. The preliminary data analysis shows that CVD is the leading cause of death in all the centres comprising 20-30% of all deaths. Cancer is ranked as the second major killer followed by accidents. Pulmonary tuberculosis has also resulted in a substantial number of deaths in some centres. The second round is in progress and the data entry has begun.

ASSESSMENT OF BURDEN OF NON-COMMUNICABLE DISEASES

An ICMR-WHO project for assessment of burden of non-communicable diseases and related risk factors was initiated during 2003-04. Till date a systematic review of all the available studies on ischaemic heart disease, stroke, diabetes and cancer and their risk factors *viz.* tobacco and hypertension has been done. The data on mortality and population have been collected combined with the prevalence/incidence data from available studies using diseases modelling.

NON-COMMUNICABLE DISEASE SURVEILLANCE

The initiative for development of NCD surveillance was started in December 2001. Two major studies were initiated, one on development of sentinel health monitoring centres in India and another on health behaviour surveillance for risk factors of NCDs.

Development of Sentinel Health Monitoring Centres in India

The study was undertaken at Ballabgarh (Haryana), Chennai (Tamil Nadu), Dibrugarh (Assam), Nagpur (Maharashtra) and Thiruvananthapuram (Kerala), using the adapted WHO STEP wise modules. The risk factors for NCDs which were studied included consumption patterns of alcohol and tobacco, fruits and vegetables, levels of physical activity, weight, height, blood pressure and waist circumference.

The study population was divided into 5 age cohorts (15-24, 25-34, 35-44, 45-54, 55-64 yr) in urban, slum and rural areas, and both the sexes were studied. In the urban areas and slums, census block was the sampling unit whereas village was the sampling unit in rural areas. Overall, 39,437 subjects were studied at all centres, of which 49.2% were males and 50.8% females. Around 6500 men and women were in rural, urban and town areas. Complete analysis of data is ongoing.

The study on health behaviour surveillance for NCD risk factors is also ongoing.

